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REAL WORLD EFFECTIVENESS OF BARICITINIB IN THE SWISS RHEUMATOID ARTHRITIS REGISTER (SCQM-RA)

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ABSTRACT

Objectives: This observational study compares the effectiveness of baricitinib (BARI), a targeted synthetic DMARD (tsDMARD) with alternative biological DMARDs (bDMARDs) in rheumatoid arthritis (RA) patients, from a prospective, longitudinal cohort.

Methods: We compared patients initiating a treatment course of BARI, tumor necrosis factor inhibitors (TNFi) or other mode of action bDMARDs (OMA), during a period when all these DMARDs where available in Switzerland. The primary outcome was drug-maintenance; secondary outcomes included discontinuation rates related specifically to ineffectiveness and to adverse events. We further analyzed rates of low disease activity (LDA) and remission (REM) at 12 months, and drug maintenance in b- and tsDMARD-naïve population.

Results: A total of 1053 treatment courses (TC) were included: 273 on BARI, 473 on TNFi and 307 on OMA. BARI was prescribed to older patients with longer disease duration and more previous treatment failures than TNFi. Compared to BARI, the adjusted drug maintenance was significantly shorter for TNFi (hazard ratio (HR) for discontinuation: 1.76; 95% CI [1.32-2.35]), but not compared to OMA (HR 1.27; 95% CI [0.93-1.72]). These results were similar in the b/tsDMARD-naïve population. The higher discontinuation of TNFi was mostly due to an increased discontinuation for ineffectiveness (HR = 1.49; 95% CI [1.03 – 2.15]), with no significant differences in drug discontinuation for adverse events (HR = 1.46; 95% CI [0.83 - 2.57]. The LDA and REM rates at 12 months did not differ significantly between the 3 groups.

Conclusions: BARI demonstrated a significantly higher drug maintenance compared to TNFi, mainly due to lower drug discontinuations for ineffectiveness, but similar maintenance to OMA. Clinical outcomes did not differ between the three groups. Our results suggest that BARI is an appropriated therapeutic alternative to bDMARDs in the management of RA.

Strengths and limitations of this study

Strengths:

- Use data derived from office-based rheumatologists
- Study period where all alternative medications were available on the market
- Several sensitivity analyses, congruent with main results

Limitations:

- Not a randomized setting
- Sub-analysis in b/tsDMARD-naïve population has limited sample size

INTRODUCTION

Rheumatoid arthritis (RA) is an auto-immune disease leading to widespread inflammation and irreversible joint damage, if insufficiently treated. New treatment paradigms have emerged in the last decades, such as “early aggressive therapy” in the so called “window of opportunity”, during which patients are more likely to reach long term remission.[1] A wide panel of biological disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been approved in the management of RA, after failure of methotrexate. In clinical-trial settings, b- and tsDMARDs have demonstrated significant reduction of joint inflammation and prevention of joint damage.[2–8]

Efficacy estimates from placebo-controlled randomized trials often differ from real-world effectiveness estimates, because of patient selection, adherence to therapy and other reasons.[9–12] Indeed, drug maintenance of many bDMARDs remains modest in observational analyses, while long term remissions are rare and secondary loss of efficacy frequent.[13] Furthermore, understanding the clinical effectiveness of bDMARDs or tsDMARDs in specific conditions, such as elderly or multi-morbid patients, may become important as we move towards personalized care. Finally, trials provide only limited data on long term effectiveness and safety because clinical-trial follow-up is typically less than 12 months.

Baricitinib (BARI) has been approved in Switzerland for the treatment of RA in 2017 as well as all around the world. Clinical trials with BARI have established efficacy and demonstrated acceptable adverse events profile, both in combination with methotrexate or in monotherapy.[14–20] However, evidence about effectiveness of BARI compared to TNFi in

real-world settings are scarce. A recently published analysis of registry data from Sweden showed that baricitinib had higher maintenance as compared to most other bDMARD.[21] Pappas et al., in the United States, also demonstrated that TNFi and non-TNFi drugs had similar outcomes when prescribed in b/tsDMARD-naïve population, an observation replicated in the RA-BE-REAL study.[22,23]

The aim of our analysis was to compare real-world drug maintenance between BARI and other approved b/tsDMARDs, using data from a European registry.

METHODS

Study population

This is a nested cohort study from a prospective, longitudinal, cohort of Swiss RA patients in a real-life setting, the Swiss Clinical Quality Management registry (SCQM). The SCQM registry was founded in 1997 with the financial support of Swiss regulatory authorities, who recommended a continuous monitoring of all patients receiving new DMARDs. Unlike many other European registries, most patients are enrolled by private office-based rheumatologists (60%), providing a population-based sample of RA patients in Switzerland. All approved RA treatments are represented in the registry. The data for this analysis was extracted from the SCQM registry on 2020-06-01.

We used “treatment courses” (TCs) as our denominator of interest, with each new treatment initiation considered as a separate “treatment course” (TC). We included all TCs with the medications of interest initiated between 2017-09-01 and 2020-06-01, with at least one follow-up visit, in adult patients with a diagnosis of RA confirmed by a rheumatologist. Thus, a given patient could potentially contribute to several TCs during the study period. To minimize the risk of confounding bias, the time window was selected to include only the period when all the therapies examined were available for prescription and reimbursed (BARI was first reimbursed on the Swiss market in September 2017). We excluded TCs with no follow-up visit at the time of data extraction.

Exposure of interest

The exposure of interest was the type of treatment used, namely BARI, TNFi, and other mode of action bDMARDs (OMA), excluding other tsDMARDs and rituximab. We decided to exclude rituximab a priori, because its long-term action impairs precise estimation of treatment discontinuation. Tofacitinib was excluded because we had insufficient TC to perform meaningful comparative effectiveness analyses against a single other specific tsDMARD agent. Included TNFi treatments were: adalimumab, etanercept, golimumab, certolizumab, infliximab. Included OMA treatments were: tocilizumab, abatacept, sarilumab, and anakinra.

Outcomes

The primary outcome of this analysis was the time to all-cause-discontinuation. This outcome, also referred to as "drug maintenance", captures both the drug's effectiveness and its tolerance.[24] The time to all-cause-discontinuation was defined as the number of days between treatment initiation and the reported date of discontinuation, or the date of initiation of a new b/tsDMARD, whatever came first. In survival analyses, death or lost-to-follow up are censored. We also report discontinuation rates at 12 months. Temporary discontinuations of less than 6 months (for instance, because of an elective surgery or a pregnancy) were not considered a permanent drug discontinuation. Discontinuation reasons are recorded by the clinician when stopping a DMARD treatment, who chooses between four options ("Adverse event", "Ineffectiveness", "Remission", or "Other").

Pre-planned secondary outcomes, were time to discontinuation due to ineffectiveness and time to discontinuation due to adverse events. Other secondary outcomes included response rates, namely the rates of low disease activity (LDA) and remission (REM), at 12 months, defined respectively as attaining a CDAI score <= 10 and CDAI score <= 2.8 (not mutually

exclusive).[25] Finally, we performed an exploratory subgroup analysis, restricting the population to b/tsDMARD-naive patients only, and re-assessing the main outcome in this setting.

Statistical analysis

Analyses were conducted and reported in accordance to EULAR recommendations for comparative effectiveness research.[9] Baseline characteristics were compared using ANOVA or χ2 tests as appropriate. For the primary outcomes, Kaplan-Meier survival analyses were used to assess crude drug maintenance, and groups were compared using Log-Rank tests. Subsequently, missing covariates were imputed using chained equations (see below for details). We then implemented Cox proportional hazard ratio models, to obtain adjusted estimates. Based on prior subject matter knowledge,[26] we adjusted our models for the following potential confounders: age, gender, BMI, concomitant csDMARDs use (yes/no), concomitant prednisone usage (yes/no), CDAI score at baseline, disease duration, smoking status (current-, former-, never-smoker) and line of therapy (1^{st}, 2^{nd}, 3^{rd}, 4^{th} or more), and seropositivity (yes/no). Detailed definitions for each variable are available in the supplement. A cluster term accounted for patients with multiple TCs. All conditions of application of the Cox model were verified. One additional sensitivity analysis was conducted for the primary outcome, using augmented inverse probability of treatment weighting (AIPTW).

In secondary analyses, we used the Fine-Gray approach to assess specific reasons for drug discontinuation (i.e. ineffectiveness, or adverse event) in a competing-risk setting. Other secondary outcomes included response rates (LDA and REM) at 12 months. To avoid overestimations, we computed the response rates using the 'confounder-adjusted response

rate with attrition correction' (CARRAC) method.[27] The latter estimates the response rates using multiple imputations, with a model including both confounders and treatment stop reason. CARRAC thus provides reliable estimates when reasons for treatment discontinuation differ between compared groups.

For all adjusted analyses, missing baseline covariates were imputed using closest value in a window of -90 to +30 days. However, this window was reduced to -30 to +7 days when imputing baseline CDAI. If still missing after this first step, baseline CDAI values were imputed using linear mixed effect regression model with quadratic time. We imputed other baseline covariates with chained equations technique, which provides unbiased estimates if the variables are missing at random.[27] Such imputations were performed using 50 datasets with 25 iterations. Imputation was done using the whole data set, before adequately subsetting the data for each group comparison.

We also imputed data required for secondary outcomes, including disease activity. If the CDAI score at 12-month was not available, the closest value in a window of +/- 45 days was used (a 3-month-wide window). If still missing, the 12-month CDAI values were imputed using nearest neighboring value, as previously described.[28]

All analyses were conducted using R (version 4.0.3), in particular with packages "*tableone*", "*survival*", "*mice*".[29] Two tailed p-values < 0.05 were considered significant. We did not adjust p value for multiple comparisons, as outcomes were pre-specified. Final analysis code is shown in the supplement (SUPP_R_CODE).

Patient and Public Involvement

Patient involvement is central to the SCQM cohort. Several patients are part of the executive board and involved in the approval of research projects.

RESULTS

Population description

During the study period, 1053 TC were initiated in 834 different patients, including 273 TC with BARI, 473 with TNFi and 307 with OMA (Figure 1). TNFi were more often given as a second line therapy after methotrexate failure. Inversely, BARI was prescribed to significantly older patients, with longer disease durations and more previous treatment failures (Table 1).

Table 1: Baseline characteristics of study population, SCQM-RA registry, 2017-2020.

Variable	BARI (TC = 273; 273 pts)		TNFi (TC = 473; 408 pts)		OMA (TC = 307; 289 pts)		p values
	n % of total in group Otherwise: Mean (SD)						
Patients		*Miss.*		*Miss.*		*Miss.*	
Female	78 %	0	74 %	1	73 %	1	0.28
Age (years)	59 (14)	0	52 (15)	1	59 (13)	1	**<0.01**
Disease duration (years)	13 (10)	4	8 (9)	19	11 (9)	5	**<0.01**
CDAI baseline (raw data)	19 (10)	175	18 (10)	301	20 (13)	204	0.25
CDAI baseline (imputed)	15 (9)	0	14 (9)	0	16 (11)	0	**0.05**
Obesity (BMI > 30)	16 %	104	14 %	134	13 %	115	0.59
Smoking Current Former Never	17 % 28 % 43 %	32	18 % 26 % 41 %	69	21 % 28 % 48 %	26	0.90
Seropositive (ACPA or RF)	75 %	1	70 %	7	77 %	5	0.07
TC		*Miss.*		*Miss.*		*Miss.*	
Concomitant csDMARD	40 %	0	61 %	0	46 %	0	**<0.01**
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	17 % 20 % 19 % 44 %	0	48 % 23 % 11 % 18 %	0	22 % 24 % 24 % 31 %	0	**<0.01**
Previous tsDMARD use (non-BARI)	33 %	0	1 %	0	5 %	0	**<0.01**
Concomitant glucocorticoid (at any time)	22 %	0	20 %	0	24 %	0	0.28
Mean dose of concomitant glucocorticoid (mg)	2.0 (4.6)	0	2.1 (5.4)	0	2.2 (5.1)	0	0.90
Dose of BARI (4mg)	86 %	0	-	-	-	-	-

Table 1 Legend: In Switzerland, BARI was prescribed to older patients, with longer disease duration and more previous treatment failures. Missing values for covariables are reported as absolute numbers

BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. P-values are

obtained by 3-way ANOVA or Chi2. In TFNi and OMA groups, some patients have contributed several TC, thus total number of TCs exceeds total number of patients.

Time to all-cause-discontinuation

Table 2: Crude treatment discontinuation by group and by reason, SCQM, 2017-2020.			
	BARI (TCs = 273)	**TNFi (TCs = 473)**	**OMA (TCs = 307)**
Treatment discontinuation (all causes)	30 %	43 %	35 %
For adverse events	8 %	10 %	10 %
For ineffectiveness	16 %	23 %	17 %
For remission	0 %	1 %	0 %
For other reason	5 %	8 %	7 %

Table 2 legend: % are computed on total number of TCs per group, for the whole study period. BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. TC = Treatment Courses. Due to rounding, the sum of the percentages of the causes of discontinuation may not correspond exactly to the total treatment discontinuation percentage.

Crude proportions of treatment discontinuation by reasons are reported in Table 2, and crude times of observation are represented on Figure S1.

At 12 months, based on the Kaplan-Meier curves (Figure 2), the estimated proportions of patients still on therapy were: 71% (95% CI [65% - 77%]) in the BARI group, 55% (95% CI [50% - 61%]) in the TNFi group, and 63% (95% CI [57% - 70%]) in the OMA group.

Overall, unadjusted time to all-cause-discontinuation was significantly longer in the BARI group compared to the TNFi group (estimated median prescription survival-time of 704 versus 448 days; Log-rank p<0.01; Figure 2). These results persisted after adjustment for confounding factors using the multivariable Cox model (HR = 1.76; 95% CI [1.32-2.35]; p<0.001; Table S1 and Figure S2; Figure S3).

BARI versus OMA time to all-cause-discontinuation was not significantly different, even after adjustment (HR 1.27; 95% CI [0.93-1.72]; p = 0.13; Table S1, Figure S2 and Figure S3).

Sensitivity analyses using AIPTW led to similar conclusions (Figure S4). Covariates significantly associated with decreased drug maintenance were high baseline CDAI scores and concomitant glucocorticoid usage (Table S1 and Figure S2).

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

In this exploratory subgroup analysis, we restricted the population to patients without prior experience of b/tsDMARDs (so-called 'bio-naïve' patients, i.e. first b/tsDMARD prescription after methotrexate failure). In thus subpopulation, patient characteristics were more balanced than in the main analysis, except for age, which remained younger in TNFi population, and concomitant csDMARDs usage (more frequent in TNFi) (Table S2). Of note, the sample size was consequently reduced to 46 BARI, 225 TNFi and 66 OMA.

When analysing only these b/tsDMARD-naïve patients, both the non-adjusted (Figure 3) and the adjusted differences between BARI and TNFi became larger (HR TNFi vs BARI = 2.5; 95% CI [1.23 – 5.16]; p=0.01), but the differences between baricitinib and OMA group remained not significantly different (HR OMA vs BARI = 1.90; 95% CI [0.71 – 5.1]; p=0.2).

Time to discontinuation for adverse events or ineffectiveness

A secondary outcome was the cumulative incidence of drug discontinuation by specific reasons for discontinuation (ineffectiveness or adverse events, Figure 4). Using Fine-Gray adjusted approach, we found no difference in the incidence of adverse event comparing BARI to TNFi (HR = 1.46; 95% CI [0.83 - 2.57]; p=0.13), or BARI to OMA (HR = 1.34; 95% CI [0.74 - 2.42]; p=0.25). The incidence of drug discontinuation for ineffectiveness was more frequent in TNFi compared to BARI (HR = 1.49; 95% CI [1.03 – 2.15]; p=0.01), but similar between OMA and BARI (HR = 1.09; 95% CI [0.72 – 1.64]; p=0.69).

Remission and low disease activity at 12 months

The estimated 12-month rates of REM and LDA, estimated using CARRAC did not differ significantly between the 3 groups (Figure 5). LDA ranged from 62% to 71% and REM ranged from 17% to 26%.

DISCUSSION

In this study, the overall drug maintenance of BARI was significantly longer compared to TNFi, despite the fact that it was prescribed to older patients, with longer disease duration, and more previous treatment failures similar to what was observed in RA-BE-REAL, another real-world study.[23] However, the adjusted 12-month response rates in terms of LDA and REM did not differ significantly between BARI, TNFi and OMA groups. The difference in drug discontinuation owes mainly to more treatment discontinuations for ineffectiveness in the TNFi group compared to the BARI group, while drug discontinuation due to adverse event did not differ significantly between the groups.

Our results are in line with previous findings comparing other JAK-inhibitors (JAKi) (i.e. tofacitinib as well as BARI) to TNFi and OMA medications,[22,30] which reported a longer drug maintenance of tsDMARD compared to TNFi, and similar maintenance to other bDMARDs. Of note, Lauper et al., using data from 19 national registers, found no difference in retention time between JAK-inhibitors and TNFi.[31] Still, Lauper et al. grouped all JAKi together in their study, thus it is not clear if these observations remain true for BARI alone, which might differ from other JAKi. For instance, Barbulescu et al. reported a higher drug maintenance for BARI as compared to tofacitinib.[21]

It was previously shown that BARI is more efficient in relieving pain as compared to adalimumab therapy [32] and some molecular mechanisms relevant to JAK-STAT signalling

have been hypothesized.[33] This observation has been hypothesised to result anti-nociceptive effect independent from inflammation.[33] This faster pain relief could partially explain why BARI has increased maintenance than other medication in our study, even though having similar 12-months LDA and REM rates. An alternative hypothesis is that the more convenient oral administration encourages patients to stay on medication longer. Yet, a third possible interpretation is that patients who experienced numerous treatment failures tend to stay on their latest therapy; however, our study accounts for this potential bias, by performing a sensitivity analysis in a subgroup of b-tsDMARD naïve patients, which showed a similar result. Finally, given recent discussion regarding tofacitinib safety,[34] future research needs to clarify whether a class effect for JAKi related adverse events exist. In this analysis, we found no indication for an increased incidence of adverse-related treatment discontinuation with BARI compared to alternative bDMARDs. Randomized controlled trials are ongoing to further compare safety profile of BARI versus TNFi (NCT04086745 and NCT03915964).

Limitations and Strengths

This work has several limitations, mostly inherent to the observational setting. First, as this is a non-randomized study, we cannot formally exclude unmeasured confounding between the groups. The available baseline variables were, in most cases, adequately balanced, except for age. When we restricted the analysis to the subgroup of b/tsDMARD naïve patients, we found largely similar results. Despite being limited by the small sample size, this exploratory subgroup analysis suggests that confounding by line of treatment was adequately accounted for in the adjusted analysis.

Secondly, the average length of follow-up was only approximatively 200 days per TC (Figure S1). Indeed, our study covers about 2 and a half years, and we only included TC newly initiated during this time-windows. Also, because of the study setting, as much as 65% of TC did not

have CDAI scores recorded at the date of initiation, and many were missing at the 12-month exact timepoint (Figure S5). Hence, our analysis of response rates relied heavily on linear interpolation techniques, using other available timepoints, which results in large confidence intervals for estimated response rates.[28]

The main strength of the study is that it relies on real-world data, and includes a relatively large number of patients. As theses patients are mostly treated by office-based rheumatologists, our study population is representative of routine clinical practice. Also, sub-group analyses and sensitivity analyses were consistent with the main results.

CONCLUSIONS

In this non-randomized prospective cohort study, we demonstrate that treatment with BARI has at least similar effectiveness outcomes as alternative bDMARDs. Based on available data, the estimated 12-month response rates did not significantly differ between BARI, TNFi and OMA groups. We found no difference in treatment discontinuation for adverse event between the three groups. Overall, our results are in line with findings from randomized trials, confirm the effectiveness of BARI in daily practice and validate this agent as an alternative to bDMARDs in RA.

OTHERS

Contributorship statement

BG: data-management, data-analysis, figures, manuscript drafting.

DM: data-management, data-analysis, figures, manuscript-revision.

RA: data-analysis (in particular, sensitivity analyses), manuscript revision.

KL: data-analysis, manuscript revision.

CL: study design, manuscript revision.

CP: study design, manuscript revision.

RM: study design, manuscript revision.

DC: study design, data-analysis and interpretation, manuscript revision.

AF: study design (principal investigator), data analysis and interpretation, manuscript revision.

Competing interests

Benoît GILBERT has been once a paid speaker (Eli Lilly) and participated in advisory board (Janssen). Clementine PERRIER is employed by Eli Lilly and holds stock options (Eli Lilly and Company). Cedric LAEDERMANN is employed by Eli Lilly and holds stock options (Eli Lilly and Novartis). Axel FINCKH has received grants or contracts (Eli-Lilly, Pfizer, Abbvie, Gilead, BMS), consulting fees (Astra-Zeneca, Abbvie, Pfizer, Gilead), honorary payments (BMIS, Abbvie, Eli Lilly, Pfizer, MSD), and participated in advisory boards (Astra-Zeneca, Gilead, Novartis, Abbvie, Eli Lilly, Pfizer, J&J, Mylan, UCB). Denis MONGIN, Romain Aymond, Rüdiger Müller and Delphine COURVOISIER have no conflicts of interest to disclose.

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Data sharing statement

Restrictions apply to the availability of these data. Data is owned by a third party, the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) foundation. Data may be obtained after approval and permission from this license holder (SCQM). Contact information for data request: scqm@hin.ch

Ethical Review and Regulatory Considerations

This observational study has been approved by the Geneva ethical review boards (ERBs) as required by local law (Project ID: 2019-00930 ; approval date 28 May 2019). Every participant has signed an information and consent form at inclusion in the SCQM registry. Hence, this study has been conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with Good Pharmacoepidemiology Practices (GPPs).

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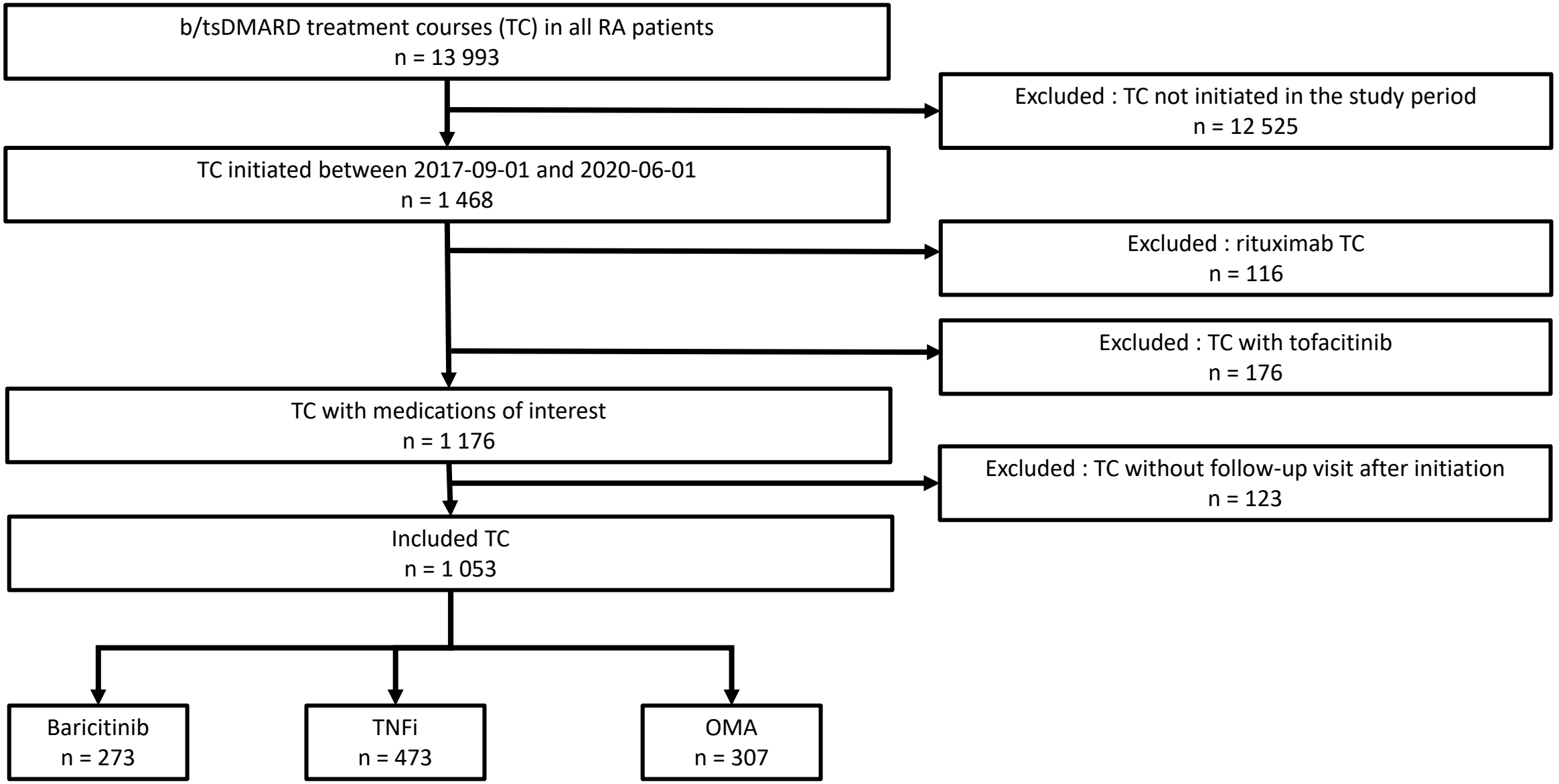
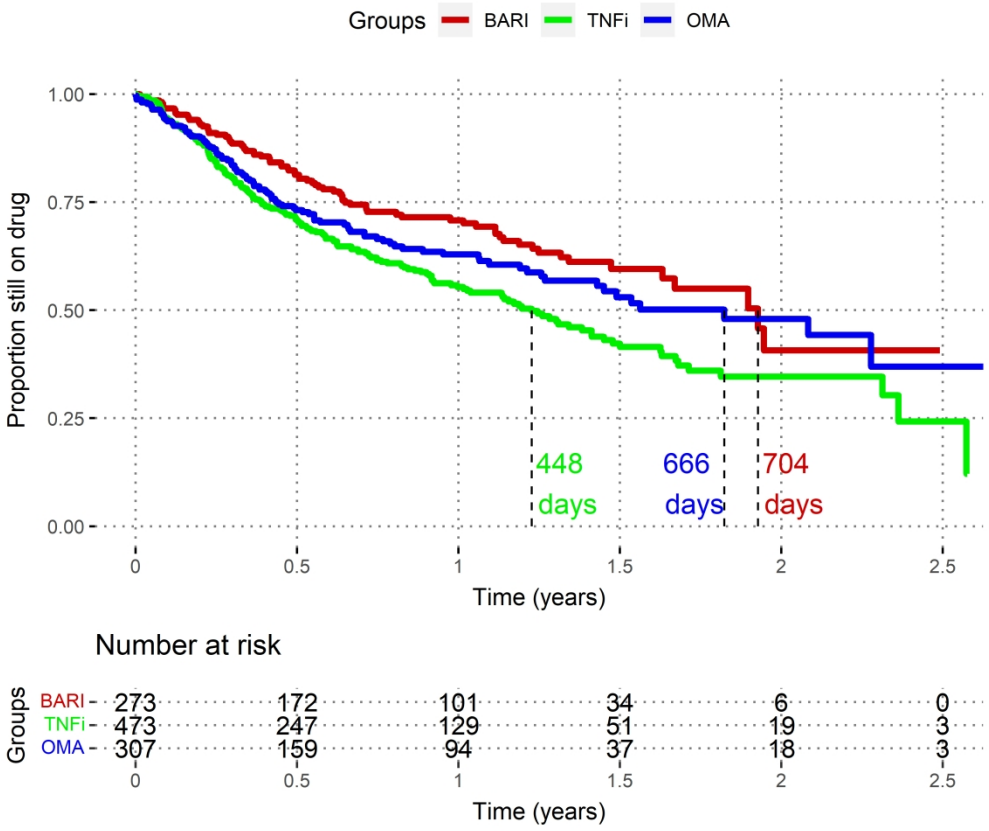
Selection of eligible treatment courses (TC)





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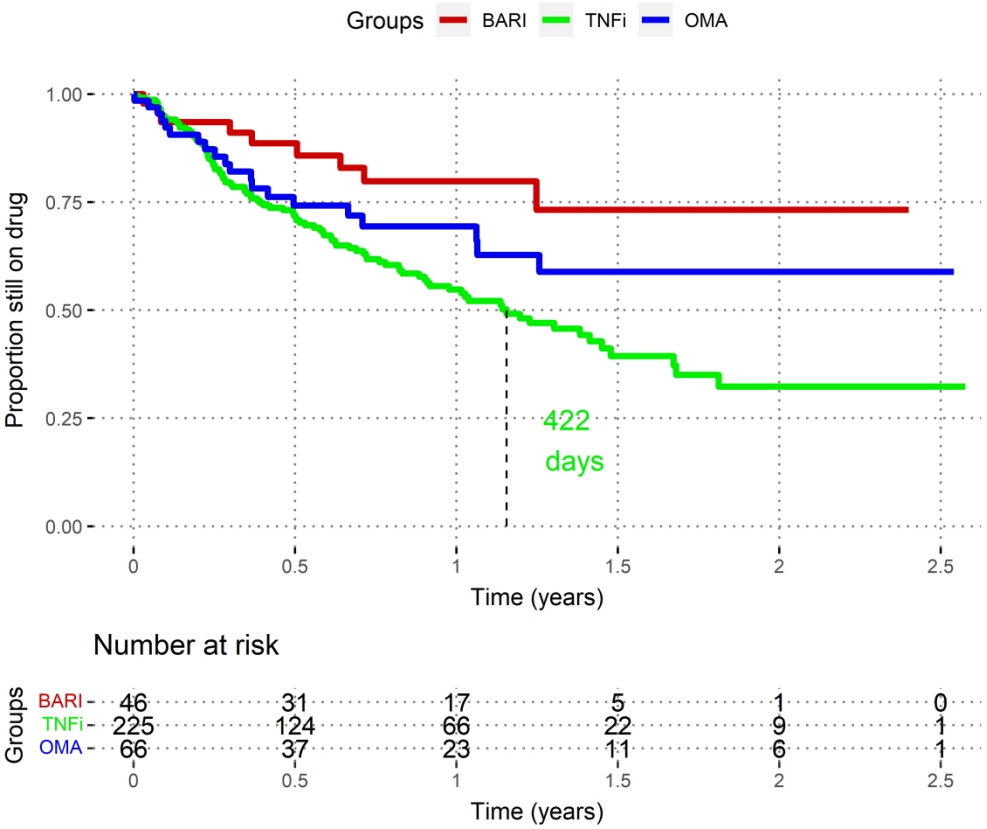

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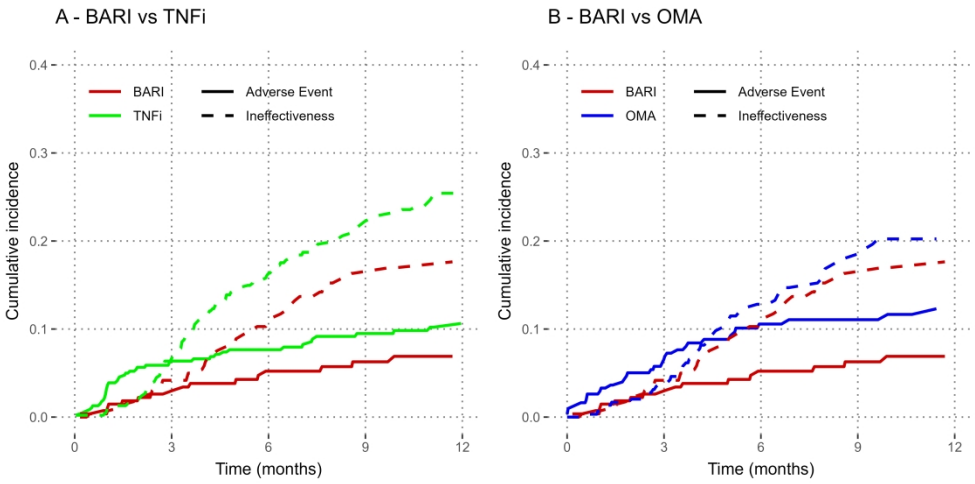

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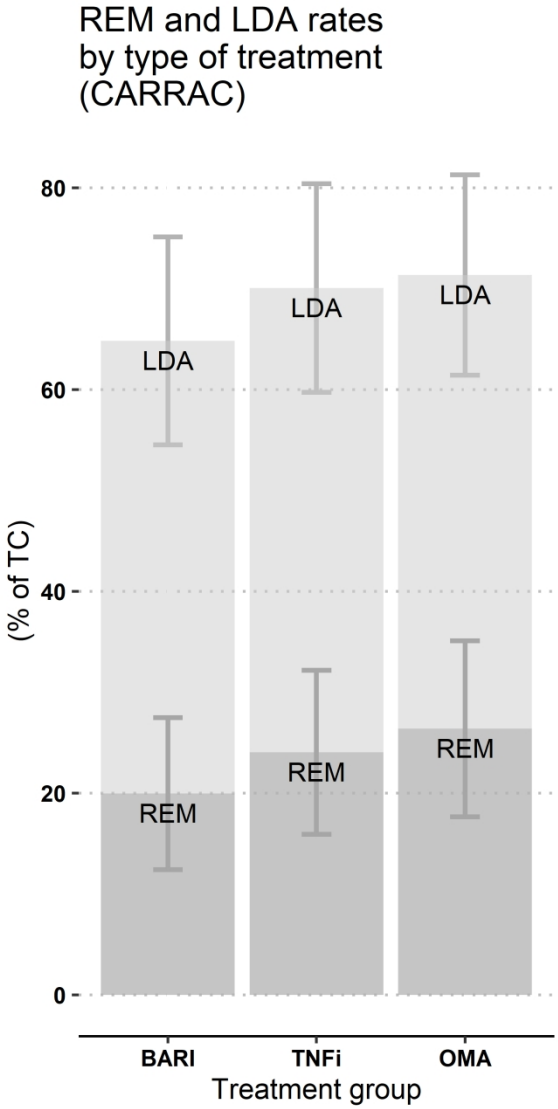

257x451mm (197 x 197 DPI)

SUPPLEMENTARY DATA

Notice on TC duration

Due to frequent changes in medication and short study period, it has to be underlined that the median duration of a TC approximates 200 days. The proportion of TC with follow-up data of at least one year is 37% for BARI, 27% for TNFi and 31% for OMA (Figure S1) - i.e. most TC were started less than 12 months before the date of data extraction.

Notice this % is different from the % of patient still under therapy that we estimate using Kaplan-Meier or Cox model. Indeed, the latter includes a censoring of the lost-to-follow-up patients, hence the denominator is different. As a consequence, this does not contradict the reported "median prescription survival timey", for instance of 704 days for BARI TCs. The latter is the output estimated by the Kaplan-Meier model, taking censoring into account; it does not imply that actual observations in the dataset have this duration.

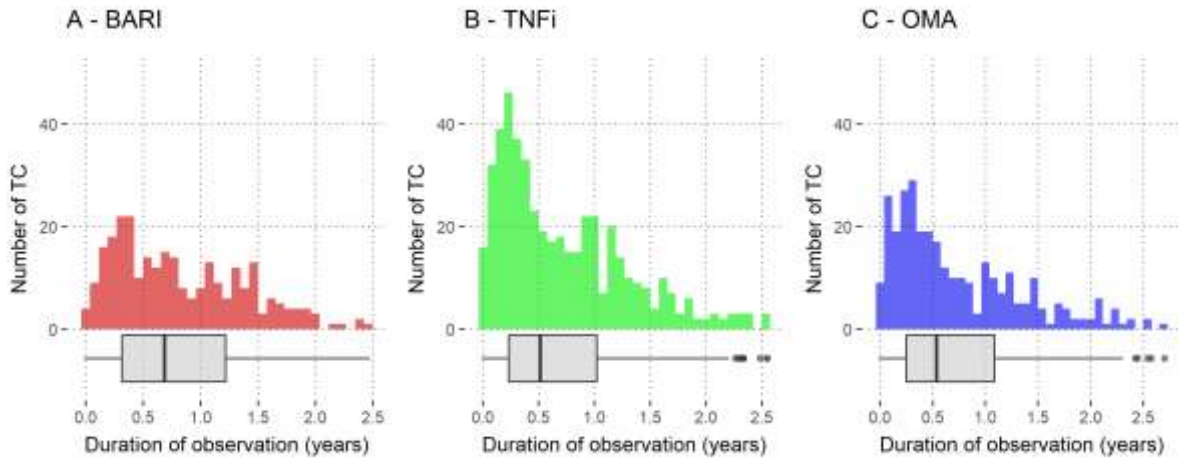

Figure S1: Distribution of the observation time for included TCs, per group, SCQM, 2017-2020. Most of the treatment courses have an actual duration and/or follow-up period of less than one year. TC = Treatment Course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs.

Variable definitions

Below we give additional detail about included covariates:

Age: age in years, at TC initiation. Continuous variable.

Gender: male or female. Categorical variable.

BMI: BMI at TC initiation. Continuous variable.

CDAI score: CDAI score at TC initiation. Continuous variable. If missing, imputed according to procedure described in methods section.

Disease duration: time interval between RA diagnosis date and TC initiation date. Continuous variable, expressed in years, but used in decades in models.

Smoking status: smoking status at TC initiation. Categorical variable (current-, former-, never-smoker).

Concomitant csDMARD: yes/no variable. A concomitant csDMARD was defined as csDMARD prescription ongoing for at least 40% of the duration of the TC. Otherwise, the TC was categorized as monotherapy. csDMARDs included: methotrexate, sulfasalazin, leflunomide, azathioprine and hydroxy-chloroquine, alone or in combination.

Concomitant glucocorticoid: Yes/no variable. Concomitant glucocorticoid usage was defined as having at least one active prescription of glucocorticoid, at any dose, at any timepoint of the TC.

Line of therapy: strictly speaking, this categorical variable is displaying: [*number of previous TC ever* + 1]. 4 or more has been grouped in the same category. Hence, it is considering all data of the SCQM registry, i.e. TCs initiated before our study period are also accounted for as previous therapies.

Seropositivity: yes/no variable. Seropositivity is defined as positivity for anti-citrullinated peptide antibodies and/or rheumatoid factor.

Time to all cause discontinuation

Cox model output

Table S1 contains the complete output of the two adjusted Cox models used in the main time-to-drug discontinuation analysis.

Table S1: Hazard ratio of drug discontinuation, Cox models, SCQM-RA registry, 2017-2020.

	BARI vs TNFi			**BARI vs OMA**		
	Hazard ratio	**95% CI**	**p**	**Hazard ratio**	**95% CI**	**p**
TNFi (vs baricitinib)	1.76	1.32-2.35	**<0.001**	-	-	-
OMA (vs baricitinib)	-	-	-	1.27	0.93-1.72	0.13
Adjusting variables:						
Age (decades)	1.03	0.92-1.14	0.61	0.98	0.86-1.10	0.69
BMI	1.01	0.98-1.04	0.51	0.98	0.94-1.02	0.31
TC with csDMARD	0.84	0.66-1.09	0.19	1.22	0.90-1.67	0.20
Glucocorticoid usage	1.29	0.93-1.79	0.12	1.86	1.32-2.61	**<0.001**
CDAI score	1.40	1.26-1.56	**<0.001**	1.15	1.03-1.28	**0.01**
Disease duration (decades)	0.95	0.81-1.10	0.46	0.85	0.70-1.03	0.10
Current smoker (vs non-smoker)	1.20	0.86-1.68	0.28	1.09	0.73-1.64	0.66
Ever smoker (vs non-smoker)	1.10	0.79-1.52	0.57	1.38	0.95-2.00	0.09
2nd line therapy (vs 1st)	1.11	0.80-1.53	0.52	1.37	0.81-2.33	0.24
3rd line therapy (vs 1st)	0.98	0.64-1.51	0.93	1.56	0.92-2.64	0.10
4th or later line (vs 1st)	1.06	0.75-1.51	0.73	1.57	0.93-2.63	0.09
Female gender	1.05	0.78-1.42	0.74	1.16	0.81-1.67	0.41
Seropositivity	0.77	0.59-1.01	0.055	0.94	0.67-1.31	0.71

Table S1: BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. CI = Confidence Interval. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index.

Figure S2 below gives the exact same information as Table S1:

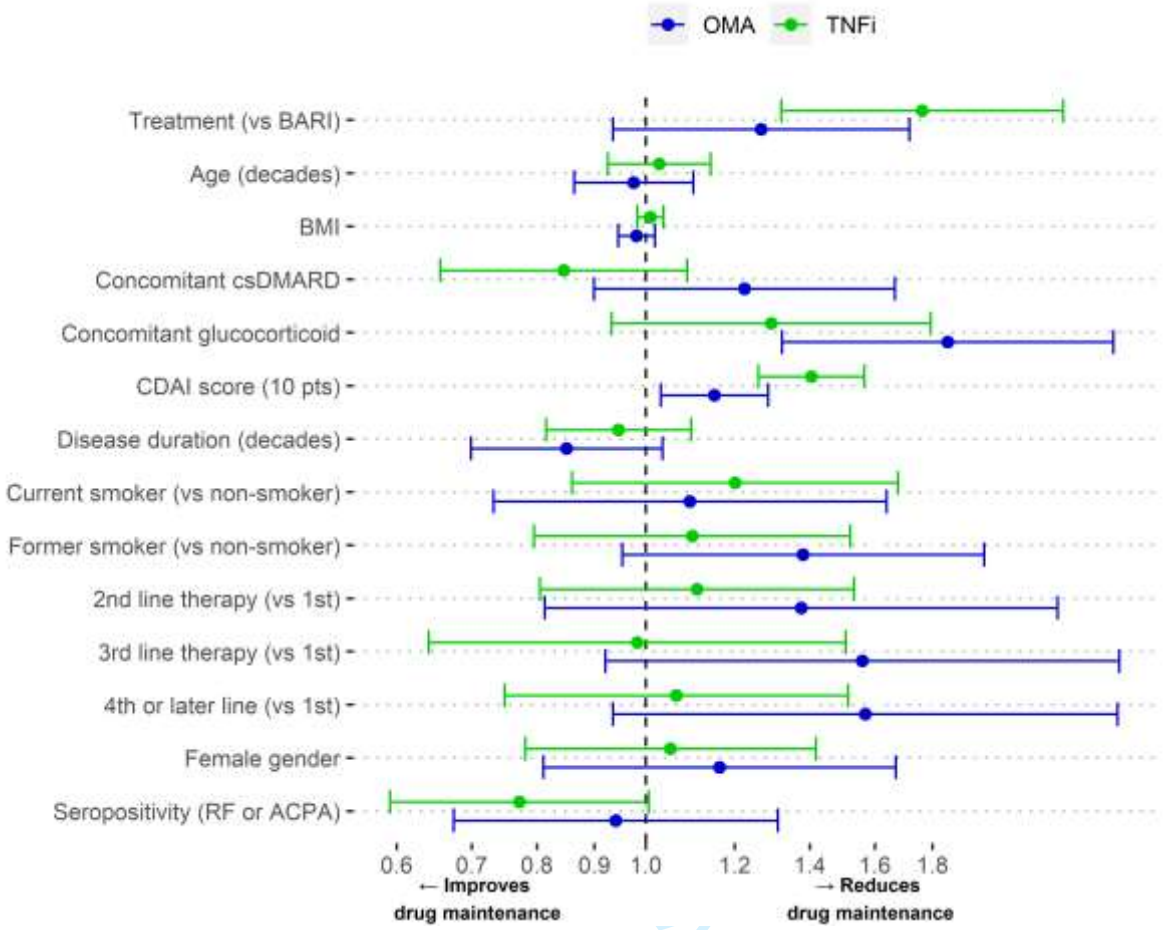

Figure S2: Hazard ratio of drug discontinuation (95% CI).

BARI = Baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other mode of Action bDMARDs. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index. RF = Rheumatoid Factor. ACPA = Anti-citrullinated Peptides Antibodies.

The corresponding cox-adjusted drug-survival curves are provided below:

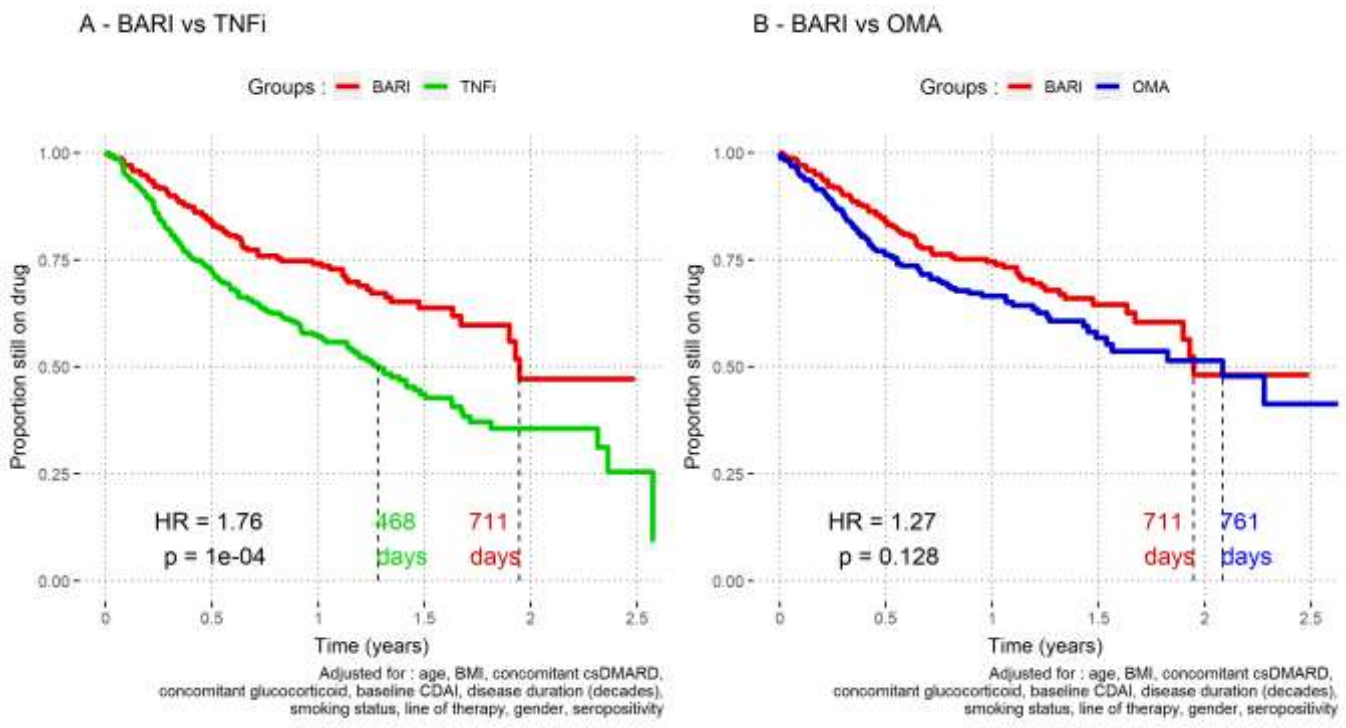

Figure S3: Multivariable Cox model of drug discontinuation by type of treatment, SCQM, 2017-2020.

These curves are merlely the visualisation of Cox models presented in Table S1 and Figure S2.

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action bDMARDs

Models are adjusted for : age, BMI, concomitant csDMARD, concomitant glucocorticoïd, baseline CDAI, disease duration, smoking status, line of therapy, gender, serpostivity.

Sensitivity analysis using AIPTW

As a sensitivity analysis, the main time to drug discontinuation was also performed using "augmented inverse probability of treatment weighting" (AIPTW), including the same covariates. In other words, we combined a propensity score using a logistic regression model and an inverse probability weighted Cox regression. We used the *RiskRegression* package in R, to obtain risk ratios.

Figure S4 represents the absolute risk of treatment discontinuation, for all included timepoints. At one year, the adjusted discontinuation risk in BARI was 19 % lower than in TNFi group (p<0.001) (Figure S4 A), with a risk ratio of 1.76 (95% CI [1.19 – 2.34]; p=0.009). Similarly, at one year, the adjusted treatment discontinuation risk in BARI was 8 % lower than in the OMA group (p=0.06) (Figure S4 B), with a risk ratio of 1.28 (95% [0.91 – 1.65]; p=0.14).

Overall, this sensitivity analysis confirms the findings reported in the main body of the article.

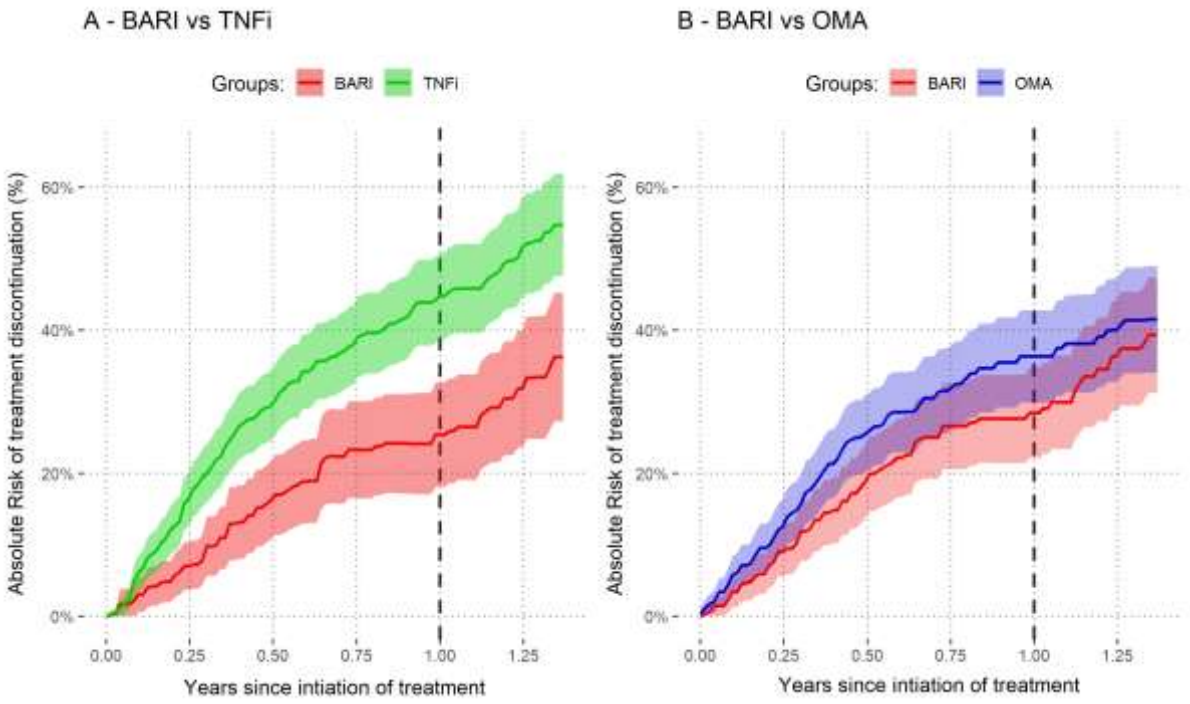

Figure S4: Absolute risk of treatment discontinuation by type of treatment (AIPTW), SCQM, 2017-2020)

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inihibitors. OMA = Other Modes of Action bDMARDs. AIPTW = Augmtented Inverse Probability of Treatment Weigthning. Adjusted for : age, bmi, concomitant csDMARDs, prednisone usage, baseline CDAI, disease duration, smoking status, line of therapy, gender, seropositivity.

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

Table S2: Baseline characteristics of study population, b/tsDMARD-naïve patients, SCQM-RA registry, 2017-2020.

	BARI (n = 46)		**TNFi (n = 225)**		**OMA (n = 66)**		**p values**
	n % Otherwise: Mean (SD)						
Patient-Variables		Miss.		Miss.		Miss.	
Female	70 %	0	71 %	1	73 %	1	0.88
Age (years)	57 (15)	0	52 (14)	1	57 (16)	1	<0.01
Disease duration (years)	6 (6)	1	5 (7)	13	7 (9)	2	0.24
CDAI baseline (raw data)	16 (8)	31	18 (10)	135	18 (14)	42	0.77
CDAI baseline (imputed)	12 (7)	0	14 (9)	0	14 (10)	0	0.61
Obesity (BMI > 30)	11 %	13	13 %	58	5 %	27	0.28
Smoking Current Former Never	 28 % 26 % 26 %	9	 18 % 24 % 39 %	42	 14 % 21 % 46 %	13	0.18
Seropositive (ACPA or RF)	80 %	1	69 %	5	76 %	2	0.20
TC variables							
Dose of BARI (4mg)	83 %	0	-	-	-	-	-
TC duration > 12-months	37 %	0	29 %	0	35 %	0	0.48
Concomitant csDMARD	41 %	0	66 %	0	50 %	0	<0.01
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	100 %	0	100 %	0	100 %	0	-
Previous tsDMARD use (non-BARI)	0 %	0	0 %	0	0 %	0	-
Concomitant glucocorticoid (at any time)	13 %	0	20 %	0	17 %	0	0.50
Mean dose of concomitant glucocorticoid (mg)	1 (4)	0	3 (6)	0	2 (6)	0	0.50

Table S2: BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. p-value are computed with either Chi^2 or ANOVA.

Response rates – raw CDAI data

Figure S6 shows the crude available values for CDAI scores, by type of treatment and time. Only a minority of CDAI scores were assessed at 0- or 12-month timepoints of TCs (i.e. 680/1053 = 65% were missing for baseline value, and 908/1053 = 86% were missing for exact 12-month value). Future research would certainly benefit having CDAI scores assessed at regular and homogenous time-intervals, based on the initiation date of biological therapies.

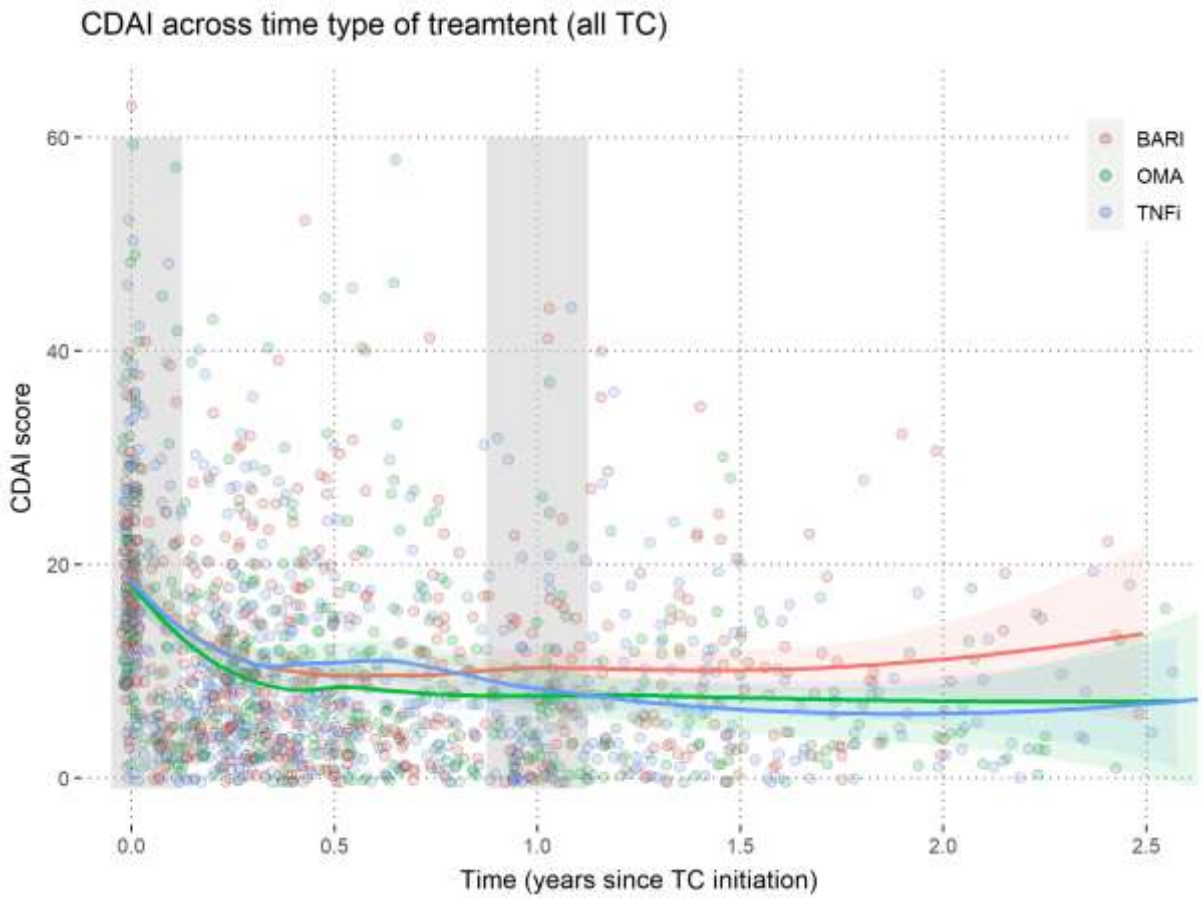

Figure S5: CDAI across time by type of treatment, raw data, SCQM, 2017-2020.

Only a minority of CDAI score were obtained sharp at 0 or 12 months of TCs. CDAI = Clinical Disease Activity Index. TC = Treatment course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action b/tsDMARDs.

Study size

Based on estimates from similar analyses with tofacitinib (TOFA) performed in this registry, we calculated the number of patients that would be needed to detect a significant decrease in time to all cause-discontinuation of treatment (hazard ratio) between treatment groups using the method described by Schoenfeld and Richter. We assumed a statistical power of 80%, a type I error probability of 0.05, a median BARI retention of 30 months, the inclusion of 3 patients on TNFi for every patient on BARI, an accrual time of 2 years, and additional follow-up of 6 months. We display below the sample size for the BARI group for a range of possible effect sizes ("hazard ratio" between 1.1 and 1.8).

If the true hazard ratio is similar to the one found with TOFA compared to TNFi after a single TNFi failure (HR:1.68) 14, we will need to study 149 patients on BARI and 447 patients on TNFi to be able to reject the null hypothesis that the experimental and control curves are equal with probability (power) of 80%. Pragmatically, we propose to start the analysis of the data only once at least 200 patients on BARI have been included and followed for an average of at least 18 months.

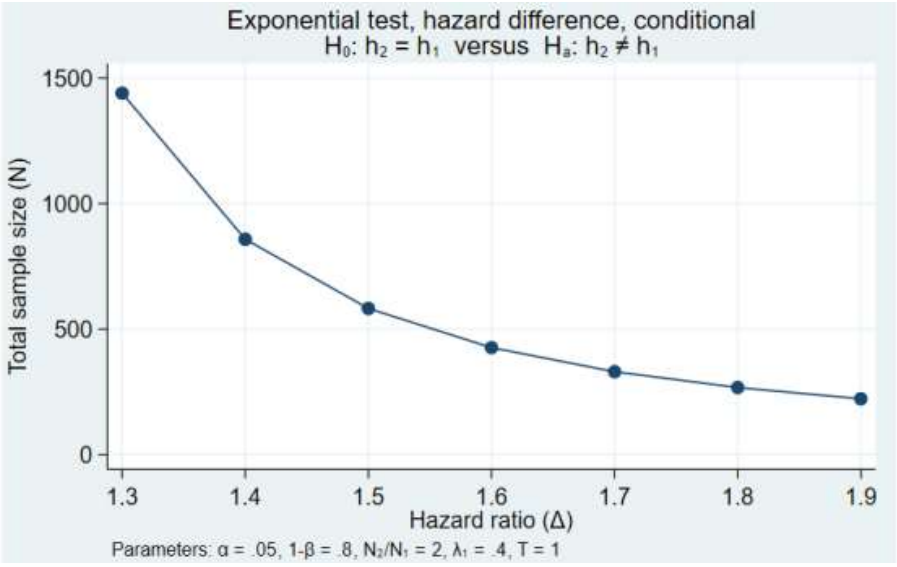

Figure 1: Estimated total sample size for two-sample comparison of survivor functions

1 - SURVIVAL ANALYSIS

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(gridExtra)
library(grid)
library(cmprsk)
library(mstate)
library(cobalt)

rm(list = ls()) # To select all loaded objects and delete them
setwd(dirname(rstudioapi::getActiveDocumentContext()$path)) # setting
up working directory in the location of the .Rmd file

load("./1_datamanaged_files/datamanaged.Rdata") # loading data.managed
data
```

Loading fonctions

```
# home-made function to force writing with two decimals
formattable = function(nbr){return(formatC(nbr,format = "f",digits =
nombreapresvirgule))}
nombreapresvirgule <- 2

# Home-made Fonction to write the p value (by denis)
writepvalue = function(pvalue) {
  if (is.na(pvalue)) {result <- NA} else {
    if(pvalue < 0.001) {
```

```
      result <- "<0.001"
    } else if (pvalue <0.01) {
      result <- formatC( pvalue ,format = "f",digits = 3)
    }
    else {
      (result <- formatC( pvalue ,format = "f",digits = 2) )
      i = 1
      while(result == 0.05) {
        result <- formatC( pvalue ,format = "f",digits = 2 + i)
        i = i + 1
      }}
    return(result)
  }
}
options(scipen = 999)
```

Mini Exploration

```
uniqueN(BARI_DATA[]$patient_id) # number of patients (< than number of
TC)
uniqueN(BARI_DATA[]$TC_id) # unmber of TC

plot <- qplot(x = BARI_DATA[]$time_on_drug)+
  geom_vline(xintercept = 365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 365 + 40, label="1 Year", y=20), colour="white",
angle=0)+

  geom_vline(xintercept = 2*365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 2*365 + 40, label="2 Year", y=20), colour="black",
angle=0)+

  geom_vline(xintercept = mean(BARI_DATA$time_on_drug), color = "red",
size = 1.2)+
  geom_text(aes(x = mean(BARI_DATA$time_on_drug) + 40, label="Mean",
y=20), colour="red", angle=0)+

  geom_vline(xintercept = median(BARI_DATA$time_on_drug), color =
"green", size = 1.2)+
  geom_text(aes(x = median(BARI_DATA$time_on_drug) - 40,
label="Median", y=20), colour="green", angle=0)+

  labs(x = "Duration of TC (days)", y = "Number of TC", title =
"Repartition of the duration of included TC (all groups)")+

  theme_pubclean()

plot

mean(BARI_DATA$time_on_drug)
```

```
median(BARI_DATA$time_on_drug)

# Nb : Research protocol said we wanted a follow-up duration of
"average of 18 months"
mean(BARI_DATA[cohort == "BARI"]$time_on_drug)/30
mean(BARI_DATA[cohort == "TNFi"]$time_on_drug)/30
mean(BARI_DATA[cohort == "OMA"]$time_on_drug)/30 # looks more like 9
months..

# ok, 24-month follow-up will be complicated
uniqueN(BARI_DATA[time_on_drug > 2*365, TC_id]) # number if TC with
duration > 24 months
```

1. [0] Table 1 BARI vs TNFi et OMA bDMARDs

Common table with all the data

Showing NA to have complete counts and accurate % in each category

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving table 1 NA

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1_NA.xlsx")
```

Without NA to obtain adequate p values

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
```

```
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving table 1

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1.xlsx")
```

Other various computations for Table 1 —-

```
uniqueN(BARI_DATA$patient_id)

mean(BARI_DATA[, time_on_drug])

median(BARI_DATA[cohort == "Bari" , time_on_drug])
median(BARI_DATA[cohort == "OMA" , time_on_drug])
median(BARI_DATA[cohort == "TNFi" , time_on_drug])

median(BARI_DATA[cohort == "OMA"]$time_on_drug)

mean(BARI_DATA[,disease_duration_base_years], na.rm = T)

table(is.na(BARI_DATA$CDAI0_raw), BARI_DATA$cohort) # number of
missing CDAI0_raw...
table(is.na(BARI_DATA$CDAI0), BARI_DATA$cohort) # number of missing
CDAI0... (after imputation)

table(is.na(BARI_DATA$CDAI12_raw), BARI_DATA$cohort) # number of
missing CDAI12_raw...
table(is.na(BARI_DATA$CDAI12), BARI_DATA$cohort) # number of missing
CDAI12 after imputation

hist(BARI_DATA$CDAI0_raw)
```

```
hist(BARI_DATA$CDAI0)

summary(BARI_DATA[cohort=="BARI", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="TNFi", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="OMA", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

table(is.na(BARI_DATA$disease_duration_base_years), BARI_DATA$cohort)
# number of missing disease duration...

table(is.na(BARI_DATA$age_base), BARI_DATA$cohort) # number of steroid
doses missing

table(is.na(BARI_DATA$PREDNISON_STEROID_dose), BARI_DATA$cohort) #
number of missing baseline steroids
```

Imputation using MICE —- BARI vs TNFi et OMA bDMARDs —-

Common imputation step with all data

```
BARI <- BARI_DATA[,c("TC_id", "patient_id", "stop_DMARD",
"stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0", "disease_duration_base_years", "time_on_drug", "bmi_base",
"smoker_base", "line_of_therapy", "obese_base", "gender", "cohort",
"adverse_event_reported", "seropositivity_base")] # choose variables
of interest

BARI$smoker_base <- as.factor(BARI$smoker_base) # put labels as factor
BARI$line_of_therapy <- as.factor(BARI$line_of_therapy)
BARI$gender <- as.factor(BARI$gender)
```

```
BARI$concomitant_csDMARD <- as.factor(BARI$concomitant_csDMARD)
BARI$PREDNISON_STEROID <- as.factor(BARI$PREDNISON_STEROID)
BARI$cohort <- as.factor(BARI$cohort)

# Imputation

if(!file.exists("./2_cached_files/imputed_data")){ # to avoid re-
computing if alsready done
  imputed_data <- mice(BARI, m=50, method="pmm", maxit=25, seed=500)
  save(imputed_data, file = "./2_cached_files/imputed_data")
} else {
  load("./2_cached_files/imputed_data")
}

# Subsettings

BARI1 <- BARI[cohort %in% c("BARI", "TNFi")] # creating subset for
BARI vs TNFi comparaison
BARI1[,cohort := as.factor(as.character(cohort))]

imputed_data1 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data1 <- imputed_data1[imputed_data1$cohort %in% c("BARI",
"TNFi"),] # to keep only BARI and TNFi rows
imputed_data1$cohort <- as.factor(as.character(imputed_data1$cohort))
imputed_data1 <- as.mids(imputed_data1) # re concateneting in previous
format, to use fit.mult.impute


BARI2 <- BARI[cohort %in% c("BARI", "OMA")] # creating subset for BARI
vs OMA comparaison
BARI2[,cohort := as.factor(as.character(cohort))]

imputed_data2 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data2 <- imputed_data2[imputed_data2$cohort %in% c("BARI",
"OMA"),] # to keep only BARI and OMA rows
imputed_data2$cohort <- as.factor(as.character(imputed_data2$cohort))
imputed_data2 <- as.mids(imputed_data2) # re concateneting in previous
format, to use fit.mult.impute
```

1. [1] SURVIVAL ANALYSIS (drug discontinuation)

Exploration

```
table(BARI_DATA$cohort, BARI_DATA$stop_DMARD)
table(BARI_DATA$cohort, BARI_DATA$stop_reasons)
```

Checking adequacy of COX models —-

For BARI vs TNFi

```
# categorization for linearity checking
test1 <- complete(imputed_data1,"long", include=T) # to put in long
format and categorize variables

test1$agecat <- cut(test1$age_base, 4)
test1$bmicat <- cut(test1$bmi_base, 4)
test1$cdaicat <- cut(test1$CDAI0, 4)
test1$duracat <- cut(test1$disease_duration_base_years, 4)

test1 <- as.mids(test1, .imp=1, .id=2) # re concateneting in previous
format, to use fit.mult.impute

# linearity checking

BARI1.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                       I(agecat)+
                                       I(bmicat)+
                                       TC_with_csDMARD+
                                       PREDNISON_STEROID+
                                       I(cdaicat)+
                                       I(duracat)+
                                       C(smoker_base, base=3)+
                                       line_of_therapy+
                                       gender+
                                       seropositivity_base+
                                       cluster(patient_id),
                                     fitter = coxph, xtrans = test1,
data = BARI1)

summary(BARI1.adj.mi.test)
rm(BARI1.adj.mi.test)

# Log-linearity of coefficients ?

# Coefs age are between 0.15 and 0.25, let's assume it's ok
# Hum bmi coefs are not so log-linear, rather close to 0
# For CDAI also
# Looks ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test1ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
```

```
as.factor(cohort)+
                              cluster(patient_id),
                        data= BARI1)
cox.zph(test1ph) # it's ok

# Hazard proportionality test on imputed data sets

test1 <- complete(test1,"long",include=T) # To reset the charges to
long format
test1 <- test1[test1$.imp==1 | test1$.imp==2 |  test1$.imp==3 |
test1$.imp==4 | test1$.imp==5 ,] # To select only 5 data sets

test1ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
~ as.factor(cohort)+
                          I(age_base/10)+
                          bmi_base+
                          TC_with_csDMARD+
                          PREDNISON_STEROID+
                          CDAI0+
                          I(disease_duration_base_years/10)+
                          C(smoker_base, base=3)+
                          line_of_therapy+
                          gender+
                          seropositivity_base+
                          cluster(patient_id),
                        data = test1)

cox.zph(test1ph.adj.mi)

schonfeldall <- cox.zph(test1ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test1ph.adj.mi, test1)
```

For BARI vs OMA

```
# categorization for linearity checking
test2 <- complete(imputed_data2,"long", include=T) # to put in long
format and categorize variables

test2$agecat <- cut(test2$age_base, 4)
test2$bmicat <- cut(test2$bmi_base, 4)
test2$cdaicat <- cut(test2$CDAI0, 4)
test2$duracat <- cut(test2$disease_duration_base_years, 4)

test2 <- as.mids(test2, .imp=1, .id=2) # re concateneting in previous
```

```
format, to use fit.mult.impute

# linearity checking

BARI2.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                        I(agecat)+
                                        I(bmicat)+
                                        TC_with_csDMARD+
                                        PREDNISON_STEROID+
                                        I(cdaicat)+
                                        I(duracat)+
                                        C(smoker_base, base=3)+
                                        line_of_therapy+
                                        gender+
                                        seropositivity_base+
                                        cluster(patient_id),
                                      fitter = coxph, xtrans = test2,
data = BARI2)

summary(BARI2.adj.mi.test)
rm(BARI2.adj.mi.test)

# Log-linearity of coeficients ?

# Coefs age are around -0.4, let's assume it's ok
# Hum bmi coefs are discusable
# For CDAI it's ok
# More or less ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test2ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                         data= BARI2)
cox.zph(test2ph) # it's ok


# Hazard proportionality test on imputed data sets

test2 <- complete(test2,"long",include=T) # To put imputed data in
ling format
test2 <- test2[test2$.imp==1 | test2$.imp==2 |  test2$.imp==3 |
test2$.imp==4 | test2$.imp==5 ,] # To select only 5 datasets

test2ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
```

```
~ as.factor(cohort)+
                          I(age_base/10)+
                          bmi_base+
                          TC_with_csDMARD+
                          PREDNISON_STEROID+
                          CDAI0+
                          I(disease_duration_base_years/10)+
                          C(smoker_base, base=3)+
                          line_of_therapy+
                          gender+
                          seropositivity_base+
                          cluster(patient_id),
                        data=test2)

cox.zph(test2ph.adj.mi)

schonfeldall <- cox.zph(test2ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test2ph.adj.mi, test2)
```

BARI vs TNFi —-

COX model

Final Cox Model

```
BARI1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort +
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data1,
data = BARI1)

summary(BARI1.adj.mi)
```

Creation of HR table and p-values

```
ploufrows <- names(BARI1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI1.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",
formattable(plouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("TNFi (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid", "CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_1 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs TNFi")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
```

```
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_1

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R

BARI vs TNFi

```
surv_object1 <- Surv(time = BARI1$time_on_drug, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
summary(coxph(surv_object1 ~ cohort, data=BARI1))
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1) # this function
creates the data for Kaplan Meyer
fit1
survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10"),
           palette = c("red2", "green3"), # specify colors
           risk.table = T)
survplot_1
```

```
summary(fit1, times = 365)
summary(fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs TNFi",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey10")
           palette = c("red2", "green3") # to change colors
           )

# adding some legends
```

```
survplot_1_adj <- survplot_1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_1_adj
# summary(BARI_fit1) # to see detailed surv probabilities at given
timepoints
summary(BARI_fit1, times = 365)
summary(BARI_fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data_adj <- survplot_1_adj$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA
library(riskRegression)

# I select only one imputed dataset. Would be even better to find a
way to pool/average the results from the 50 imputed datasets, but it
does not seem doable by default
test.data <- complete(imputed_data1, 1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment <- glm(cohort~I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                    I(age_base/10)+
```

```
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data, x = TRUE, y =
TRUE)

m.censor <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base
                                    , x =TRUE, y = TRUE,
                                    data = test.data)


# And we measure the average treatment effect using function "ate",
specifying the time at which we want to compute the ATE

out <- ate(event = m.event ,
             treatment = m.treatment,
             censor = m.censor,
             data = test.data,
             cause = 1,
             estimator = "AIPTW",
             times = seq(from = 0, to = 500, by = 5))

dt.out <- as.data.table(out)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data$pscores <- m.treatment$fitted.values
test.data %>% setDT()

pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
```

```
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))
pscore_plot # overlap


## Computing the weights
test.data$weights <- ifelse(test.data$cohort == "TNFi",
1/test.data$pscores, 1/(1-test.data$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS <- subset(test.data, select = c(cohort,age_base,
                                     bmi_base,
                                     TC_with_csDMARD,
                                     PREDNISON_STEROID,
                                     CDAI0,
                                     disease_duration_base_years,
                                     smoker_base,
                                     line_of_therapy,
                                     gender,
                                     seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS, treat = test.data$cohort, thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort,  v.threshold = 2)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
v.threshold = 2)


# But plotting is clearer:
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("mean.diffs"), thresholds = c(m = .1), var.order =
"adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
```

```
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 1)+
  #geom_vline(xintercept = 90)+

  scale_colour_manual(values = c("lightblue","darkseagreen3"))+
  scale_fill_manual(values = c("lightblue","darkseagreen3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:")+
  labs(group = "Groups:")+
  theme_bw(base_size = 14)+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

We can also consider the AIPTW estimate at a specific time point. For example at365-day.

```
r.one <- dt.out[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
table <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(table) <- ploufrows
colnames(table) <- ploufcols

library(formattable)
table[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
table[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
table[1,"p"] <-  writepvalue(r.one$p.value)
table[2,"Estimate"] <-  paste0(r.two$estimate)
table[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
table[2,"p"] <-  writepvalue(r.two$p.value)

table

# Interpretation: If every patient had received BARI, the 365-day risk
of treatment discontinuation would have been 19.34% (points) lower
compared to when every patient had received TNFi.
```

BARI vs OMA —-

COX model

```
BARI2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data2,
data = BARI2)

summary(BARI2.adj.mi)
```

Creation of HR table and p-values (denis)

```
ploufrows <- names(BARI2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI2.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("OMA (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid","CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
            "Former smoker (vs non-smoker)", "2nd line therapy (vs
1st)", "3rd line therapy (vs 1st)", "4th or later line (vs 1st)",
"Female gender", "Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_2 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs OMA")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
```

```
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_2

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R)

BARI vs OMA

```
surv_object2 <- Surv(time = BARI2$time_on_drug, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50"),
           palette = c("red2", "blue3"), # to put colors
           risk.table = T)
survplot_2
summary(fit2, times = 365)
summary(fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )

# adding some legends
survplot_2_adj <- survplot_2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")
```

```
survplot_2_adj
summary(BARI_fit2, times = 365) # to see detailed surv probabilities
at given timepoints
summary(BARI_fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data_adj <- survplot_2_adj$data.survplot
write.xlsx(plot_BARI_vs_OMA_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# I select only one imputed dataset. Would be good to find a way to
pool the results from the 50 datasets imputed.
test.data2 <- complete(imputed_data2,1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment2 <- glm(cohort~I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base,
                                  data = test.data2, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event2 <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base,
                                  data = test.data2, x = TRUE, y =
```

```
TRUE)

m.censor2 <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base
                                    , x =TRUE, y = TRUE,
                                    data = test.data2)

# And we measure the average treatment effect using function "ate",
specifying the times at which we want to compute the ATE

out2 <- ate(event = m.event2 ,
             treatment = m.treatment2,
             censor = m.censor2,
             data = test.data2,
             cause = 1,
             estimator = "AIPTW",
             times = seq(from = 0, to = 500, by = 5))

dt.out2 <- as.data.table(out2)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data2$pscores <- m.treatment2$fitted.values
test.data2 %>% setDT()

pscore_plot2 <- ggplot(test.data2,aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y=element_blank(),
          panel.grid.minor=element_blank(),
          legend.title=element_blank(),
          text = element_text(size = 16),
          axis.title.x =element_text(hjust = 0.2, size = 16))
pscore_plot2
# Good overlap
```

```
## Computing the weights
test.data2$weights <- ifelse(test.data2$cohort == "OMA",
1/test.data2$pscores, 1/(1-test.data2$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS_2 <- subset(test.data2, select = c(cohort,age_base,
                                        bmi_base,
                                        TC_with_csDMARD,
                                        PREDNISON_STEROID,
                                        CDAI0,
                                        disease_duration_base_years,
                                        smoker_base,
                                        line_of_therapy,
                                        gender,
                                        seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS_2, treat = test.data2$cohort, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort,  v.threshold = 2)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, v.threshold = 2)
#

#But plotting it is better:
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights,stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
```

```
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "Absolute risk of
treatment discontinuation by type of treatment - BARI vs TNFi")+
  labs(group = "Groups:")

plot.ate.diff2
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

We can also consider the AIPTW estimate at a specific time point. For example at 365-day.

```
r.one <- dt.out2[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out2[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols

library(formattable)
coxtable[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
coxtable[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
coxtable[1,"p"] <-  writepvalue(r.one$p.value)
```

```
coxtable[2,"Estimate"] <-  paste0(r.two$estimate)
coxtable[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
coxtable[2,"p"] <-  writepvalue(r.two$p.value)

coxtable

# Interpretation: If every patient had received BARI, the 365-day risk
of treatment discontinuation would have been xx% (points) lower
compared to when every patient had received TNFi.
```

.

[3] 1st LINE vs 1st LINE analysis

Common Table 1

Table 1 with NA, to have exact counts and proportions

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection of TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1 NA.xlsx")
```

Table 1 without NA to have adequate p values to interpret

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1.xlsx")

summary(BARI_first[cohort=="BARI", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="TNFi", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="OMA", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
```

```
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables
```

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])

surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50", "grey10"),
           palette = c("red2", "green3"), # to get colors
           risk.table = T
           )

survplot_first1
table(BARI_first1$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
           pval = T,
```

```
            pval.method = TRUE,
            legend.title = "Groups :",
            legend.labs = c("Baricitinib", "OMA"),
            xlab = "Time (days)",
            xlim = c(0, 700),
            censor = FALSE,
            title = "Non-adjusted model of drug discontinuation by type
of treatment",
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )

survplot_first2
table(BARI_first2$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

Adjusted survival analyses

BARI vs TNFi

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                             cluster(patient_id),
                       data= BARI_first1)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data1_first <- complete(imputed_data1,"long",include=T) # to
put in the long format
imputed_data1_first <- filter(imputed_data1_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data1_first <- as.mids(imputed_data1_first) # put back in
previous format, to use fit.mult.impute

BARI_first1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                      I(age_base/10)+
                                      bmi_base+
                                      concomitant_csDMARD+
                                      PREDNISON_STEROID+
```

```
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base+
                                    cluster(patient_id),
                                  fitter = coxph, xtrans =
imputed_data1_first, data = BARI_first1)
summary(BARI_first1.adj.mi)

Creation of HR table with p-values
ploufrows <- names(BARI_first1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first1.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR 1st
lines.xlsx") # save in excel format

Adjusted curves with imputed data
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
```

```
                                gender+
                                seropositivity_base+
                                cluster(patient_id)+
                                strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10")
           palette = c("red2", "green3"), # to get colors
           )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

BARI vs OMA

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                            cluster(patient_id),
                       data= BARI_first2)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data2_first <- complete(imputed_data2,"long",include=T) # to
put in the long format
imputed_data2_first <- filter(imputed_data2_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data2_first <- as.mids(imputed_data2_first) # put back in
```

```
previous format, to use fit.mult.impute

BARI_first2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                      I(age_base/10)+
                                      bmi_base+
                                      concomitant_csDMARD+
                                      PREDNISON_STEROID+
                                      I(CDAI0/10)+
                                      I(disease_duration_base_years/10)+
                                      C(smoker_base, base=3)+
                                      line_of_therapy+
                                      gender+
                                      seropositivity_base+
                                      cluster(patient_id),
                                    fitter = coxph, xtrans =
imputed_data2_first, data = BARI_first2)
summary(BARI_first2.adj.mi)
```

Creation of HR table with p-values

```
ploufrows <- names(BARI_first2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first2.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR 1st
lines.xlsx") # save in excel format
```

Adjusted curves with imputed data

```
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
```

```
                                    I(age_base/10)+
                                    bmi_base+
                                    concomitant_csDMARD+
                                    PREDNISON_STEROID+
                                    CDAI0+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base+
                                    cluster(patient_id)+
                                    strata(cohort),dummy_cox_impute_first2),
        data = dummy_cox_impute_first2)


        survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
        dummy_cox_impute_first2, variable = "cohort",
                  xlab = "Time (days)",
                  title = "Multivariable Cox model of drug discontinuation by
        type of treatment - 1st line vs 1st line",
                  legend.title = "Groups :",
                  legend.labs = c("Baricitinib", "OMA bDMARDs"),
                  censor = FALSE,
                  xlim = c(0, 700),
                  surv.median.line = "v",
                  linetype = 1,
                  size = 1.5,
                  ggtheme = theme_minimal(),
                  #palette = c("grey78", "grey50")
                  palette = c("red2", "blue3"), # to get colors
                  )

        survplot_first2_adj <- survplot_first2_adj +
            labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
        concomitant glucocorticoid, baseline CDAI, disease duration (decades),
        smoking status, line of therapy, gender, seropositivity")

        survplot_first2_adj
        table(BARI_first2$cohort)
        rm(dummy_cox_impute_first2, BARI_first2_fit)
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_T <- BARI_comp[cohort %in% c("TNFi")] #TNFi only
ci_TNFi <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_T)
ci_TNFi <- ci_TNFi[,-c(2,6,7,8,9)]
ci_long_TNFi <- reshape2::melt(ci_TNFi,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_TNFi$cohort <- 1
ci_long <- rbind(ci_long_BARI,ci_long_TNFi)
ci_long$cohort <- as.factor(ci_long$cohort)

plot2 <- ggplot(data = ci_long, aes(x = time,
                                    y = value,
                                    linetype =
interaction(cohort,variable),
                                    col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values
=c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
```

```
(BARI)","Other (TNFi)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
(BARI)","Other (TNFi)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot2
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat

imputed_data1_long <- complete(imputed_data1, action = "long") %>%
setDT()
imputed_data1_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data1_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data1_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data1_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data1$m
```

```
mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data1_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                   status = c("continue","stop_ae","stop_lae"),
                   data = as.data.frame(data_sub),
                   trans = tmat,
                   keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)

  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                            paste0(tmp_cov,collapse = " + "),
                            "+ strata(trans)")),
            data = tmp,
            method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
# estimate = Hazard ratio

summary(est, conf.int = T, exponentiate = T)

# Conclusion
# => The hazard ratio of lack of efficacy (lae) for TNFi is 65% higher
than for BARI. Significant.
# => No difference between TNFi and BARI for Adverse Event (ae)
```

Clean table with confidence intervals & p-values

```
# Hazard ratios
ploufrows <- as.character(summary(est)$term)

ploufcols  <- c("HR","95%CI","p")
coxtable_csh <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh) <- ploufrows
colnames(coxtable_csh) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()
```

```
for(row in ploufrows)
{
  coxtable_csh[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

output <- coxtable_csh
row.names(output)[1:2] <- c("TNFi Adverse Event (vs BARI)", "TNFi Lack
of Eff (vs BARI)")

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
output
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data1_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data1_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data1_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data1_long[stop_reasons == "CONTINUE", status := 0]

## ATTENTION levels() re-ecrit juste l'étiquette!! Change pas la
donnée !!! Donc ça re écrit les lablels

imputed_data1_long$line_of_therapy <-
as.factor(imputed_data1_long$line_of_therapy)
imputed_data1_long$seropositivity_base <-
as.factor(imputed_data1_long$seropositivity_base)

levels(imputed_data1_long$cohort) <- c("0","1")
levels(imputed_data1_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data1_long$gender) <- c("0","1")
levels(imputed_data1_long$smoker_base) <- c("2","1","0")
levels(imputed_data1_long$smoker_base)
levels(imputed_data1_long$seropositivity_base) <- c("0","1")

M <- imputed_data1$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    # subdistribution hazard model
```

```
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY

mice_fit2 <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()

est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of adverse event between TNFi
and BARI
# Increased incidence of lack of efficacy for TNFi compared to BARI.
# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Clean tables with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae) <- ploufrows
colnames(coxtable_ae) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae[row,"95%CI"] <-  paste0(formattable(plouf[term %in% row,
`2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_ae[row,"p"] <-  writepvalue(plouf[term %in% row, p.value])}
```

```
row.names(coxtable_ae)[1] <- c("TNFi vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae) <- ploufrows
colnames(coxtable_lae) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_lae[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae)[1] <- c("TNFi vs BARI Lack of Eff")

# output
coxtable_ae
coxtable_lae

write.xlsx(coxtable_ae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray LAE.xlsx") # saving excel file
```

(BARI vs OMA)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
```

```
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_O <- BARI_comp[cohort %in% c("OMA")] #OMA only
ci_OMA <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_O)
ci_OMA <- ci_OMA[,-c(2,6,7,8,9)]
ci_long_OMA <- reshape2::melt(ci_OMA,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_OMA$cohort <- 1
ci_long_2 <- rbind(ci_long_BARI,ci_long_OMA)
ci_long_2$cohort <- as.factor(ci_long_2$cohort)

plot3 <- ggplot(data = ci_long_2, aes(x = time,
                                      y = value,
                                      linetype =
interaction(cohort,variable),
                                      col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values =
c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot3
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
library(mstate)
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat

imputed_data2_long <- complete(imputed_data2, action = "long") %>%
setDT()
imputed_data2_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data2_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data2_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data2_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data2$m

mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data2_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                     status = c("continue","stop_ae","stop_lae"),
                     data = as.data.frame(data_sub),
                     trans = tmat,
                     keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)

  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                                  paste0(tmp_cov,collapse = " + "),
```

```
                                "+ strata(trans)")),
              data = tmp,
              method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Transition 1 = Adverse Event
# Transition 2 = Lack of Efficacy

# Conclusion
# => No difference between OMA and BARI for Adverse Event (ae) and for
Lack of Event (lae)
```

Cleaner table with Hazard ratios with confidence intervals & p-values

```
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_csh2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh2) <- ploufrows
colnames(coxtable_csh2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_csh2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_csh2)[1:2] <- c("OMA vs BARI Adverse event", "OMA
vs BARI Lack of Eff" )
coxtable_csh2
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data2_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data2_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data2_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data2_long[stop_reasons == "CONTINUE", status := 0]

imputed_data2_long$line_of_therapy <-
as.factor(imputed_data2_long$line_of_therapy)
```

```
imputed_data2_long$seropositivity_base <-
as.factor(imputed_data2_long$seropositivity_base)
levels(imputed_data2_long$cohort) <- c("0","1")
levels(imputed_data2_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data2_long$gender) <- c("0","1")
levels(imputed_data2_long$smoker_base) <- c("2","1","0")
levels(imputed_data2_long$smoker_base)
levels(imputed_data2_long$seropositivity_base) <- c("0","1")

M <- imputed_data2$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data2_long[.imp == m]

  #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY
mice_fit2 <- lapply(1:M,function(m){

  # subset
  BARI_toto <- imputed_data2_long[.imp == m]

  # subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()
est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of "adverse event" and "lack
of efficacy" between TNFi and BARI

# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Cleaner Table with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae2) <- ploufrows
colnames(coxtable_ae2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_ae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_ae2)[1] <- c("OMA vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae2) <- ploufrows
colnames(coxtable_lae2) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_lae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae2)[1] <- c("OMA vs BARI Lack of Eff")

#Output
coxtable_ae2
coxtable_lae2

write.xlsx(coxtable_ae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray LAE.xlsx") # saving excel file
```

1. Saving

```
save.image(file="./3_clean_output/full_workspaces/workspace_1.RData")
```

2 - LDA and REM ANALYSIS

10/11/2020

```
{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)
```

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./1_datamanaged_files/datamanaged.Rdata")
```

This code aims at providing estimates for the remssion rates of the different treatments groups REM = REMmission LDA = Low Disease Activity

Both outcome are base on the CDAI CDAI = Clinical Disease Activity Index

CDAI is an index computed by the physician, which scores the severity of the disease.

1. [0] Exploration

See all available raw CDAI measures :

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

nrow(BARI_DATA)
summary(BARI_DATA[, .(CDAI0_raw, CDAI12_raw)])
```

1. [1] CARRAC (confirm covariates for confounding and for attrition)

For LDA with updated function

```
library(modules)
source_comp_eff <- modules::use("ETAPE_2_supp_code.R")

LDA_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
  seed = 123)

LDA_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
  seed = 123)

LDA_BARI_TNF
LDA_BARI_OMA
```

For REM with updated function

```
REM_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
   seed = 123)

REM_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
```

```
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
   seed = 123)

REM_BARI_TNF
REM_BARI_OMA
```

This methods was developed by Mongin et al,
https://ard.bmj.com/content/early/2022/01/12/annrheumdis-2021-221477

Pooled table

```
table <- rbind(LDA_BARI_TNF, LDA_BARI_OMA, REM_BARI_TNF, REM_BARI_OMA)

write.xlsx(table, file = "./3_clean_output/table_LDA_REM_CARRAC.xlsx",
row.names = F)
```

1. Saving

```
save.image(file="./3_clean_output/full_workspaces/workspace_2.RData")
```

2 - LDA and REM supp CODE

10/11/2020

```
{r setup, include=FALSE} import("data.table") import("plyr")
import("data.table") import("mice") import("ipw") import("survey")
import("geepack") import("futile.logger") import("emmeans")
import("stats") import("survival")
```

function to perform checks on data

```{r setup, include=FALSE} check_data = function(datain, var = “CDAI_fu”, ttt_var = “ttt”, ref_ttt = “ttt_ref”, ID_ttt = NULL, othervar = c())

{

data <- setDT(copy(datain))

vartocheck <- Reduce(union,list(var,ttt_var,othervar)) notindata <- setdiff(vartocheck,names(data))

if(length(notindata)>0){ stop(paste0(“the variables”,paste0(notindata,collapse = “,”),” are not in the dataplease correct”)) }

# force ttt as var name setnames(data,ttt_var,“ttt”)

if( data[,uniqueN(ttt)]>2){ stop(“there are more than two treatments. The analysis has been implemented only for 2 treatments”) }

if(!any(data$ttt == ref_ttt)){ stop(paste0(“The variable”,ttt_var,” does not contain any “,ttt_ref,” value”)) }

data[,ttt := relevel(as.factor(ttt),ref_ttt)] if(is.null(ID_ttt))
{ data[,ID_ttt := .I] }else{ setnames(data,ID_ttt,“ID_ttt”) data[,N := .N,by = ID_ttt] if(any(data$N>1)){ stop(“there are”,data[N>1,uniqueN(ID_ttt)],” treatment course which have more than one entry in the table. Each row should be an unique treatment”) } }
return(data) }

adjusted_model = function(data, weights = NULL, covariates = NULL){

# transform char to factor to_fact <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “character”,var]

data[,c(to_fact) := lapply(.SD,factor),.SDcols = to_fact]

#droplevels facto_vars <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “factor”,var] data[,c(facto_vars) := lapply(.SD,droplevels),.SDcols = facto_vars]
```

define forumla formula <- as.formula(paste0("LDA ~",paste0(c("ttt",covariates),collapse = " + ")))

if(!is.null(covariates)){ # fit fit <- geeglm(formula, data = data, id = ID_ttt, family = gaussian) }else{ fit <- geeglm(LDA ~ ttt , data = data, weights = weights, id = ID_ttt, family = gaussian) }

fitsummary <- summary(fit) # create table with difference between the two treatments diff <- data.table(ttt = "diff", LDA = fitsummary$coefficients[2,"Estimate"], LDA_var = fitsummary$coefficients[2,"Std.err"]^2, LDA_sup = fitsummary$coefficients[2,"Estimate"] + 1.96*fitsummary$coefficients[2,"Std.err"], LDA_inf = fitsummary$coefficients[2,"Estimate"] - 1.96*fitsummary$coefficients[2,"Std.err"], methods = "CC_adjusted")

marginal effects: margi_df <- emmeans(fit, "ttt") %>% as.data.table()

margi_df[,methods := "CC_adjusted"] setnames(margi_df,"emmean","LDA") margi_df[,LDA_inf := LDA - 1.96*SE] margi_df[,LDA_sup := LDA + 1.96*SE] margi_df[,LDA_var := SE^2]

output <- rbind(diff,margi_df[,.(ttt,LDA,LDA_sup,LDA_inf,LDA_var,methods)])

return(list(output = output,fit = fit)) }

Not adjusted complete case imputation

```{r setup, include=FALSE}

```
export("CC_raw")
CC_raw <- function(datain,
                   # data
                   var = "CDAI_fu",
                   # variable measuring effctiveness
                   thres = 10,
                   # threshold for remission or LDA
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref")
  # variable name containing the treatment
  {
  data <- check_data(datain,var,ttt,ref_ttt)
  # raw proportion
  raw_prop <- data[!is.na(get(var)),
                   .(LDA = sum(get(var)<=thres)/.N,
                     methods = "CC_raw",
                     N = .N),
                   by = ttt]
```
```

```
  # calculation of the Standard error
  raw_prop[,c("LDA_inf","LDA_sup") := lapply(c(-1.96,1.96),function(z)
{
    LDA + z*sqrt(LDA*(1-LDA)/N)
  })]

  # difference between treatments
  diff_tmp <- raw_prop[,.(ttt = "diff",
                          LDA = LDA[ttt == "ttt_1"]-LDA[ttt ==
"ttt_ref" ],
                      methods = methods[1] ,
                      SE = (sum(1/N))/2 +  1.96*sqrt(sum( LDA*(1-LDA)/N
)))]

  diff_tmp[,LDA_inf := LDA - SE]
  diff_tmp[,LDA_sup := LDA + SE]

  # bind outputs
  output <- rbind(diff_tmp[,.(ttt,LDA,LDA_inf,LDA_sup,methods)],
                  raw_prop[,-"N"])
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Adjusted complete case imputation

```{r setup, include=FALSE} export("CC_adjusted") CC_adjusted = function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0") ) # variable name containing the treatment { data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] output <- adjusted_model(data = data[!is.na(get(var))], covariates = covariates)$output

output[,methods := "CC_adjusted"] # change name back setnames(output,"ttt",ttt_var) return(output) }

```
LOCF imputation


```{r setup, include=FALSE}
export("LOCF")

LOCF <- function(datain,
                 var = "CDAI_fu",
                 var_before = "CDAI_beforefu",
```

```
                thres = 10,
                ttt_var = "ttt",
                ref_ttt = "ttt_ref",
                covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
){
  data <- copy(datain)

  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[is.na(get(var)),c(var) := get(var_before)]
  data[,LDA := get(var) <= thres]

  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  output[,methods := "LOCF"]
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Lundex imputation

```{r setup, include=FALSE} export("Lundex") Lundex <- function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", treatment_duration = "treatment_duration", stop_var = "stopany", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"), boot_num = 1000) {

data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] #### bootstrap for SE data[,tmp := 1] # replicated data for bootstrap replicateddata <- data[CJ(tmp = 1,boot = 1:boot_num),on = "tmp",allow.cartesian=TRUE] # sample with replacement for each boot sampled_idx <- replicateddata[,.I[sample(1:.N,replace = T)],by = boot]$V1 bootstrapdata <- replicateddata[sampled_idx]

# raw proportions raw_prop <- bootstrapdata[!is.na(get(var)), { adjusted_model(data = .SD)$output %>% .[ttt != "diff",.(ttt,LDA_raw = LDA)] }, by = .(boot)]

# surv analysis for each bootstraped dataset surv_formula <- as.formula(paste0("Surv(",treatment_duration,",",stop_var,") ~ ttt"))

surv_coeff <- bootstrapdata[, { temp.km <- survfit(surv_formula, data = .SD) list(surv = summary(temp.km, times = 1)$surv,  ttt = gsub("ttt=","",unique(summary(temp.km) $strata))) }, by = boot]

# LDA: LDA raw * surv coeff tmp_bootstrap <- merge(raw_prop,surv_coeff,by = c("boot","ttt")) tmp_bootstrap[,LDA := LDA_raw*surv]
```

difference between treatments diff_boot <- tmp_bootstrap[,.(ttt = “diff”, LDA = LDA[ttt != ref_ttt] - LDA[ttt == ref_ttt]), by = boot]

tot_bottstrap <- rbind(diff_boot[, .(ttt, LDA, boot)], tmp_bootstrap[, .(ttt, LDA, boot)])

calculate the mean and the SE: output <- tot_bottstrap[, .(LDA = mean(LDA), LDA_sup = quantile(LDA, 0.975), LDA_inf = quantile(LDA, 0.025)), by = ttt] # change name back output[,methods := “LUNDEX”]

setnames(output,“ttt”,ttt_var) return(output) }

non-responder imputation

```{r setup, include=FALSE}
export("NRI")
NRI = function(datain,
               var="CDAI_fu",
               thres = 10,
               ttt_var = "ttt",
               ref_ttt = "ttt_ref",
               covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
)
  # variable name containing the treatment
{
  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[,LDA := get(var) <= thres]
  data[is.na(LDA),LDA := 0] # missing are non responders
  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  # change name back
  setnames(output,"ttt",ttt_var)
  output[,methods := "NRI"]
  return(output)
}
```

Inverse probability weighting imputation

```{r setup, include=FALSE} export(“IPW”) IPW <- function(datain, var = “CDAI_fu”, thres = 10, ttt_var = “ttt”, ref_ttt = “ttt_ref”, counfunders = c(“Disease_duration”,“concomitantCsDMARD”,“Prev_bDMARD3”,“CDAI0”), attrition = c(“Disease_duration”,“concomitantCsDMARD”, “Prev_bDMARD3”,“CDAI0”,“stopreason”)) {

data <- check_data(datain, var, ttt_var, ref_ttt, othervar = c(counfunders,attrition))
```

data[,ttt2 := as.numeric(ttt != ref_ttt)] # weight for confounding formula_coeff <- paste0("~",paste0(counfunders,collapse = "+")) function_call <- paste0('IPWT <- ipwpoint(exposure = ttt2 , family = "binomial", link = "logit", numerator = ~ 1, denominator =',formula_coeff,', data = data, trunc = 0.01)') eval(parse(text = function_call)) data$sw <- IPWT$ipw.weights

weights for attrition formula_attr <- paste0("~",paste0(attrition,collapse = "+")) data[,MISS := as.numeric(is.na(get(var)))] function_call <- paste0('IPCT <- ipwpoint(exposure = MISS , family = "binomial", link = "logit", numerator = ~ 1, denominator =',formula_attr,', data = data)') eval(parse(text = function_call)) data $swc <- IPCT$ipw.weights

dataNoNA <- na.omit(data[,.(ttt,get(var),sw,swc,ID_ttt) %>% setNames(c("ttt",var,"sw","swc","ID_ttt"))]) dataNoNA[,LDA := as.numeric(get(var) <= thres)]

output <- adjusted_model(data = dataNoNA, weights = dataNoNA$sw*dataNoNA$swc) $output

output[,methods := "IPW"]

change name back setnames(output,"ttt",ttt_var) return(output)

}

Confounder-Adjusted Response Rate with Attrition Correction (CARRAC) imputation

```{r setup, include=FALSE}
export("CARRAC")
CARRAC <- function(datain,
                   var = "CDAI_fu",
                   thres = 10,
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref",
                   counfunders =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"),
                   attrition =
c("Disease_duration","concomitantCsDMARD",

"Prev_bDMARD3","CDAI0","stopreason"),
                   seed = NA) {

  data <- check_data(datain,var,ttt_var,ref_ttt)
  dataS <- data[,.SD,.SDcols =
c("ID_ttt",var,"ttt",union(counfunders,attrition))]
```

```
  impute_data <- mice(
    dataS,
    m = 10,
    method = "pmm",
    maxit = 5,
    printFlag = F,seed = seed
  )
  # open the data
  impute_data_complete <- setDT(complete(impute_data,action = "long"))
  # calculate LDA
  impute_data_complete[,LDA := get(var) <= thres]

  # get LDA and error for each imputation
  res_mice <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$output

  }) %>% rbindlist()

  res_mice_2 <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$fit

  })

  test <- pool(res_mice_2)
  df_pval <- summary(test)  %>% as.data.table()
  p.output <- df_pval[grepl("ttt",term),p.value]

# pooling
  pool_res <- res_mice[,.(
    LDA_mi = mean(LDA),
    w = mean(LDA_var),
    m = .N,
    b = 1/(.N-1)*sum( (LDA-mean(LDA))^2 )
              ),by = ttt]

  pool_res[,LDA_var := w + (1+1/m)*b]
  pool_res[,LDA_sd := sqrt(LDA_var)]

  # mean, 95% CI
  output <- pool_res[,.(ttt,
                        LDA_mi,
                        LDA_mi + 1.96*LDA_sd,
                        LDA_mi-1.96*LDA_sd) %>%
                       setNames(c("ttt","LDA","LDA_sup","LDA_inf"))]

  output[,methods := "CARRAC"]
```

```
  output[ttt == "diff",p := p.output]

  # change name back
  setnames(output,"ttt",ttt_var)

  return(output)
}
```

3 - FINAL FIGURES CODE

10/11/2020

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(patchwork) # package to compose multiplots !
library(ggpubr)
library(grid)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./3_clean_output/full_workspaces/workspace_1.RData")
load("./3_clean_output/full_workspaces/workspace_2.RData")
load("./3_clean_output/full_workspaces/workspace_3.RData")
```

1. Common theme

```
theme_benoit = function(){
theme_pubclean()+
  theme(panel.grid.major.x = element_line(linetype = "dotted", colour
= "grey50"),
        panel.grid.major.y = element_line(linetype = "dotted", colour
= "grey50"),
        axis.title.y = element_text(margin = margin(r = .2, unit =
"cm")),
        axis.title.x = element_text(margin = margin(t = .2, unit =
```

```
"cm")),
        plot.title = element_text(margin = margin(b = .5, unit =
"cm")))
}
```

1. [0] Mini explation

TC lenght

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

p1 <- ggplot(BARI_DATA)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/12)+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "Time of observation for all included TC")+
  ylim(-25,NA)+
  theme_benoit()
p1

p2 <- ggplot(BARI_DATA)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration
```

Saving plot

```
png("./3_clean_output/figures/PLOT_Exploration_TC_duration.png",
    width = 7,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
plot_mini_exploration
dev.off() # closing graphic device
```

TC lenght for BARI only

```
data_sub <- BARI_DATA[cohort == "BARI"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "red3")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "A - BARI")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_bari <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_bari
```

TC lenght for TNFi only

```
data_sub <- BARI_DATA[cohort == "TNFi"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "green2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "B - TNFi")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_tnfi <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_tnfi
```

TC lenght for OMA only

```
data_sub <- BARI_DATA[cohort == "OMA"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "blue2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "C - OMA")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_oma <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_oma
```

multiplot

```
multi_plot <- plot_mini_exploration_bari + plot_mini_exploration_tnfi
+ plot_mini_exploration_oma
multi_plot

median(BARI_DATA[cohort == "BARI", time_on_drug])
median(BARI_DATA[cohort == "TNFi", time_on_drug])
median(BARI_DATA[cohort == "OMA", time_on_drug])
```

Saving plot

```
png("./3_clean_output/figures/
PLOT_Exploration_TC_duration_3_groups.png",
    width = 9,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
multi_plot
dev.off() # closing graphic device
```

1. [1] Survival analysis

Forest plot BARI vs TNFi + BARI vs OMA

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("Treatment (vs BARI)", "Age (decades)", "BMI",
"Concomitant csDMARD", "Concomitant glucocorticoid", "CDAI score (10
pts)", "Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")
```

```
dfall1 <- data.table(textall, meanall, lowerall, upperall)
dfall1[,ttt := "TNFi"]

meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
dfall2 <- data.table(textall, meanall, lowerall, upperall)
dfall2[, ttt := "OMA"]

dfall <- rbind(dfall1,dfall2)
dfall$textall <- factor(dfall$textall, levels = rev(textall))

text_high <- textGrob("\u2192 Reduces \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))
text_low <- textGrob("\u2190 Improves \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))

HR_plot <- ggplot(data=dfall,
                  aes(x = textall,
                      y = meanall,
                      ymin = lowerall,
                      ymax = upperall,
                      color = ttt))+
  geom_hline(yintercept =1, linetype=2)+
  geom_point(size=2,position = position_dodge(width = .7))+
  geom_errorbar(position = position_dodge(width = .7))+
  labs(x = "",y = "",color = "")+
  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  theme(axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", color = "black"),
        legend.position="top",
        legend.key = element_blank(),
        plot.margin = unit(c(1,3,2,1),"lines"))+
  coord_flip(clip = "off")+
  annotation_custom(text_high,
           xmin=-0.64,xmax=-0.64,ymin=.2,ymax=.2)+
  annotation_custom(text_low,
           xmin=-0.64,xmax=-0.64,ymin=-.15,ymax=-.15)+
  theme_pubclean()+
  scale_color_manual(breaks = c("OMA","TNFi"),values =
c("blue3","green3"),labels = c("OMA","TNFi"))

HR_plot
```

Saving the plot in PNG file

```
png("./3_clean_output/figures/PLOT FOREST BARI vs TNFi vs OMA HR.png",

    width = 7,
```

```
    height = 5.5,
    units = "in",
    res = 300)

HR_plot

dev.off() # closing graphic device
```

BARI vs TNFi

Non-adjusted Kaplan-Meier curves

BARI vs TNFi

```
BARI1[,time_on_drug_year := time_on_drug/365.25]

surv_object1 <- Surv(time = BARI1$time_on_drug_year, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1)

survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
                         pval = T,
                         pval.method = TRUE,
                         legend.title = "Groups :",
                         legend.labs = c("BARI", "TNFi"),
                         xlab = "Time (years)",
                         xlim = c(0, 2.5),
                         censor = FALSE,
                         title = "Non-adjusted model of drug
discontinuation \nby type of treatment",
                         surv.median.line = "v",
                         linetype = 1,
                         size = 1.5,
                         #palette = c("grey78", "grey10"),
                         palette = c("red3", "green2"), # pour mettre
les couleurs
                         ggtheme = theme_benoit(),
                         risk.table = T)

values <- summary(fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.2,label =
as.character(round(values,2)))

survplot_1$plot <- survplot_1$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2"), size = 5)


print(survplot_1)
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves non adjusted
COLOR.png",
     width = 7,
       height = 7, units = "in",
       res = 300) # opening graphic device
survplot_1

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]
dummy_cox_impute1$time_on_drug_year <-
dummy_cox_impute1$time_on_drug/365.25

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
                           xlab = "Time (years)",
                           title = "A - BARI vs TNFi",
                           legend.title = "Groups :",
                           legend.labs = c("BARI", "TNFi"),
                           censor = FALSE,
                           xlim = c(0, 2.5),
```

```
                                surv.median.line = "v",
                                linetype = 1,
                                size = 1.5,
                                ggtheme = theme_benoit(),
                                # palette = c("grey78", "grey10")
                                palette = c("red2", "green3") )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,\n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding days label
values <- summary(BARI_fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_1_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green3"), size = 5)

# adding HR et p val label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI1.adj.mi$coefficients[1]), 2), "\n", "p =",
round(summary(BARI1.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)

# final print
survplot_1_adj
```

Saving the survival plot in PNG file

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves adjusted.png",

    width = 7,
    height = 5,
    units = "in",
    res = 300)

survplot_1_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression Package)

First plot to get the difference in average treatment effect in percentage

```
dt.out$time_years <- dt.out$time/365.25

plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  scale_colour_manual(values = c("red2","green3"))+
  scale_fill_manual(values = c("red2","green3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "A - BARI vs TNFi")
+
  labs(group = "Groups:")+
  theme_benoit()+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Saving Plot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves AIPTW.png",
width = 1300, height = 650, res = 120) # opening graphic device

plot.ate.diff

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
```

```
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

BARI vs OMA

Non-adjusted Kaplan-Meier curves

BARI vs OMA

```
BARI2[,time_on_drug_year := time_on_drug/365.25]

surv_object2 <- Surv(time = BARI2$time_on_drug_year, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 2.5),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           #palette = c("grey78", "grey50"),
           palette = c("red3", "blue2"), # to put colors
           risk.table = T)
survplot_2
```

Saving surplot

```
png("./3_clean_output/PLOT BARI vs OMA curves non adjusted COLOR.png",
width = 1000, height = 600, res = 100) # opening graphic device

survplot_2

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]
dummy_cox_impute2$time_on_drug_year <-
dummy_cox_impute2$time_on_drug/365.25

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (years)",
           title = "B - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           censor = FALSE,
           xlim = c(0, 2.5),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD, \n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding Days label
values <- summary(BARI_fit2)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
```

```
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_2_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"blue2"), size = 5)

# adding HR et pval label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI2.adj.mi$coefficients[1]), 2),  "\n", "p =",
round(summary(BARI2.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)



# final print
survplot_2_adj

summary(BARI_fit2, times = 1) # to see detailed surv probabilities at
given timepoints
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA curves adjusted.png", width =
1000, height = 600, res = 100) # opening graphic device

survplot_2_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression package)

First plot to get the difference in average treatment effect in percentage

```
dt.out2$time_years <- dt.out2$time/365.25

plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit() + theme(legend.spacing.x = unit(0.2, 'cm'),
```

```
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "B - BARI vs OMA")+
  labs(group = "Groups:")+

  scale_colour_manual(values = c("red2","blue3"))+
  scale_fill_manual(values = c("red2","blue3"))

plot.ate.diff2
```

Saving Plot

```
png("./3_clean_output/PLOT BARI vs OMA curves AIPTW.png", width =
1300, height = 650, res = 120) # opening graphic device

plot.ate.diff2

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

Multipanel plots

To update using patchwork

For the paper Non adjuted curves

```
# Creating list object

plots <- list()
```

```
plots[[1]] <- survplot_1
plots[[2]] <- survplot_2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)
```

Option 2 putting all data on one panel Kaplan Meier

BARI vs TNFi vs OMA

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

surv_object3 <- Surv(time = BARI_DATA$time_on_drug_year, event =
BARI_DATA$stop_DMARD)
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_DATA) # this
function creates the data for Kaplan Meyer
survplot_3 <- ggsurvplot(fit3, data = BARI_DATA,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit3)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[3,2] <- 1.72

survplot_3$plot <- survplot_3$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2", "blue2"), size = 5)

survplot_3$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_3
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA curves non
adjusted COLOR.png", width = 800, height = 600, res = 100) # opening
```

```
graphic device

survplot_3

dev.off() # closing graphic device
```

Adjusted curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1_adj
plots[[2]] <- survplot_2_adj

# Nice function

multi_plot_cox <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device

multi_plot_cox

dev.off() # closing graphic device
```

All curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1
plots[[3]] <- survplot_2
plots[[2]] <- survplot_1_adj
plots[[4]] <- survplot_2_adj

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2, nrow =
2)

# but does not display properly now.. :(
```

AIPTW absolute risk of treatment discontinuation biplot

```
plot.ate.diff + plot.ate.diff2

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA AIPTW curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device
```

```
plot.ate.diff + plot.ate.diff2

dev.off() # closing graphic device
```

Diagnostic multipanel plots

Asked by Lilly statistician to show balance in this analysis.

```
pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","green3"))+
    scale_fill_manual(values = c("red2","green3"))+

    xlab("Probability of being assigned BARI or TNFi") +
    ylab("Density") +
    labs(title = "A1 - BARI vs TNFi")

pscore_plot # overlap

pscore_plot2 <- ggplot(test.data2, aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","blue3"))+
    scale_fill_manual(values = c("red2","blue3"))+

    xlab("Probability of being assigned BARI or OMA") +
    ylab("Density") +
    labs(title = "A2 - BARI vs OMA")

pscore_plot2
# Good overlap
```

```
library(cobalt)

# BARI vs TNFi
B1 <- love.plot(COVS, treat = test.data$cohort, weights =
test.data$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B1 - BARI vs TNFi", color =
c("#FD8D3C", "#08306B"), themes = theme_pubclean() )

# BARI vs OMA
B2 <- love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B2 - BARI vs OMA", color =
c("#FD8D3C", "#08306B") , themes = theme_pubclean() )

one <- (  pscore_plot + B1)

two <- ( pscore_plot2 + B2 )

png("./3_clean_output/figures/AIPTW diagnositc COLOR.png", width =
1300, height = 900, res = 100) # opening graphic device

one / two

dev.off() # closing graphic device
```

1. [3] Fist line analysis

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])

surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "A - BARI vs TNFi",
           surv.median.line = "v",
           linetype = 1,
```

```
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50"),
            palette = c("red2", "green3"), # to get colors
            risk.table = T
            )

survplot_first1$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first1

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1

dev.off() # closing graphic device
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
            pval = T,
            pval.method = TRUE,
            legend.title = "Groups :",
            legend.labs = c("BARI", "OMA"),
            xlab = "Time (days)",
            xlim = c(0, 700),
            censor = FALSE,
            title = "B - BARI vs OMA",
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )
```

```
survplot_first2$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first2

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs OMA first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs TNFi)

```
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
```

```
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            #palette = c("grey78", "grey10")
            palette = c("red2", "green3"), # to get colors
            )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1_adj

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs OMA)

```
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           concomitant_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute_first2),
data = dummy_cox_impute_first2)


survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
```

```
dummy_cox_impute_first2, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50")
           palette = c("red2", "blue3"), # to get colors
           )

survplot_first2_adj <- survplot_first2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first2_adj
table(BARI_first2$cohort)
rm(dummy_cox_impute_first2, BARI_first2_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2_adj

dev.off() # closing graphic device
```

Multipanel plots

Non adjusted curves

```
plots <- list()
plots[[1]] <- survplot_first1
plots[[2]] <- survplot_first2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA 1st Line
curves non-adjusted COLOR.png", width = 1000, height = 600, res = 100)
# opening graphic device
```

```
multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

dev.off() # closing graphic device
```

All in one BARI vs TNFi vs OMA

```
BARI_first[,time_on_drug_year := time_on_drug/365.25]

surv_object4 <- Surv(time = BARI_first$time_on_drug_year, event =
BARI_first$stop_DMARD)
fit4 <- survfit(surv_object4 ~ cohort, data = BARI_first) # this
function creates the data for Kaplan Meyer

survplot_4 <- ggsurvplot(fit4, data = BARI_first,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit4)$table[,"median"]
df <- data.frame(y = .2,x = values+.2,label =
as.character(paste(round(values*365.25,2), "\n days")))
df <- df[2,]

survplot_4$plot <- survplot_4$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("green2"),
size = 5)

survplot_4$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_4
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA first curves
non adjusted COLOR.png", width = 800, height = 600, res = 100) #
opening graphic device
```

```
survplot_4

dev.off() # closing graphic device
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
ci_long$time_months <- ci_long$time/365.25*12

plot2 <-  ggplot(data = ci_long, aes(x = time_months,
                                     y = value,
                                     linetype = variable  ,
                                     col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","green2"),
                     labels = c("BARI","TNFi"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"),
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+ # not showing the "other category"
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "A - BARI vs TNFi")

plot2

ggsave(filename = "PLOT BARI vs TNFi cumulative incidence.png",plot =
plot2, path = "./3_clean_output/", device = "png", width = 829, height
= 550, units = "px", scale = 3.2)
```

(BARI vs OMA)

Cumulative incidence function

```
ci_long_2$time_months <- ci_long_2$time/365.25*12

plot3 <-  ggplot(data = ci_long_2, aes(x = time_months,
                                       y = value,
                                       linetype = variable  ,
                                       col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","blue2"),
                     labels = c("BARI","OMA"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"), # not showing the
"other" category
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "B - BARI vs OMA")

plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs OMA
cumulative incidence.png", plot3, height = 4, width = 6, units =
"in",dpi = 300)
```

Multipanel

```
plot2_3 <- plot2 + plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs TNFi and BARI
vs OMA cumulative incidence.png", plot2_3, height = 4, width = 8,
units = "in",dpi = 300)
```

1. [6] LDA - REM

Exploration

See all available raw CDAI measures : :)

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

plot_data <- copy(BARI_long[!is.na(TC_id) & TC_id %in%
BARI_DATA$TC_id])
plot_data <- merge(plot_data, BARI_DATA[,.(TC_id, cohort)], by =
"TC_id")

CDAI_plot <- ggplot(data = plot_data,
                    aes(x = time, y = CDAI, fill = cohort) )+

  annotate("rect",xmin = 0.875,xmax = 1.125,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+
  annotate("rect",xmin = -.05,xmax = 0+1.5/12,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+

  geom_point(data = plot_data[cohort != "BARI"], alpha = 0.2, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+
  geom_point(data = plot_data[cohort == "BARI"], alpha = 0.25, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+


  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort !=
"BARI"], alpha = 0.2, size = 2, shape = 21, show.legend = F )+
  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort ==
"BARI"], alpha = 0.25, size = 2, shape = 21 , show.legend = F, )+

  geom_smooth(alpha = 0.1, size = 1, aes(color = cohort), show.legend
= F)+

  coord_cartesian(xlim = c(0,2.5))+
    labs(title = "CDAI across time type of treamtent (all TC)",
         x = "Time (years since TC initiation)",
         y = "CDAI score",
         color = "",
         fill = "")+
  theme_benoit()+
  theme(legend.position = c(1,1),
        legend.justification = c(1,1))+
  guides(color = guide_legend(override.aes = list(linetype = NA,size =
3)))

CDAI_plot
```

To me this figure is the best results to be discussed regarding REM and LDA

saving plot

```
png("./3_clean_output/figures/PLOT CDAI across time raw.png",
    width = 8,
    height = 6,
    units = "in",
    res = 120) # opening graphic device

CDAI_plot

dev.off() # closing graphic device
```

CARRAC histogram

Building large format data table from the CARRAC output

```
# Extracting LDA BARI
LDA_BARI <- rbind(LDA_BARI_TNF[2,1:4], LDA_BARI_OMA[2,1:4]) # I have
one estimation per comparison
LDA_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
LDA_BARI <- LDA_BARI[1]

# REM BARI
REM_BARI <- rbind(REM_BARI_TNF[2,1:4], REM_BARI_OMA[2,1:4]) # I have
one estimation per comparison
REM_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
REM_BARI <- REM_BARI[1]

# IDem for TNFi and OMA
LDA_TNFi <- LDA_BARI_TNF[3,1:4]
REM_TNFi <- REM_BARI_TNF[3,1:4]

LDA_OMA <- LDA_BARI_OMA[3,1:4]
REM_OMA <- REM_BARI_OMA[3,1:4]

# Binding together
LDA <- rbind(LDA_BARI, LDA_TNFi, LDA_OMA)
setnames(LDA, c("ttt", "LDA", "LDA_sup", "LDA_inf")) #putting right
labels
REM <- rbind(REM_BARI, REM_TNFi, REM_OMA)
setnames(REM, c("ttt", "REM", "REM_sup", "REM_inf"))

histo_carrac <- cbind(LDA, REM[,-1])
```

plotting

```
carrac_plot <- ggplot(data = histo_carrac, aes(x = ttt, group = ttt))
+

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +

  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "A - REM and
LDA rates \nby type of treatment \n(CARRAC)")

carrac_plot
```

also Saving CARRAC plot only

```
png("./3_clean_output/figures/PLOT BARI 3 CARRAC ONLY.png", width =
350, height = 600, res = 100) # opening graphic device

ggplot(data = histo_carrac, aes(x = ttt, group = ttt)) +

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +
```

```
  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "REM and LDA
rates \nby type of treatment \n(CARRAC)")

dev.off() # closing graphic device
```

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p4-5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7 & supp p2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supp p2
Bias	9	Describe any efforts to address potential sources of bias	p16
Study size	10	Explain how the study size was arrived at	supp p9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p8-9
		(*b*) Describe any methods used to examine subgroups and interactions	supp p 5-6
		(*c*) Explain how missing data were addressed	p8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	p8-9
		(*e*) Describe any sensitivity analyses	p9 & supp p5-6

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p13-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p14-15 & supp
Discussion			
Key results	18	Summarise key results with reference to study objectives	p15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Filled in by Benoît GILBERT, 30-01-2023

BMJ Open

REAL WORLD EFFECTIVENESS OF BARICITINIB IN THE SWISS RHEUMATOID ARTHRITIS REGISTER (SCQM-RA)

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REAL WORLD EFFECTIVENESS OF BARICITINIB IN THE SWISS RHEUMATOID ARTHRITIS REGISTER (SCQM-RA)

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ABSTRACT

Objectives: This observational study compares the effectiveness of baricitinib (BARI), a targeted synthetic DMARD (tsDMARD) with alternative biological DMARDs (bDMARDs) in rheumatoid arthritis (RA) patients, from a prospective, longitudinal cohort.

Methods: We compared patients initiating a treatment course of BARI, tumor necrosis factor inhibitors (TNFi) or other mode of action bDMARDs (OMA), during a period when all these DMARDs where available in Switzerland. The primary outcome was drug-maintenance; secondary outcomes included discontinuation rates related specifically to ineffectiveness and to adverse events. We further analyzed rates of low disease activity (LDA) and remission (REM) at 12 months, and drug maintenance in b- and tsDMARD-naïve population.

Results: A total of 1053 treatment courses (TC) were included: 273 on BARI, 473 on TNFi and 307 on OMA. BARI was prescribed to older patients with longer disease duration and more previous treatment failures than TNFi. Compared to BARI, the adjusted drug maintenance was significantly shorter for TNFi (hazard ratio (HR) for discontinuation: 1.76; 95% CI [1.32-2.35]), but not compared to OMA (HR 1.27; 95% CI [0.93-1.72]). These results were similar in the b/tsDMARD-naïve population. The higher discontinuation of TNFi was mostly due to an increased discontinuation for ineffectiveness (HR = 1.49; 95% CI [1.03 – 2.15]), with no significant differences in drug discontinuation for adverse events (HR = 1.46; 95% CI [0.83 - 2.57]. The LDA and REM rates at 12 months did not differ significantly between the 3 groups.

Conclusions: BARI demonstrated a significantly higher drug maintenance compared to TNFi, mainly due to lower drug discontinuations for ineffectiveness. We found no difference in drug-maintenance between BARI and OMA. Clinical outcomes did not differ between the three groups. Our results suggest that BARI is an appropriate therapeutic alternative to bDMARDs in the management of RA.

Strengths and limitations of this study

Strengths:

- Use data derived from office-based rheumatologists
- Study period where all alternative medications were available on the market
- Several sensitivity analyses, congruent with main results

Limitations:

- Not a randomized setting
- Sub-analysis in b/tsDMARD-naïve population has limited sample size

INTRODUCTION

Rheumatoid arthritis (RA) is an auto-immune disease leading to widespread inflammation and irreversible joint damage, if insufficiently treated. New treatment paradigms have emerged in the last decades, such as “early aggressive therapy” in the so called “window of opportunity”, during which patients are more likely to reach long term remission.[1] A wide panel of biological disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been approved in the management of RA, after failure of methotrexate. In clinical-trial settings, b- and tsDMARDs have demonstrated significant reduction of joint inflammation and prevention of joint damage.[2–8]

Efficacy estimates from placebo-controlled randomized trials often differ from real-world effectiveness estimates, because of patient selection, adherence to therapy and other reasons.[9–12] Indeed, drug maintenance of many bDMARDs remains modest in observational analyses, while long term remissions are rare and secondary loss of efficacy frequent.[13] Furthermore, understanding the clinical effectiveness of bDMARDs or tsDMARDs in specific conditions, such as elderly or multi-morbid patients, may become important as we move towards personalized care. Finally, trials provide only limited data on long term effectiveness and safety because clinical-trial follow-up is typically less than 12 months.

Baricitinib (BARI) has been approved in Switzerland for the treatment of RA in 2017 as well as all around the world. Clinical trials with BARI have established efficacy and demonstrated acceptable adverse events profile, both in combination with methotrexate or in monotherapy.[14–20] However, evidence about effectiveness of BARI compared to TNFi in

real-world settings are scarce. A recently published analysis of registry data from Sweden showed that baricitinib had higher maintenance as compared to most other bDMARD.[21] Pappas et al., in the United States, also demonstrated that TNFi and non-TNFi drugs had similar outcomes when prescribed in b/tsDMARD-naïve population, an observation replicated in the RA-BE-REAL study.[22,23]

The aim of our analysis was to compare real-world drug maintenance between BARI and other approved b/tsDMARDs, using data from a European registry.

METHODS

Study population

This is a nested cohort study from a prospective, longitudinal, cohort of Swiss RA patients in a real-life setting, the Swiss Clinical Quality Management registry (SCQM). The SCQM registry was founded in 1997 with the financial support of Swiss regulatory authorities, who recommended a continuous monitoring of all patients receiving new DMARDs. Unlike many other European registries, most patients are enrolled by private office-based rheumatologists (60%), providing a population-based sample of RA patients in Switzerland. All approved RA treatments are represented in the registry. The data for this analysis was extracted from the SCQM registry on 2020-06-01.

We used “treatment courses” (TCs) as our denominator of interest, with each new treatment initiation considered as a separate “treatment course” (TC). We included all TCs with the medications of interest initiated between 2017-09-01 and 2020-06-01, with at least one follow-up visit, in adult patients with a diagnosis of RA confirmed by a rheumatologist. Thus, a given patient could potentially contribute to several TCs during the study period. To minimize the risk of confounding bias, the time window was selected to include only the period when all the therapies examined were available for prescription and reimbursed (BARI was first reimbursed on the Swiss market in September 2017). We excluded TCs with no follow-up visit at the time of data extraction.

Exposure of interest

The exposure of interest was the type of treatment used, namely BARI, TNFi, and other mode of action bDMARDs (OMA), excluding other tsDMARDs and rituximab. We decided to exclude rituximab a priori, because its long-term action impairs precise estimation of treatment discontinuation. Tofacitinib was excluded because we had insufficient TC to perform meaningful comparative effectiveness analyses against a single other specific tsDMARD agent. Included TNFi treatments were: adalimumab, etanercept, golimumab, certolizumab, infliximab. Included OMA treatments were: tocilizumab, abatacept, sarilumab, and anakinra.

Outcomes

The primary outcome of this analysis was the time to all-cause-discontinuation. This outcome, also referred to as "drug maintenance", captures both the drug's effectiveness and its tolerance.[24] The time to all-cause-discontinuation was defined as the number of days between treatment initiation and the reported date of discontinuation, or the date of initiation of a new b/tsDMARD, whatever came first. In survival analyses, death or lost-to-follow up are censored. We also report discontinuation rates at 12 months. Temporary discontinuations of less than 6 months (for instance, because of an elective surgery or a pregnancy) were not considered a permanent drug discontinuation. Discontinuation reasons are recorded by the clinician when stopping a DMARD treatment, who chooses between four options ("Adverse event", "Ineffectiveness", "Remission", or "Other").

Pre-planned secondary outcomes, were time to discontinuation due to ineffectiveness and time to discontinuation due to adverse events. Other secondary outcomes included response rates, namely the rates of low disease activity (LDA) and remission (REM), at 12 months, defined respectively as attaining a CDAI score <= 10 and CDAI score <= 2.8 (not mutually

exclusive).[25] Finally, we performed an exploratory subgroup analysis, restricting the population to b/tsDMARD-naive patients only, and re-assessing the main outcome in this setting.

Statistical analysis

Analyses were conducted and reported in accordance to EULAR recommendations for comparative effectiveness research.[9] Baseline characteristics were compared using generalized linear mixed models to account for repeated treatments within the same patients. For the primary outcomes, Kaplan-Meier survival analyses were used to assess crude drug maintenance, and groups were compared using Log-Rank tests. Subsequently, missing covariates were imputed using chained equations (see below for details). We then implemented Cox proportional hazard ratio models, to obtain adjusted estimates. Based on prior subject matter knowledge,[26] we adjusted our models for the following potential confounders: age, gender, BMI, concomitant csDMARDs use (yes/no), concomitant prednisone usage (yes/no), CDAI score at baseline, disease duration, smoking status (current-, former-, never-smoker) and line of therapy (1^{st}, 2^{nd}, 3^{rd}, 4^{th} or more), and seropositivity (yes/no). Detailed definitions for each variable are available in the supplement (Supplementary Material 1). The main analysis (survival analysis) accounted for clustering resulting from patients with multiple treatment courses, inducing correlation within the patient-level data. The cluster term is used to compute a robust variance for the model, by applying the so-called Huber sandwich estimator.[27] . All conditions of application of the Cox model were verified. One additional sensitivity analysis was conducted for the primary outcome, using augmented inverse probability of treatment weighting (AIPTW).

In secondary analyses, we used the Fine-Gray approach to assess specific reasons for drug discontinuation (i.e. ineffectiveness, or adverse event) in a competing-risk setting. The Fine-Gray method takes competing risks into account when estimating the cumulative incidence function, modelling the sub-distribution hazard without treating competing events as censoring events.[28] Other secondary outcomes included response rates (LDA and REM) at 12 months. To avoid overestimations, we computed the response rates using the 'confounder-adjusted response rate with attrition correction' (CARRAC) method.[29] The latter estimates the response rates using multiple imputations, with a model including both confounders and treatment stop reason. CARRAC thus provides reliable estimates when reasons for treatment discontinuation differ between compared groups.

For all adjusted analyses, missing baseline covariates were imputed using closest value in a window of -90 to +30 days. However, this window was reduced to -30 to +7 days when imputing baseline CDAI. If still missing after this first step, baseline CDAI values were imputed using linear mixed effect regression model with quadratic time. We imputed other baseline covariates with chained equations technique, which provides unbiased estimates if the variables are missing at random.[29] Such imputations were performed using 50 datasets with 25 iterations. Imputation was done using the whole data set, before adequately subsetting the data for each group comparison.

We also imputed data required for secondary outcomes, including disease activity. If the CDAI score at 12-month was not available, the closest value in a window of +/- 45 days was used (a 3-month-wide window). If still missing, the 12-month CDAI values were imputed using nearest neighboring value, as previously described.[30]

All analyses were conducted using R (version 4.0.3), in particular with packages "*tableone*", "*survival*", "*mice*".[31] Two tailed p-values < 0.05 were considered significant. We did not

adjust p value for multiple comparisons, as outcomes were pre-specified. Final analysis code is shown in the supplement (Supplementary Material 2).

Patient and Public Involvement

Patient involvement is central to the SCQM cohort. Several patients are part of the executive board and involved in the approval of research projects.

RESULTS

Population description

During the study period, 1053 TC were initiated in 834 different patients, including 273 TC with BARI, 473 with TNFi and 307 with OMA (Figure 1; Figure S1). TNFi were more often given as a second line therapy after methotrexate failure. Inversely, BARI was prescribed to significantly older patients, with longer disease durations and more previous treatment failures (Table 1).

Table 1: Baseline characteristics of study population, SCQM-RA registry, 2017-2020.

Variable	BARI (TC = 273; 273 pts)		TNFi (TC = 473; 408 pts)		OMA (TC = 307; 289 pts)		p values
	n % of total in group Otherwise: Mean (SD)						
Patients		*Miss.*		*Miss.*		*Miss.*	
Female	78 %	0	74 %	1	73 %	1	0.097
Age (years)	59 (14)	0	52 (15)	1	59 (13)	1	**0.021**
Disease duration (years)	13 (10)	4	8 (9)	19	11 (9)	5	**0.027**
CDAI baseline (raw data)	19 (10)	175	18 (10)	301	20 (13)	204	0.34
CDAI baseline (imputed)	15 (9)	0	14 (9)	0	16 (11)	0	0.06
Obesity (BMI > 30)	16 %	104	14 %	134	13 %	115	0.85
Smoking Current Former Never	17 % 28 % 43 %	32	18 % 26 % 41 %	69	21 % 28 % 48 %	26	Ref. 0.95 0.98
Seropositive (ACPA or RF)	75 %	1	70 %	7	77 %	5	0.92
TC		*Miss.*		*Miss.*		*Miss.*	
Concomitant csDMARD	40 %	0	61 %	0	46 %	0	**<0.01**
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	17 % 20 % 19 % 44 %	0	48 % 23 % 11 % 18 %	0	22 % 24 % 24 % 31 %	0	**Ref.** **<0.01** **<0.01** **<0.01**
Previous tsDMARD use (non-BARI)	33 %	0	1 %	0	5 %	0	**<0.01**
Concomitant glucocorticoid (at any time)	22 %	0	20 %	0	24 %	0	0.35
Mean dose of concomitant glucocorticoid (mg)	2.0 (4.6)	0	2.1 (5.4)	0	2.2 (5.1)	0	0.95
Dose of BARI (4mg)	86 %	0	-	-	-	-	-

Table 1 Legend: In Switzerland, BARI was prescribed to older patients, with longer disease duration and more previous treatment failures. Missing values for covariables are reported as absolute numbers

BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. Ref. = Reference

category for p-values (pairwise comparisons). P-values are obtained by generalized linear mixed models to account for repeated treatments within the same patients. In TFNi and OMA groups, some patients have contributed several TC, thus total number of TCs exceeds total number of patients.

Time to all-cause-discontinuation

Table 2: Crude treatment discontinuation by group and by reason, SCQM, 2017-2020.			
	BARI (TCs = 273; 273 pts)	**TNFi (TCs = 473; 408 pts)**	**OMA (TCs = 307; 289 pts)**
Treatment discontinuation (all causes)	30 %	43 %	35 %
For adverse events	8 %	10 %	10 %
For ineffectiveness	16 %	23 %	17 %
For remission	0 %	1 %	0 %
For other reason	5 %	8 %	7 %

Table 2 legend: % are computed on total number of TCs per group, for the whole study period. BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. TC = Treatment Courses. Pts = Number of patients. Due to rounding, the sum of the percentages of the causes of discontinuation may not correspond exactly to the total treatment discontinuation percentage.

Crude proportions of treatment discontinuation by reasons are reported in Table 2, and crude times of observation are represented on Figure S1.

At 12 months, based on the Kaplan-Meier curves (Figure 2), the estimated proportions of patients still on therapy were: 71% (95% CI [65% - 77%]) in the BARI group, 55% (95% CI [50% - 61%]) in the TNFi group, and 63% (95% CI [57% - 70%]) in the OMA group.

Overall, unadjusted time to all-cause-discontinuation was significantly longer in the BARI group compared to the TNFi group (estimated median prescription survival-time of 704 versus 448 days; Log-rank p<0.01; Figure 2). These results persisted after adjustment for confounding factors using the multivariable Cox model (HR = 1.76; 95% CI [1.32-2.35]; p<0.001; Table S1 and Figure S2; Figure S3).

BARI versus OMA time to all-cause-discontinuation was not significantly different, even after adjustment (HR 1.27; 95% CI [0.93-1.72]; p = 0.13; Table S1, Figure S2 and Figure S3).

Sensitivity analyses using AIPTW led to similar conclusions (Figure S4). Covariates significantly associated with decreased drug maintenance were high baseline CDAI scores and concomitant glucocorticoid usage (Table S1 and Figure S2).

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

In this exploratory subgroup analysis, we restricted the population to patients without prior experience of b/tsDMARDs (so-called 'bio-naïve' patients, i.e. first b/tsDMARD prescription after methotrexate failure). In thus subpopulation, patient characteristics were more balanced than in the main analysis, except for age, which remained younger in TNFi population, and concomitant csDMARDs usage (more frequent in TNFi) (Table S2). Of note, the sample size was consequently reduced to 46 BARI, 225 TNFi and 66 OMA.

When analysing only these b/tsDMARD-naïve patients, both the non-adjusted (Figure 3) and the adjusted differences between BARI and TNFi became larger (HR TNFi vs BARI = 2.5; 95% CI [1.23 – 5.16]; p=0.01), but the differences between baricitinib and OMA group remained not significantly different (HR OMA vs BARI = 1.90; 95% CI [0.71 – 5.1]; p=0.2).

Time to discontinuation for adverse events or ineffectiveness

A secondary outcome was the cumulative incidence of drug discontinuation by specific reasons for discontinuation (ineffectiveness or adverse events, Figure 4). Using Fine-Gray adjusted approach, we found no difference in the incidence of adverse event comparing BARI to TNFi (HR = 1.46; 95% CI [0.83 - 2.57]; p=0.13), or BARI to OMA (HR = 1.34; 95% CI [0.74 - 2.42]; p=0.25). The incidence of drug discontinuation for ineffectiveness was more frequent in TNFi compared to BARI (HR = 1.49; 95% CI [1.03 – 2.15]; p=0.01), but similar between OMA and BARI (HR = 1.09; 95% CI [0.72 – 1.64]; p=0.69).

Remission and low disease activity at 12 months

The estimated 12-month rates of REM and LDA, estimated using CARRAC did not differ significantly between the 3 groups (Figure 5). LDA ranged from 62% to 71% and REM ranged from 17% to 26%.

DISCUSSION

In this study, the overall drug maintenance of BARI was significantly longer compared to TNFi, despite the fact that it was prescribed to older patients, with longer disease duration, and more previous treatment failures similar to what was observed in RA-BE-REAL, another real-world study.[23] However, the adjusted 12-month response rates in terms of LDA and REM did not differ significantly between BARI, TNFi and OMA groups. The difference in drug discontinuation owes mainly to more treatment discontinuations for ineffectiveness in the TNFi group compared to the BARI group, while drug discontinuation due to adverse event did not differ significantly between the groups.

Our results are in line with previous findings comparing other JAK-inhibitors (JAKi) (i.e. tofacitinib as well as BARI) to TNFi and OMA medications,[22,32] which reported a longer drug maintenance of tsDMARD compared to TNFi, and similar maintenance to other bDMARDs. Of note, Lauper et al., using data from 19 national registers, found no difference in retention time between JAK-inhibitors and TNFi.[33] Still, Lauper et al. grouped all JAKi together in their study, thus it is not clear if these observations remain true for BARI alone, which might differ from other JAKi. For instance, Barbulescu et al. reported a higher drug maintenance for BARI as compared to tofacitinib.[21]

It was previously shown that BARI is more efficient in relieving pain as compared to adalimumab therapy [34] and some molecular mechanisms relevant to JAK-STAT signalling

have been hypothesized.[35] This observation has been hypothesised to result anti-nociceptive effect independent from inflammation.[35] This faster pain relief could partially explain why BARI has increased maintenance than other medication in our study, even though having similar 12-months LDA and REM rates. An alternative hypothesis is that the more convenient oral administration encourages patients to stay on medication longer. Yet, a third possible interpretation is that patients who experienced numerous treatment failures tend to stay on their latest therapy; however, our study accounts for this potential bias, by performing a sensitivity analysis in a subgroup of b-tsDMARD naïve patients, which showed a similar result. Finally, given recent discussion regarding tofacitinib safety,[36] future research needs to clarify whether a class effect for JAKi related adverse events exist. In this analysis, we found no indication for an increased incidence of adverse-related treatment discontinuation with BARI compared to alternative bDMARDs. Randomized controlled trials are ongoing to further compare safety profile of BARI versus TNFi (NCT04086745 and NCT03915964).

Limitations and Strengths

This work has several limitations, mostly inherent to the observational setting. First, as this is a non-randomized study, we cannot formally exclude unmeasured confounding between the groups. The available baseline variables were, in most cases, adequately balanced, except for age. When we restricted the analysis to the subgroup of b/tsDMARD naïve patients, we found largely similar results. Despite being limited by the small sample size, this exploratory subgroup analysis suggests that confounding by line of treatment was adequately accounted for in the adjusted analysis.

Secondly, the average length of follow-up was only approximatively 200 days per TC (Figure S1). Indeed, our study covers about 2 and a half years, and we only included TC newly initiated during this time-windows. Also, because of the study setting, as much as 65% of TC did not

have CDAI scores recorded at the date of initiation, and many were missing at the 12-month exact timepoint (Figure S5). Hence, our analysis of response rates relied heavily on linear interpolation techniques, using other available timepoints, which results in large confidence intervals for estimated response rates.[30]

The main strength of the study is that it relies on real-world data, and includes a relatively large number of patients. As these patients are mostly treated by office-based rheumatologists, our study population is representative of routine clinical practice. Also, sub-group analyses and sensitivity analyses were consistent with the main results.

CONCLUSIONS

In this non-randomized cohort study, drug maintenance of BARI was significantly higher than TNFi. However, we found no difference in drug maintenance when comparing BARI with other bDMARDs. Based on available data, the estimated 12-month response rates did not significantly differ between BARI, TNFi and OMA groups. We found no difference in treatment discontinuation for adverse event between the three groups. Overall, our results are in line with findings from randomized trials..

OTHERS

Contributorship statement

Benoît GILBERT contributed to data-management, data-analysis, figures, manuscript drafting. Denis MONGIN contributed to data-management, data-analysis, figures, manuscript-revision. Romain AYMOND contributed to data-analysis (in particular, sensitivity analyses), manuscript revision. Kim LAUPER took part in data-analysis and manuscript revision. Céline LAMACCHIA was involved in the study design and manuscript revision. Clémentine PERRIER was involved in the study design and manuscript revision. Ruediger MUELLER contributed to the study design and manuscript revision. Delphine COURVOISIER was involved in the study design, data-analysis and interpretation, manuscript revision. Axel FINCKH was in charge of the study design (principal investigator), data analysis, data interpretation and manuscript revision.

Competing interests

Benoît GILBERT has been once a paid speaker (Eli Lilly) and participated in advisory board (Janssen). Clementine PERRIER is employed by Eli Lilly and holds stock options (Eli Lilly and Company). Cedric LAEDERMANN is employed by Eli Lilly and holds stock options (Eli Lilly and Novartis). Axel FINCKH has received grants or contracts (Eli-Lilly, Pfizer, Abbvie, Gilead, BMS), consulting fees (Astra-Zeneca, Abbvie, Pfizer, Gilead), honorary payments (BMIS, Abbvie, Eli Lilly, Pfizer, MSD), and participated in advisory boards (Astra-Zeneca, Gilead, Novartis, Abbvie, Eli Lilly, Pfizer, J&J, Mylan, UCB). Denis MONGIN, Romain Aymond, Rüdiger Müller and Delphine COURVOISIER have no conflicts of interest to disclose.

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industries and donors, including Eli Lilly. A list of financial supporters can be found on www.scqm.ch/sponsors .

Data sharing statement

Restrictions apply to the availability of these data. Data is owned by a third party, the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) foundation. Data may be obtained after approval and permission from this license holder (SCQM). Contact information for data request: scqm@hin.ch

Ethical Review and Regulatory Considerations

This observational study has been approved by the Geneva ethical review boards (ERBs) as required by local law (Project ID: 2019-00930 ; approval date 28 May 2019). Every participant has signed an information and consent form at inclusion in the SCQM registry. Hence, this study has been conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with Good Pharmacoepidemiology Practices (GPPs).

Acknowledgements

Almut Scherer, from the SCQM. Also, all of the participating physicians of the SCQM in Rheumatic Diseases. A complete list of rheumatology offices and hospitals that are contributing to the SCQM registries can be found on www.scqm.ch/institutions .

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FIGURE LEGEND

Figure 1 - Selection of eligible treatment courses, SCQM, 2017-2020.

Selection of Treatment courses included in final analysis. TC = Treatment Courses. RA = Rheumatoid Arthritis. bDMARD = biological DMARD. tsDMARD = targeted synthestic DMARD. b/tsDMARD = biological and/or targeted synthetic DMARD. TNFi = TNF inhibitors. OMA = Other Mode of Action bDMARDs.

Figure 2 - Non-adjusted time to drug discontinuation analyses (Kaplan-Meier), SCQM, 2017-2020.

These “survival curves” represent the drug maintenance after initiation, as the estimated proportion of patients still on therapy, by treatment group. Death and loss to follow-up were censored. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : $p < 0.001$. Log-Rank BARI vs OMA: $p = 0.11$.

Figure 3 - Unadjusted time to drug discontinuation in b/tsDMARD-naïve patients, SCQM, 2017-2020.

These Kaplan-Meier curves represent the crude “survival” of drug prescription, by treatment group. Death and loss to follow-up are censored. BARI = baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : $p = 0.003$. Log-Rank BARI vs OMA : $p = 0.15$.

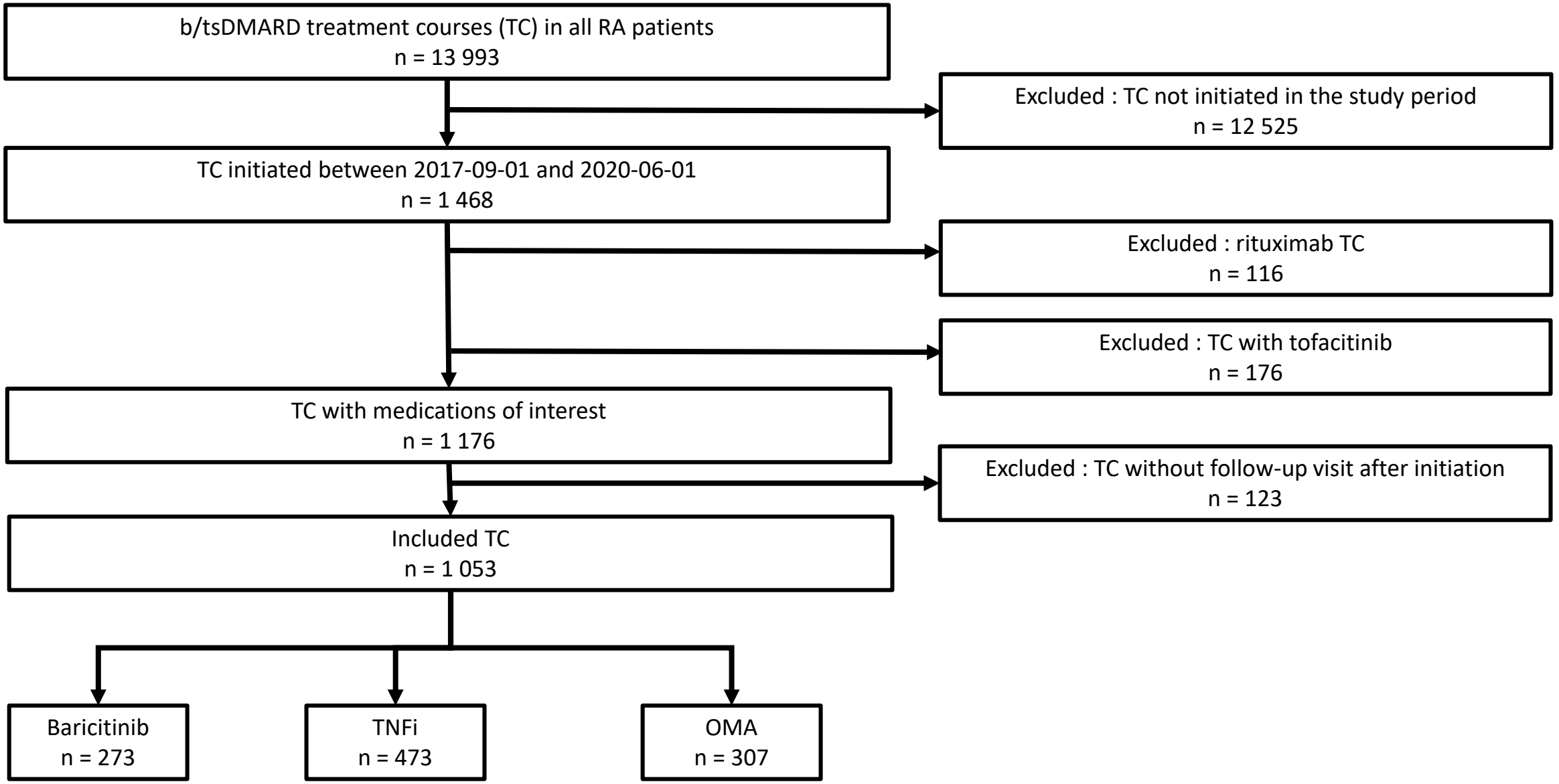
Figure 4 - Cumulative incidence of drug discontinuation by stop reason and by type of treatment, SCQM, 2017-2020.

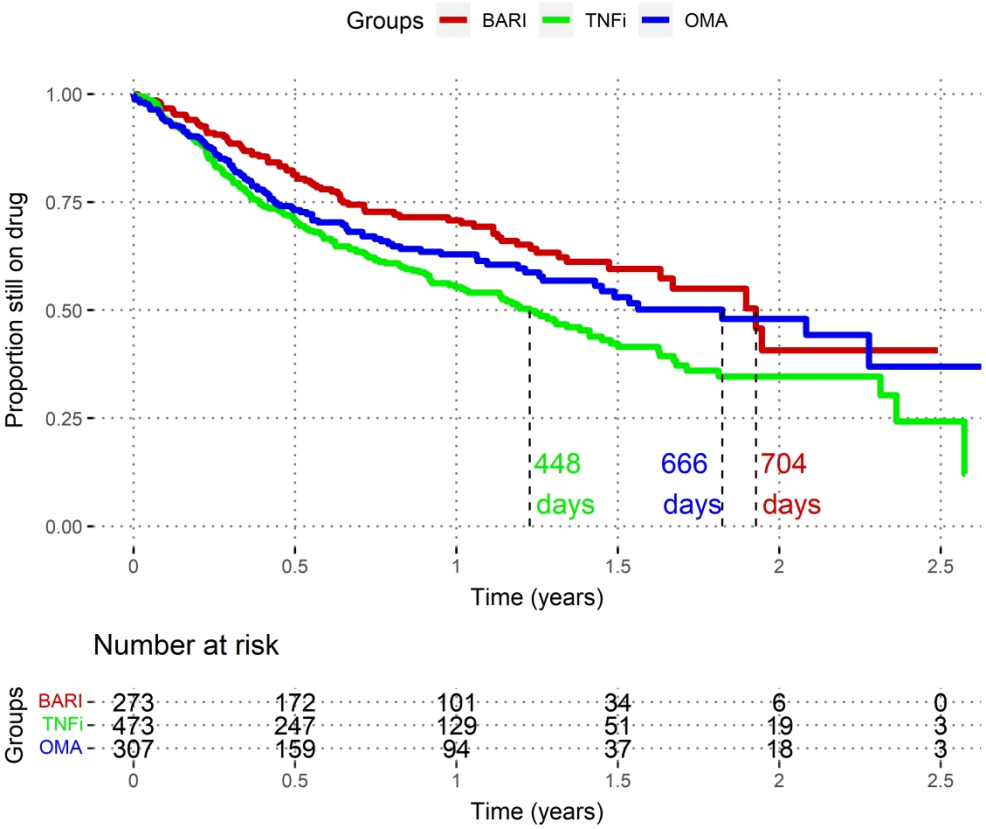
This figure represents the unadjusted cumulative incidence of drug discontinuation, by group and by reason of discontinuation. BARI = baricitinib. TNFi = Tumor Necrosis Factor. OMA = Other mode of Action bDMARDs.

Figure 5 - Estimated response rates at 12-months (CARRAC), SCQM, 2017-2020.

BARI = baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other Mode of Action bDMARDs. LDA = Low Disease Activity (i.e. CDAI score <= 10), in light grey. REM = Remission (i.e. CDAI score <= 2.8), in dark grey. 95% CI are represented. This method does not allow computing p-values. Nb: two estimates were obtained in the BARI group and averaged to display only one representative value on the plot. Actual row output was 68% (95%CI [55% ; 80%]) (BARI vs TNFi model) or 62% (95% CI [54% ; 70%]) (BARI vs OMA model) for LDA, and 23% (95% CI [14% ; 31%]) (BARI vs TNFi model) or 17 % (95% CI [10% ; 24%]) (BARI vs OMA model) for REM.

Selection of eligible treatment courses (TC)





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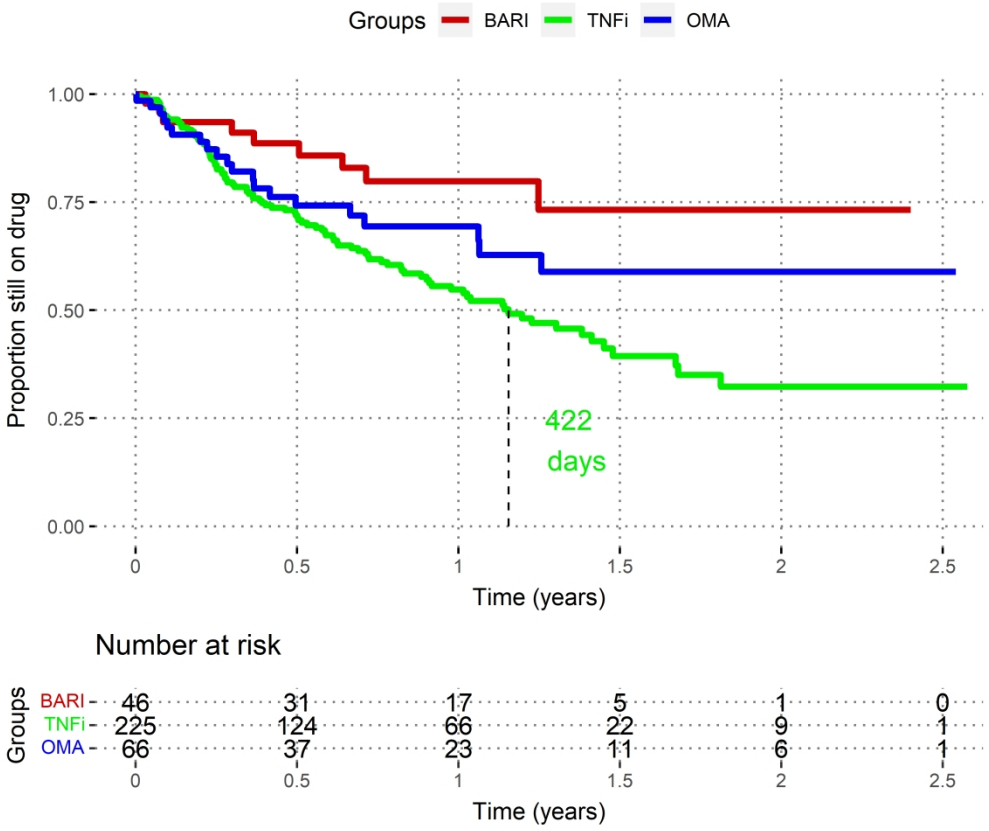

Figure 3 - Unadjusted time to drug discontinuation in b/tsDMARD-naïve patients, SCQM, 2017-2020. These Kaplan-Meier curves represent the crude "survival" of drug prescription, by treatment group. Death and loss to follow-up are censored. BARI = baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : p = 0.003. Log-Rank BARI vs OMA : p = 0.15.

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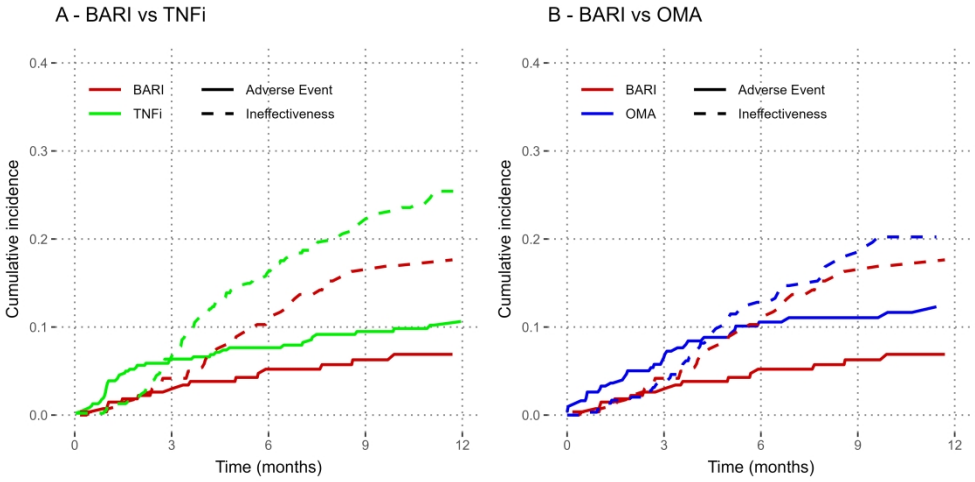

Figure 4 - Cumulative incidence of drug discontinuation by stop reason and by type of treatment, SCQM, 2017-2020.
This figure represents the unadjusted cumulative incidence of drug discontinuation, by group and by reason of discontinuation. BARI = baricitinib. TNFi = Tumor Necrosis Factor. OMA = Other mode of Action bDMARDs.

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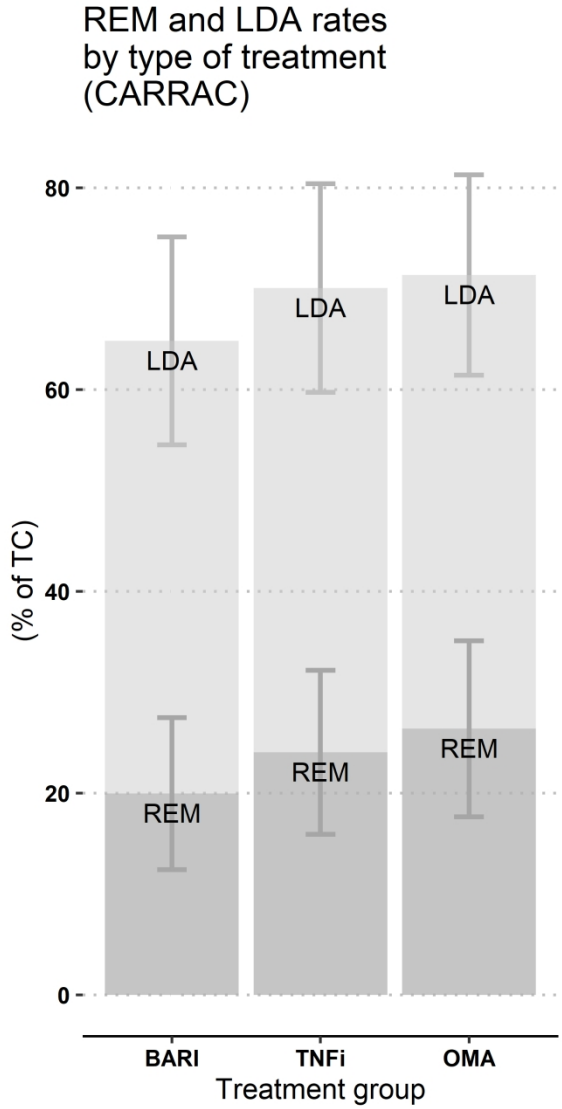

Figure 5 - Estimated response rates at 12-months (CARRAC), SCQM, 2017-2020.
BARI = baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other Mode of Action bDMARDs. LDA = Low Disease Activity (i.e. CDAI score <= 10), in light grey. REM = Remission (i.e. CDAI score <= 2.8), in dark grey. 95% CI are represented. This method does not allow computing p-values. Nb: two estimates were obtained in the BARI group and averaged to display only one representative value on the plot. Actual row output was 68% (95%CI [55% ; 80%]) (BARI vs TNFi model) or 62% (95% CI [54% ; 70%]) (BARI vs OMA model) for LDA, and 23% (95% CI [14% ; 31%]) (BARI vs TNFi model) or 17 % (95% CI [10% ; 24%]) (BARI vs OMA model) for REM.

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SUPPLEMENTARY DATA

Notice on TC duration

Due to frequent changes in medication and short study period, it has to be underlined that the median duration of a TC approximates 200 days. The proportion of TC with follow-up data of at least one year is 37% for BARI, 27% for TNFi and 31% for OMA (Figure S1) - i.e. most TC were started less than 12 months before the date of data extraction.

Notice this % is different from the % of patient still under therapy that we estimate using Kaplan-Meier or Cox model. Indeed, the latter includes a censoring of the lost-to-follow-up patients, hence the denominator is different. As a consequence, this does not contradict the reported "median prescription survival timey", for instance of 704 days for BARI TCs. The latter is the output estimated by the Kaplan-Meier model, taking censoring into account; it does not imply that actual observations in the dataset have this duration.

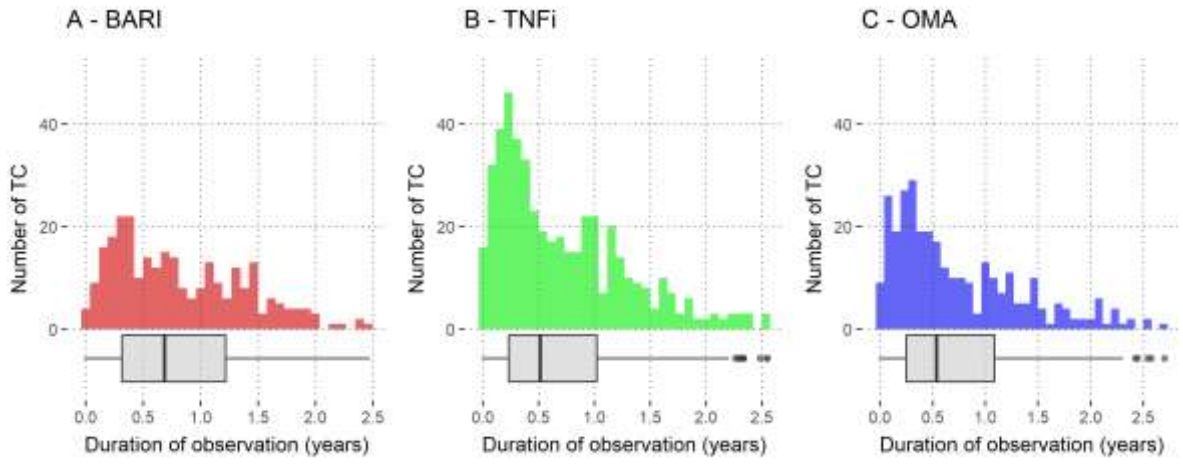

Figure S1: Distribution of the observation time for included TCs, per group, SCQM, 2017-2020. Most of the treatment courses have an actual duration and/or follow-up period of less than one year. TC = Treatment Course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs.

Variable definitions

Below we give additional detail about included covariates:

Age: age in years, at TC initiation. Continuous variable.

Gender: male or female. Categorical variable.

BMI: BMI at TC initiation. Continuous variable.

CDAI score: CDAI score at TC initiation. Continuous variable. If missing, imputed according to procedure described in methods section.

Disease duration: time interval between RA diagnosis date and TC initiation date. Continuous variable, expressed in years, but used in decades in models.

Smoking status: smoking status at TC initiation. Categorical variable (current-, former-, never-smoker).

Concomitant csDMARD: yes/no variable. A concomitant csDMARD was defined as csDMARD prescription ongoing for at least 40% of the duration of the TC. Otherwise, the TC was categorized as monotherapy. csDMARDs included: methotrexate, sulfasalazin, leflunomide, azathioprine and hydroxy-chloroquine, alone or in combination.

Concomitant glucocorticoid: Yes/no variable. Concomitant glucocorticoid usage was defined as having at least one active prescription of glucocorticoid, at any dose, at any timepoint of the TC.

Line of therapy: strictly speaking, this categorical variable is displaying: [*number of previous TC ever* + 1]. 4 or more has been grouped in the same category. Hence, it is considering all data of the SCQM registry, i.e. TCs initiated before our study period are also accounted for as previous therapies.

Seropositivity: yes/no variable. Seropositivity is defined as positivity for anti-citrullinated peptide antibodies and/or rheumatoid factor.

Time to all cause discontinuation

Cox model output

Table S1 contains the complete output of the two adjusted Cox models used in the main time-to-drug discontinuation analysis.

Table S1: Hazard ratio of drug discontinuation, Cox models, SCQM-RA registry, 2017-2020.

	BARI vs TNFi			**BARI vs OMA**		
	Hazard ratio	**95% CI**	**p**	**Hazard ratio**	**95% CI**	**p**
TNFi (vs baricitinib)	1.76	1.32-2.35	**<0.001**	-	-	-
OMA (vs baricitinib)	-	-	-	1.27	0.93-1.72	0.13
Adjusting variables:						
Age (decades)	1.03	0.92-1.14	0.61	0.98	0.86-1.10	0.69
BMI	1.01	0.98-1.04	0.51	0.98	0.94-1.02	0.31
TC with csDMARD	0.84	0.66-1.09	0.19	1.22	0.90-1.67	0.20
Glucocorticoid usage	1.29	0.93-1.79	0.12	1.86	1.32-2.61	**<0.001**
CDAI score	1.40	1.26-1.56	**<0.001**	1.15	1.03-1.28	**0.01**
Disease duration (decades)	0.95	0.81-1.10	0.46	0.85	0.70-1.03	0.10
Current smoker (vs non-smoker)	1.20	0.86-1.68	0.28	1.09	0.73-1.64	0.66
Ever smoker (vs non-smoker)	1.10	0.79-1.52	0.57	1.38	0.95-2.00	0.09
2nd line therapy (vs 1st)	1.11	0.80-1.53	0.52	1.37	0.81-2.33	0.24
3rd line therapy (vs 1st)	0.98	0.64-1.51	0.93	1.56	0.92-2.64	0.10
4th or later line (vs 1st)	1.06	0.75-1.51	0.73	1.57	0.93-2.63	0.09
Female gender	1.05	0.78-1.42	0.74	1.16	0.81-1.67	0.41
Seropositivity	0.77	0.59-1.01	0.055	0.94	0.67-1.31	0.71

Table S1: BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. CI = Confidence Interval. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index.

Figure S2 below gives the exact same information as Table S1:

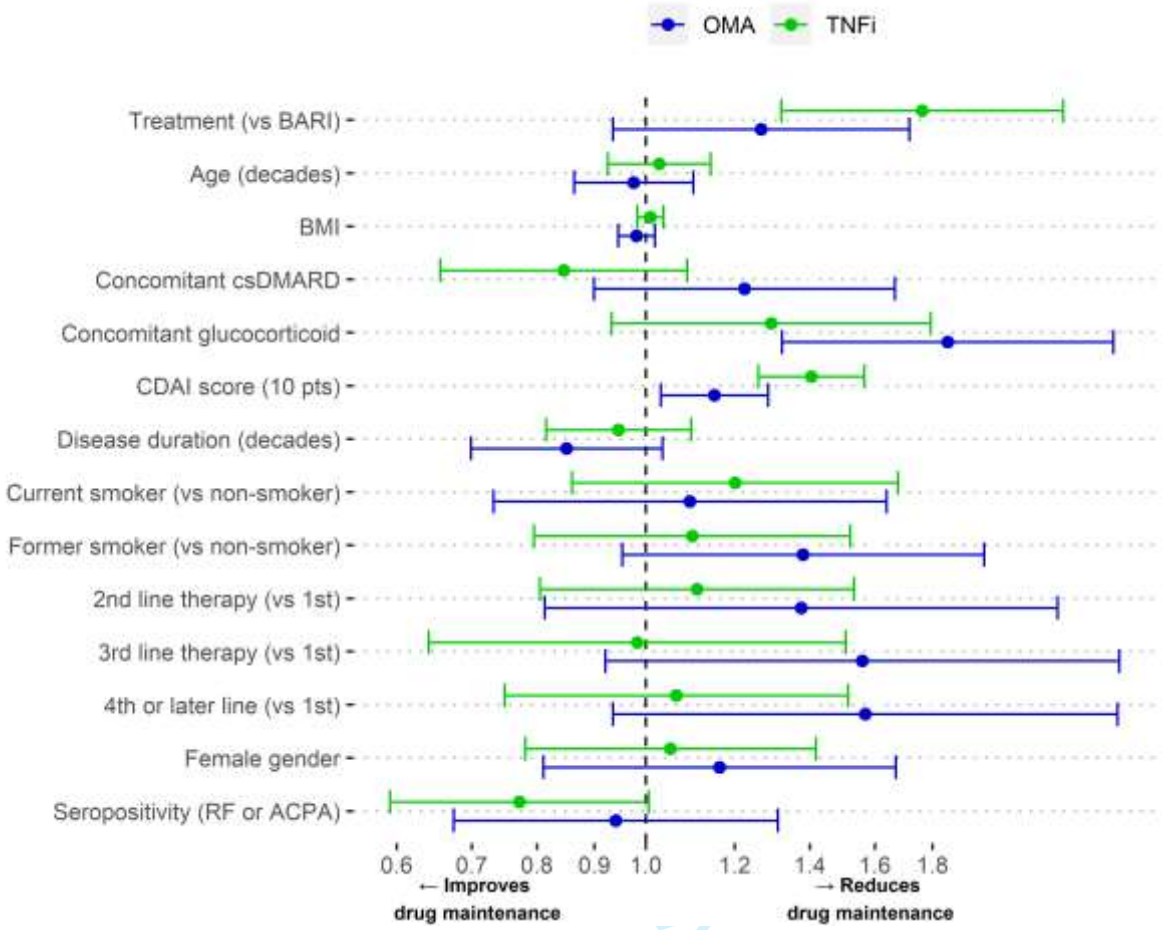

Figure S2: Hazard ratio of drug discontinuation (95% CI).

BARI = Baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other mode of Action bDMARDs. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index. RF = Rheumatoid Factor. ACPA = Anti-citrullinated Peptides Antibodies.

The corresponding cox-adjusted drug-survival curves are provided below:

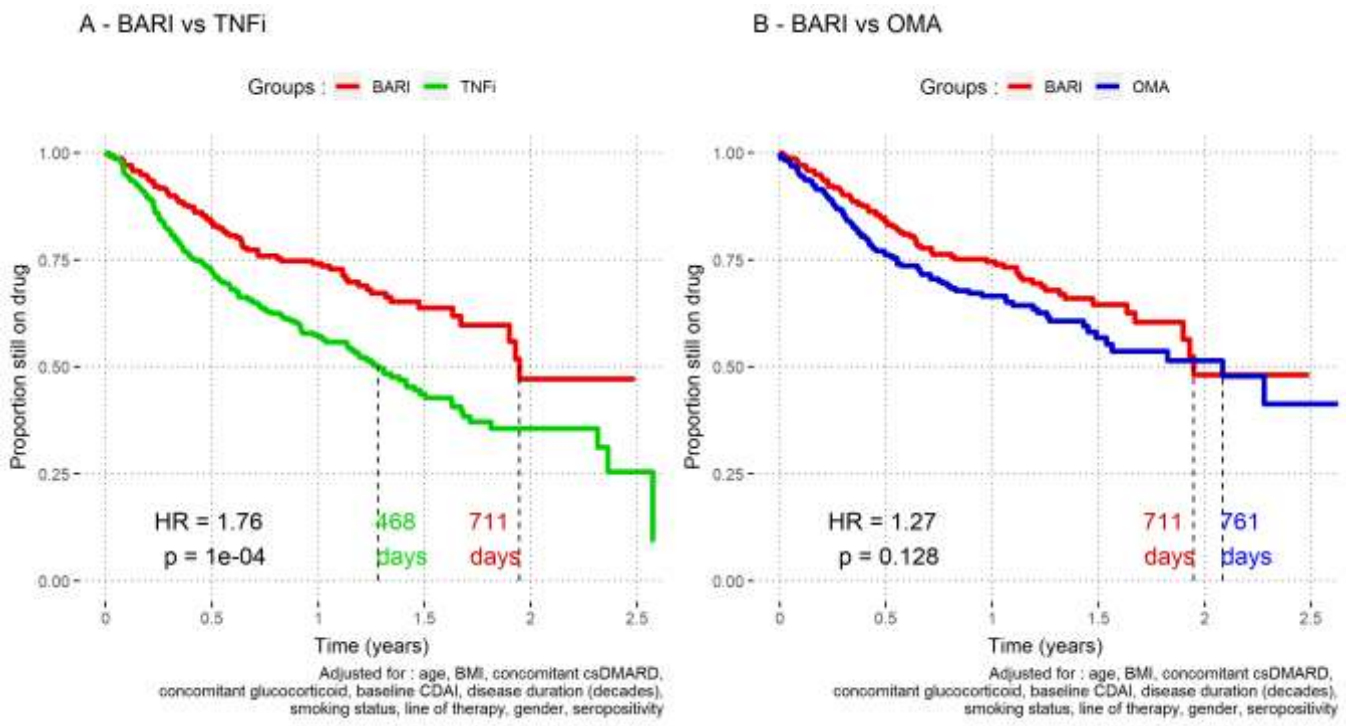

Figure S3: Multivariable Cox model of drug discontinuation by type of treatment, SCQM, 2017-2020.

These curves are merlely the visualisation of Cox models presented in Table S1 and Figure S2.

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action bDMARDs

Models are adjusted for : age, BMI, concomitant csDMARD, concomitant glucocorticoïd, baseline CDAI, disease duration, smoking status, line of therapy, gender, serpostivity.

Sensitivity analysis using AIPTW

As a sensitivity analysis, the main time to drug discontinuation was also performed using "augmented inverse probability of treatment weighting" (AIPTW), including the same covariates. In other words, we combined a propensity score using a logistic regression model and an inverse probability weighted Cox regression. We used the *RiskRegression* package in R, to obtain risk ratios.

Figure S4 represents the absolute risk of treatment discontinuation, for all included timepoints. At one year, the adjusted discontinuation risk in BARI was 19 % lower than in TNFi group (p<0.001) (Figure S4 A), with a risk ratio of 1.76 (95% CI [1.19 – 2.34]; p=0.009). Similarly, at one year, the adjusted treatment discontinuation risk in BARI was 8 % lower than in the OMA group (p=0.06) (Figure S4 B), with a risk ratio of 1.28 (95% [0.91 – 1.65]; p=0.14).

Overall, this sensitivity analysis confirms the findings reported in the main body of the article.

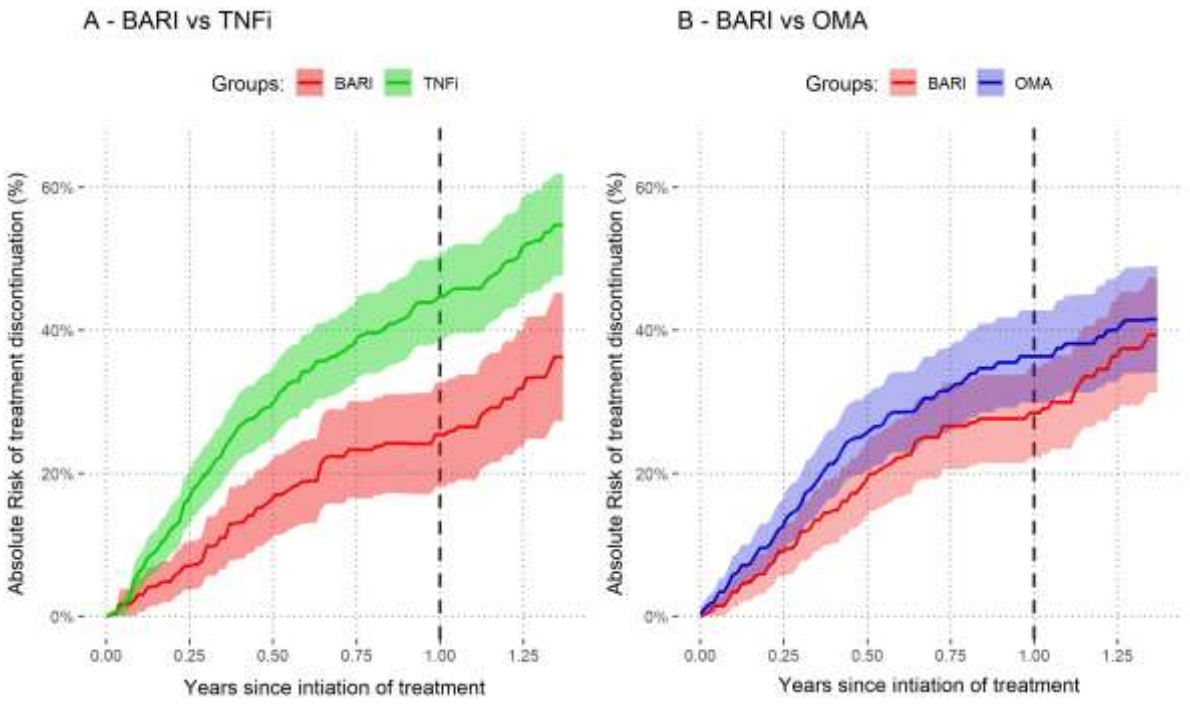

Figure S4: Absolute risk of treatment discontinuation by type of treatment (AIPTW), SCQM, 2017-2020)

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inihibitors. OMA = Other Modes of Action bDMARDs. AIPTW = Augmtented Inverse Probability of Treatment Weigthning. Adjusted for : age, bmi, concomitant csDMARDs, prednisone usage, baseline CDAI, disease duration, smoking status, line of therapy, gender, seropositivity.

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

Table S2: Baseline characteristics of study population, b/tsDMARD-naïve patients, SCQM-RA registry, 2017-2020.

	BARI (n = 46)		**TNFi (n = 225)**		**OMA (n = 66)**		**p values**
	n % Otherwise: Mean (SD)						
Patient-Variables		Miss.		Miss.		Miss.	
Female	70 %	0	71 %	1	73 %	1	0.88
Age (years)	57 (15)	0	52 (14)	1	57 (16)	1	<0.01
Disease duration (years)	6 (6)	1	5 (7)	13	7 (9)	2	0.24
CDAI baseline (raw data)	16 (8)	31	18 (10)	135	18 (14)	42	0.77
CDAI baseline (imputed)	12 (7)	0	14 (9)	0	14 (10)	0	0.61
Obesity (BMI > 30)	11 %	13	13 %	58	5 %	27	0.28
Smoking Current Former Never	 28 % 26 % 26 %	9	 18 % 24 % 39 %	42	 14 % 21 % 46 %	13	0.18
Seropositive (ACPA or RF)	80 %	1	69 %	5	76 %	2	0.20
TC variables							
Dose of BARI (4mg)	83 %	0	-	-	-	-	-
TC duration > 12-months	37 %	0	29 %	0	35 %	0	0.48
Concomitant csDMARD	41 %	0	66 %	0	50 %	0	<0.01
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	100 %	0	100 %	0	100 %	0	-
Previous tsDMARD use (non-BARI)	0 %	0	0 %	0	0 %	0	-
Concomitant glucocorticoid (at any time)	13 %	0	20 %	0	17 %	0	0.50
Mean dose of concomitant glucocorticoid (mg)	1 (4)	0	3 (6)	0	2 (6)	0	0.50

Table S2: BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. p-value are computed with either Chi^2 or ANOVA.

Response rates – raw CDAI data

Figure S6 shows the crude available values for CDAI scores, by type of treatment and time. Only a minority of CDAI scores were assessed at 0- or 12-month timepoints of TCs (i.e. 680/1053 = 65% were missing for baseline value, and 908/1053 = 86% were missing for exact 12-month value). Future research would certainly benefit having CDAI scores assessed at regular and homogenous time-intervals, based on the initiation date of biological therapies.

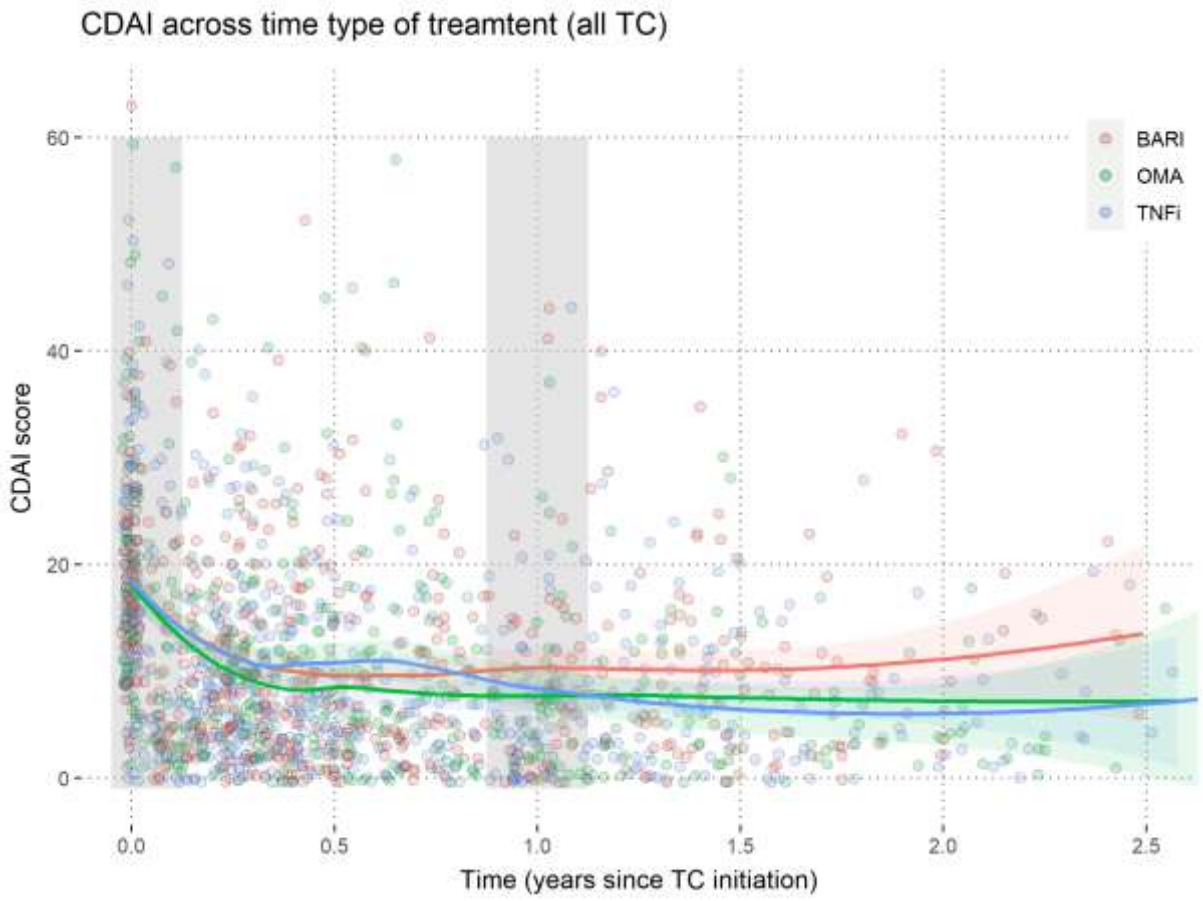

Figure S5: CDAI across time by type of treatment, raw data, SCQM, 2017-2020.

Only a minority of CDAI score were obtained sharp at 0 or 12 months of TCs. CDAI = Clinical Disease Activity Index. TC = Treatment course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action b/tsDMARDs.

Study size

Based on estimates from similar analyses with tofacitinib (TOFA) performed in this registry, we calculated the number of patients that would be needed to detect a significant decrease in time to all cause-discontinuation of treatment (hazard ratio) between treatment groups using the method described by Schoenfeld and Richter. We assumed a statistical power of 80%, a type I error probability of 0.05, a median BARI retention of 30 months, the inclusion of 3 patients on TNFi for every patient on BARI, an accrual time of 2 years, and additional follow-up of 6 months. We display below the sample size for the BARI group for a range of possible effect sizes ("hazard ratio" between 1.1 and 1.8).

If the true hazard ratio is similar to the one found with TOFA compared to TNFi after a single TNFi failure (HR:1.68) 14, we will need to study 149 patients on BARI and 447 patients on TNFi to be able to reject the null hypothesis that the experimental and control curves are equal with probability (power) of 80%. Pragmatically, we propose to start the analysis of the data only once at least 200 patients on BARI have been included and followed for an average of at least 18 months.

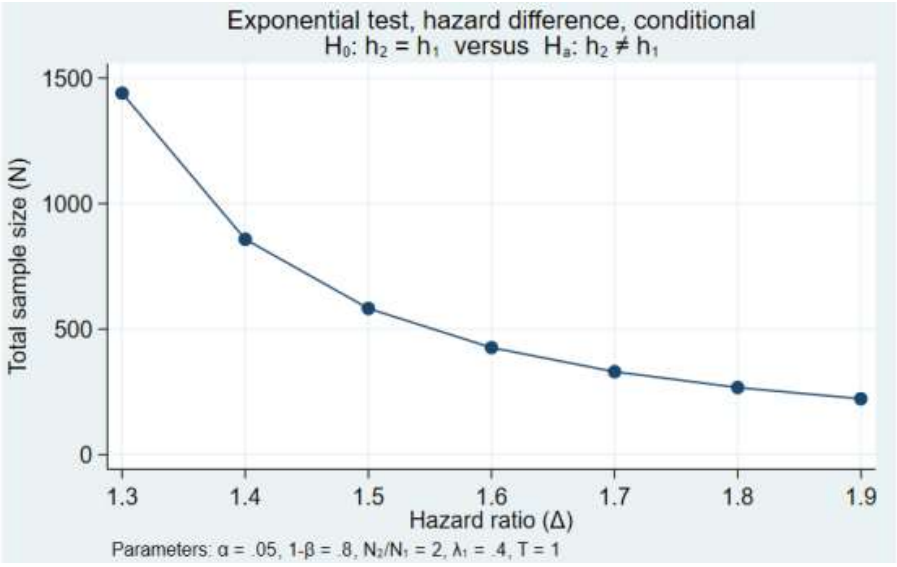

Figure 1: Estimated total sample size for two-sample comparison of survivor functions

1 - SURVIVAL ANALYSIS

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(gridExtra)
library(grid)
library(cmprsk)
library(mstate)
library(cobalt)

rm(list = ls()) # To select all loaded objects and delete them
setwd(dirname(rstudioapi::getActiveDocumentContext()$path)) # setting
up working directory in the location of the .Rmd file

load("./1_datamanaged_files/datamanaged.Rdata") # loading data.managed
data
```

Loading fonctions

```
# home-made function to force writing with two decimals
formattable = function(nbr){return(formatC(nbr,format = "f",digits =
nombreapresvirgule))}
nombreapresvirgule <- 2

# Home-made Fonction to write the p value (by denis)
writepvalue = function(pvalue) {
  if (is.na(pvalue)) {result <- NA} else {
    if(pvalue < 0.001) {
```

```
      result <- "<0.001"
    } else if (pvalue <0.01) {
      result <- formatC( pvalue ,format = "f",digits = 3)
    }
    else {
      (result <- formatC( pvalue ,format = "f",digits = 2) )
      i = 1
      while(result == 0.05) {
        result <- formatC( pvalue ,format = "f",digits = 2 + i)
        i = i + 1
      }}
    return(result)
  }
}
options(scipen = 999)
```

Mini Exploration

```
uniqueN(BARI_DATA[]$patient_id) # number of patients (< than number of
TC)
uniqueN(BARI_DATA[]$TC_id) # unmber of TC

plot <- qplot(x = BARI_DATA[]$time_on_drug)+
  geom_vline(xintercept = 365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 365 + 40, label="1 Year", y=20), colour="white",
angle=0)+

  geom_vline(xintercept = 2*365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 2*365 + 40, label="2 Year", y=20), colour="black",
angle=0)+

  geom_vline(xintercept = mean(BARI_DATA$time_on_drug), color = "red",
size = 1.2)+
  geom_text(aes(x = mean(BARI_DATA$time_on_drug) + 40, label="Mean",
y=20), colour="red", angle=0)+

  geom_vline(xintercept = median(BARI_DATA$time_on_drug), color =
"green", size = 1.2)+
  geom_text(aes(x = median(BARI_DATA$time_on_drug) - 40,
label="Median", y=20), colour="green", angle=0)+

  labs(x = "Duration of TC (days)", y = "Number of TC", title =
"Repartition of the duration of included TC (all groups)")+

  theme_pubclean()

plot

mean(BARI_DATA$time_on_drug)
```

```
median(BARI_DATA$time_on_drug)

# Nb : Research protocol said we wanted a follow-up duration of
"average of 18 months"
mean(BARI_DATA[cohort == "BARI"]$time_on_drug)/30
mean(BARI_DATA[cohort == "TNFi"]$time_on_drug)/30
mean(BARI_DATA[cohort == "OMA"]$time_on_drug)/30 # looks more like 9
months..

# ok, 24-month follow-up will be complicated
uniqueN(BARI_DATA[time_on_drug > 2*365, TC_id]) # number if TC with
duration > 24 months
```

1. [0] Table 1 BARI vs TNFi et OMA bDMARDs

Common table with all the data

Showing NA to have complete counts and accurate % in each category

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving table 1 NA

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1_NA.xlsx")
```

Without NA to obtain adequate p values

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
```

```
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving table 1

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1.xlsx")
```

But BMJ-Open reviewer 2 aksed for p-values in Table 1 that account for patients providing multiple TCs. Here is how to proceed (it is a bit less conservative):

```
library(lme4)
library(lmerTest)

# Two glmer() models have to be compared, to assess the impact of
grouping, for each baseline variable).

# gender
gender.tab1 <- glmer(gender ~ cohort + (1|patient_id), data =
BARI_DATA , family = "binomial")
gender.null <- glmer(gender ~ (1|patient_id), data = BARI_DATA ,
family = "binomial")
anova(gender.tab1, gender.null)

# Age_base
age_base.tab1 <- lmer(age_base ~ cohort + (1|patient_id), data =
BARI_DATA )
age_base.null <- lmer(age_base ~ (1|patient_id), data = BARI_DATA)
anova(age_base.tab1, age_base.null)

# Disease duration
disease_duration_base_years.tab1 <- lmer(disease_duration_base_years ~
cohort + (1|patient_id), data = BARI_DATA )
```

```
disease_duration_base_years.null <- lmer(disease_duration_base_years ~
(1|patient_id), data = BARI_DATA)
anova(disease_duration_base_years.tab1,
disease_duration_base_years.null)


# CDAI raw
CDAI0_raw.tab1 <- lmer(CDAI0_raw ~ cohort + (1|patient_id), data =
BARI_DATA )
CDAI0_raw.null <- lmer(CDAI0_raw ~ (1|patient_id), data = BARI_DATA)
anova(CDAI0_raw.tab1, CDAI0_raw.null)


# CDAI (imputed)
CDAI0.tab1 <- lmer(CDAI0 ~ cohort + (1|patient_id), data = BARI_DATA )
CDAI0.null <- lmer(CDAI0 ~ (1|patient_id), data = BARI_DATA)
anova(CDAI0.tab1, CDAI0.null)


# obesity
obese_base.tab1 <- glmer(obese_base ~ cohort + (1|patient_id), data =
BARI_DATA , family = "binomial")
obese_base.null <- glmer(obese_base ~ (1|patient_id), data = BARI_DATA
, family = "binomial")
anova(obese_base.tab1, obese_base.null)


# smoker base - 1st level vs second level
smoker_base.tab1 <- glmer(smoker_base ~ cohort + (1|patient_id), data
= BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "FORMER_SMOKER")]  ,
family = "binomial")
smoker_base.null <- glmer(smoker_base ~ (1|patient_id), data =
BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "FORMER_SMOKER")]  ,
family = "binomial")
anova(smoker_base.tab1, smoker_base.null)


# smoker base - 2nd level versus third
smoker_base.tab1 <- glmer(smoker_base ~ cohort + (1|patient_id), data
= BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "NEVER_SMOKER")]  ,
family = "binomial")
smoker_base.null <- glmer(smoker_base ~ (1|patient_id), data =
BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "NEVER_SMOKER")]  ,
family = "binomial")
anova(smoker_base.tab1, smoker_base.null)


# seropositivity
seropositivity_base.tab1 <- glmer(seropositivity_base ~ cohort + (1|
```

```
patient_id), data = BARI_DATA , family = "binomial")
seropositivity_base.null <- glmer(seropositivity_base ~ (1|
patient_id), data = BARI_DATA , family = "binomial")
anova(seropositivity_base.tab1, seropositivity_base.null)


# Concomittant csDMARD
TC_with_csDMARD.tab1 <- glmer(TC_with_csDMARD ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
TC_with_csDMARD.null <- glmer(TC_with_csDMARD ~ (1|patient_id), data =
BARI_DATA , family = "binomial")
anova(TC_with_csDMARD.tab1, TC_with_csDMARD.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "2nd")]
, family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "2nd")] ,
family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "3rd")]
, family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "3rd")] ,
family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st",
"4th_or_later")] , family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st",
"4th_or_later")] , family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# N_prev_tsDMARD
N_prev_tsDMARD.tab1 <- glmer(as.factor(N_prev_tsDMARD) ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
N_prev_tsDMARD.null <- glmer(as.factor(N_prev_tsDMARD) ~ (1|
patient_id), data = BARI_DATA , family = "binomial")
```

```
anova(N_prev_tsDMARD.tab1, N_prev_tsDMARD.null)


# Concomittant prednisone
PREDNISON_STEROID.tab1 <- glmer(PREDNISON_STEROID ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
PREDNISON_STEROID.null <- glmer(PREDNISON_STEROID ~ (1|patient_id),
data = BARI_DATA , family = "binomial")
anova(PREDNISON_STEROID.tab1, PREDNISON_STEROID.null)


# Dose of PREDNISONE
PREDNISON_STEROID_dose.tab1 <- lmer(PREDNISON_STEROID_dose ~ cohort +
(1|patient_id), data = BARI_DATA )
PREDNISON_STEROID_dose.null <- lmer(PREDNISON_STEROID_dose ~ (1|
patient_id), data = BARI_DATA)
anova(PREDNISON_STEROID_dose.tab1, PREDNISON_STEROID_dose.null)
```

Other various computations for Table 1 —-

```
uniqueN(BARI_DATA$patient_id)

mean(BARI_DATA[, time_on_drug])

median(BARI_DATA[cohort == "Bari" , time_on_drug])
median(BARI_DATA[cohort == "OMA" , time_on_drug])
median(BARI_DATA[cohort == "TNFi" , time_on_drug])

median(BARI_DATA[cohort == "OMA"]$time_on_drug)

mean(BARI_DATA[,disease_duration_base_years], na.rm = T)

table(is.na(BARI_DATA$CDAI0_raw), BARI_DATA$cohort) # number of
missing CDAI0_raw...
table(is.na(BARI_DATA$CDAI0), BARI_DATA$cohort) # number of missing
CDAI0... (after imputation)

table(is.na(BARI_DATA$CDAI12_raw), BARI_DATA$cohort) # number of
missing CDAI12_raw...
table(is.na(BARI_DATA$CDAI12), BARI_DATA$cohort) # number of missing
CDAI12 after imputation

hist(BARI_DATA$CDAI0_raw)
hist(BARI_DATA$CDAI0)

summary(BARI_DATA[cohort=="BARI", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
```

```
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="TNFi", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="OMA", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID", "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

table(is.na(BARI_DATA$disease_duration_base_years), BARI_DATA$cohort)
# number of missing disease duration...

table(is.na(BARI_DATA$age_base), BARI_DATA$cohort) # number of steroid
doses missing

table(is.na(BARI_DATA$PREDNISON_STEROID_dose), BARI_DATA$cohort) #
number of missing baseline steroids
```

Imputation using MICE —- BARI vs TNFi et OMA bDMARDs —-

Common imputation step with all data

```
BARI <- BARI_DATA[,c("TC_id", "patient_id", "stop_DMARD",
"stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0", "disease_duration_base_years", "time_on_drug", "bmi_base",
"smoker_base", "line_of_therapy", "obese_base", "gender", "cohort",
"adverse_event_reported", "seropositivity_base")] # choose variables
of interest

BARI$smoker_base <- as.factor(BARI$smoker_base) # put labels as factor
BARI$line_of_therapy <- as.factor(BARI$line_of_therapy)
BARI$gender <- as.factor(BARI$gender)
BARI$concomitant_csDMARD <- as.factor(BARI$concomitant_csDMARD)
BARI$PREDNISON_STEROID <- as.factor(BARI$PREDNISON_STEROID)
BARI$cohort <- as.factor(BARI$cohort)

# Imputation

if(!file.exists("./2_cached_files/imputed_data")){ # to avoid re-
```

```
computing if alsready done
  imputed_data <- mice(BARI, m=50, method="pmm", maxit=25, seed=500)
  save(imputed_data, file = "./2_cached_files/imputed_data")
} else {
  load("./2_cached_files/imputed_data")
}

# Subsettings

BARI1 <- BARI[cohort %in% c("BARI", "TNFi")] # creating subset for
BARI vs TNFi comparaison
BARI1[,cohort := as.factor(as.character(cohort))]

imputed_data1 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data1 <- imputed_data1[imputed_data1$cohort %in% c("BARI",
"TNFi"),] # to keep only BARI and TNFi rows
imputed_data1$cohort <- as.factor(as.character(imputed_data1$cohort))
imputed_data1 <- as.mids(imputed_data1) # re concateneting in previous
format, to use fit.mult.impute


BARI2 <- BARI[cohort %in% c("BARI", "OMA")] # creating subset for BARI
vs OMA comparaison
BARI2[,cohort := as.factor(as.character(cohort))]

imputed_data2 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data2 <- imputed_data2[imputed_data2$cohort %in% c("BARI",
"OMA"),] # to keep only BARI and OMA rows
imputed_data2$cohort <- as.factor(as.character(imputed_data2$cohort))
imputed_data2 <- as.mids(imputed_data2) # re concateneting in previous
format, to use fit.mult.impute
```

1. [1] SURVIVAL ANALYSIS (drug discontinuation)

Exploration

```
table(BARI_DATA$cohort, BARI_DATA$stop_DMARD)
table(BARI_DATA$cohort, BARI_DATA$stop_reasons)
```

Checking adequacy of COX models —-

For BARI vs TNFi

```
# categorization for linearity checking
test1 <- complete(imputed_data1,"long", include=T) # to put in long
format and categorize variables
```

```
test1$agecat <- cut(test1$age_base, 4)
test1$bmicat <- cut(test1$bmi_base, 4)
test1$cdaicat <- cut(test1$CDAI0, 4)
test1$duracat <- cut(test1$disease_duration_base_years, 4)

test1 <- as.mids(test1, .imp=1, .id=2) # re concateneting in previous
format, to use fit.mult.impute

# linearity checking

BARI1.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                        I(agecat)+
                                        I(bmicat)+
                                        TC_with_csDMARD+
                                        PREDNISON_STEROID+
                                        I(cdaicat)+
                                        I(duracat)+
                                        C(smoker_base, base=3)+
                                        line_of_therapy+
                                        gender+
                                        seropositivity_base+
                                        cluster(patient_id),
                                      fitter = coxph, xtrans = test1,
data = BARI1)

summary(BARI1.adj.mi.test)
rm(BARI1.adj.mi.test)

# Log-linearity of coefficients ?

# Coefs age are between 0.15 and 0.25, let's assume it's ok
# Hum bmi coefs are not so log-linear, rather close to 0
# For CDAI also
# Looks ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test1ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                         data= BARI1)
cox.zph(test1ph) # it's ok

# Hazard proportionality test on imputed data sets

test1 <- complete(test1,"long",include=T) # To reset the charges to
```

```
long format
test1 <- test1[test1$.imp==1 | test1$.imp==2 |  test1$.imp==3 |
test1$.imp==4 | test1$.imp==5 ,] # To select only 5 data sets

test1ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
~ as.factor(cohort)+
                          I(age_base/10)+
                          bmi_base+
                          TC_with_csDMARD+
                          PREDNISON_STEROID+
                          CDAI0+
                          I(disease_duration_base_years/10)+
                          C(smoker_base, base=3)+
                          line_of_therapy+
                          gender+
                          seropositivity_base+
                          cluster(patient_id),
                        data = test1)

cox.zph(test1ph.adj.mi)

schonfeldall <- cox.zph(test1ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test1ph.adj.mi, test1)
```

For BARI vs OMA

```
# categorization for linearity checking
test2 <- complete(imputed_data2,"long", include=T) # to put in long
format and categorize variables

test2$agecat <- cut(test2$age_base, 4)
test2$bmicat <- cut(test2$bmi_base, 4)
test2$cdaicat <- cut(test2$CDAI0, 4)
test2$duracat <- cut(test2$disease_duration_base_years, 4)

test2 <- as.mids(test2, .imp=1, .id=2) # re concateneting in previous
format, to use fit.mult.impute

# linearity checking

BARI2.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                       I(agecat)+
                                       I(bmicat)+
```

```
                                          TC_with_csDMARD+
                                          PREDNISON_STEROID+
                                          I(cdaicat)+
                                          I(duracat)+
                                          C(smoker_base, base=3)+
                                          line_of_therapy+
                                          gender+
                                          seropositivity_base+
                                          cluster(patient_id),
                                        fitter = coxph, xtrans = test2,
data = BARI2)

summary(BARI2.adj.mi.test)
rm(BARI2.adj.mi.test)

# Log-linearity of coeficients ?

# Coefs age are around -0.4, let's assume it's ok
# Hum bmi coefs are discusable
# For CDAI it's ok
# More or less ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test2ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                         data= BARI2)
cox.zph(test2ph) # it's ok


# Hazard proportionality test on imputed data sets

test2 <- complete(test2,"long",include=T) # To put imputed data in
ling format
test2 <- test2[test2$.imp==1 | test2$.imp==2 |  test2$.imp==3 |
test2$.imp==4 | test2$.imp==5 ,] # To select only 5 datasets

test2ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
~ as.factor(cohort)+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
```

```
                          line_of_therapy+
                          gender+
                          seropositivity_base+
                          cluster(patient_id),
                        data=test2)

cox.zph(test2ph.adj.mi)

schonfeldall <- cox.zph(test2ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test2ph.adj.mi, test2)
```

BARI vs TNFi —-

COX model

Final Cox Model

```
BARI1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort +
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data1,
data = BARI1)

summary(BARI1.adj.mi)
```

Creation of HR table and p-values

```
ploufrows <- names(BARI1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI1.adj.mi)
```

```
for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",
formattable(plouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("TNFi (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid", "CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_1 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs TNFi")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
```

```
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_1

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R

BARI vs TNFi

```
surv_object1 <- Surv(time = BARI1$time_on_drug, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
summary(coxph(surv_object1 ~ cohort, data=BARI1))
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1) # this function
creates the data for Kaplan Meyer
fit1
survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib","TNFi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10"),
           palette = c("red2", "green3"), # specify colors
           risk.table = T)
survplot_1
summary(fit1, times = 365)
summary(fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs TNFi",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib","TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey10")
           palette = c("red2", "green3") # to change colors
           )

# adding some legends
survplot_1_adj <- survplot_1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_1_adj
# summary(BARI_fit1) # to see detailed surv probabilities at given
timepoints
```

```
summary(BARI_fit1, times = 365)
summary(BARI_fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data_adj <- survplot_1_adj$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA
library(riskRegression)

# I select only one imputed dataset. Would be even better to find a
way to pool/average the results from the 50 imputed datasets, but it
does not seem doable by default
test.data <- complete(imputed_data1, 1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment <- glm(cohort~I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
```

```
                                    seropositivity_base,
                                    data = test.data, x = TRUE, y =
TRUE)

m.censor <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base
                                    , x =TRUE, y = TRUE,
                                    data = test.data)


# And we measure the average treatment effect using function "ate",
specifying the time at which we want to compute the ATE

out <- ate(event = m.event ,
             treatment = m.treatment,
             censor = m.censor,
             data = test.data,
             cause = 1,
             estimator = "AIPTW",
             times = seq(from = 0, to = 500, by = 5))

dt.out <- as.data.table(out)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data$pscores <- m.treatment$fitted.values
test.data %>% setDT()

pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
```

```
          axis.title.x = element_text(hjust = 0.2, size = 16))
pscore_plot # overlap


## Computing the weights
test.data$weights <- ifelse(test.data$cohort == "TNFi",
1/test.data$pscores, 1/(1-test.data$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS <- subset(test.data, select = c(cohort,age_base,
                                     bmi_base,
                                     TC_with_csDMARD,
                                     PREDNISON_STEROID,
                                     CDAI0,
                                     disease_duration_base_years,
                                     smoker_base,
                                     line_of_therapy,
                                     gender,
                                     seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS, treat = test.data$cohort, thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort,  v.threshold = 2)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
v.threshold = 2)


# But plotting is clearer:
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("mean.diffs"), thresholds = c(m = .1), var.order =
"adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
```

```
  geom_line(aes(y = estimate, color = level), size = 1)+
  #geom_vline(xintercept = 90)+

  scale_colour_manual(values = c("lightblue","darkseagreen3"))+
  scale_fill_manual(values = c("lightblue","darkseagreen3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:")+
  labs(group = "Groups:")+
  theme_bw(base_size = 14)+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

We can also consider the AIPTW estimate at a specific time point. For example at365-day.

```
r.one <- dt.out[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
```

```
table <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(table) <- ploufrows
colnames(table) <- ploufcols

library(formattable)
table[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
table[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
table[1,"p"] <-  writepvalue(r.one$p.value)
table[2,"Estimate"] <-  paste0(r.two$estimate)
table[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
table[2,"p"] <-  writepvalue(r.two$p.value)

table

# Interpretation: If every patient had received BARI, the 365-day risk
of treatment discontinuation would have been 19.34% (points) lower
compared to when every patient had received TNFi.
```

BARI vs OMA —-

COX model

```
BARI2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data2,
data = BARI2)

summary(BARI2.adj.mi)
```

Creation of HR table and p-values (denis)

```
ploufrows <- names(BARI2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI2.adj.mi)
```

```
for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("OMA (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid", "CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
            "Former smoker (vs non-smoker)", "2nd line therapy (vs
1st)", "3rd line therapy (vs 1st)", "4th or later line (vs 1st)",
"Female gender", "Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_2 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs OMA")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
```

```
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_2

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R)

BARI vs OMA

```
surv_object2 <- Surv(time = BARI2$time_on_drug, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50"),
           palette = c("red2", "blue3"), # to put colors
           risk.table = T)
survplot_2
summary(fit2, times = 365)
summary(fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )

# adding some legends
survplot_2_adj <- survplot_2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_2_adj
summary(BARI_fit2, times = 365) # to see detailed surv probabilities
at given timepoints
summary(BARI_fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data_adj <- survplot_2_adj$data.survplot
write.xlsx(plot_BARI_vs_OMA_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# I select only one imputed dataset. Would be good to find a way to
pool the results from the 50 datasets imputed.
test.data2 <- complete(imputed_data2,1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment2 <- glm(cohort~I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data2, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event2 <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data2, x = TRUE, y =
TRUE)

m.censor2 <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
```

```
                                        I(disease_duration_base_years/10)+
                                        C(smoker_base, base=3)+
                                        line_of_therapy+
                                        gender+
                                        seropositivity_base
                                        , x =TRUE, y = TRUE,
                                        data = test.data2)

# And we measure the average treatment effect using function "ate",
specifying the times at which we want to compute the ATE

out2 <- ate(event = m.event2 ,
            treatment = m.treatment2,
            censor = m.censor2,
            data = test.data2,
            cause = 1,
            estimator = "AIPTW",
            times = seq(from = 0, to = 500, by = 5))

dt.out2 <- as.data.table(out2)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data2$pscores <- m.treatment2$fitted.values
test.data2 %>% setDT()

pscore_plot2 <- ggplot(test.data2,aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y=element_blank(),
          panel.grid.minor=element_blank(),
          legend.title=element_blank(),
          text = element_text(size = 16),
          axis.title.x =element_text(hjust = 0.2, size = 16))
pscore_plot2
# Good overlap

## Computing the weights
test.data2$weights <- ifelse(test.data2$cohort == "OMA",
1/test.data2$pscores, 1/(1-test.data2$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS_2 <- subset(test.data2, select = c(cohort,age_base,
                                        bmi_base,
```

```
                                    TC_with_csDMARD,
                                    PREDNISON_STEROID,
                                    CDAI0,
                                    disease_duration_base_years,
                                    smoker_base,
                                    line_of_therapy,
                                    gender,
                                    seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS_2, treat = test.data2$cohort, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort,  v.threshold = 2)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, v.threshold = 2)
#

#But plotting it is better:
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights,stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "Absolute risk of
treatment discontinuation by type of treatment - BARI vs TNFi")+
```

```
  labs(group = "Groups:")

plot.ate.diff2
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

We can also consider the AIPTW estimate at a specific time point. For example at 365-day.

```
r.one <- dt.out2[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out2[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols

library(formattable)
coxtable[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
coxtable[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
coxtable[1,"p"] <-  writepvalue(r.one$p.value)
coxtable[2,"Estimate"] <-  paste0(r.two$estimate)
coxtable[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
coxtable[2,"p"] <-  writepvalue(r.two$p.value)

coxtable

# Interpretation: If every patient had received BARI, the 365-day risk
```

of treatment discontinuation would have been xx% (points) lower compared to when every patient had received TNFi.

.

[3] 1st LINE vs 1st LINE analysis

Common Table 1

Table 1 with NA, to have exact counts and proportions

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection of TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1 NA.xlsx")
```

Table 1 without NA to have adequate p values to interpret

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
```

```
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1.xlsx")

summary(BARI_first[cohort=="BARI", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="TNFi", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="OMA", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables
```

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])
```

```
surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50", "grey10"),
           palette = c("red2", "green3"), # to get colors
           risk.table = T
           )

survplot_first1
table(BARI_first1$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
```

```
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )

survplot_first2
table(BARI_first2$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

Adjusted survival analyses

BARI vs TNFi

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                       data= BARI_first1)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data1_first <- complete(imputed_data1,"long",include=T) # to
put in the long format
imputed_data1_first <- filter(imputed_data1_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data1_first <- as.mids(imputed_data1_first) # put back in
previous format, to use fit.mult.impute

BARI_first1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                      I(age_base/10)+
                                      bmi_base+
                                      concomitant_csDMARD+
                                      PREDNISON_STEROID+
                                      I(CDAI0/10)+
                                      I(disease_duration_base_years/10)+
                                      C(smoker_base, base=3)+
                                      line_of_therapy+
                                      gender+
                                      seropositivity_base+
                                      cluster(patient_id),
                                    fitter = coxph, xtrans =
```

```
imputed_data1_first, data = BARI_first1)
summary(BARI_first1.adj.mi)

Creation of HR table with p-values
ploufrows <- names(BARI_first1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first1.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR 1st
lines.xlsx") # save in excel format

Adjusted curves with imputed data
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
```

```
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10")
           palette = c("red2", "green3"), # to get colors
           )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

BARI vs OMA

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                            cluster(patient_id),
                       data= BARI_first2)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data2_first <- complete(imputed_data2,"long",include=T) # to
put in the long format
imputed_data2_first <- filter(imputed_data2_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data2_first <- as.mids(imputed_data2_first) # put back in
previous format, to use fit.mult.impute

BARI_first2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                      I(age_base/10)+
                                      bmi_base+
                                      concomitant_csDMARD+
                                      PREDNISON_STEROID+
```

```
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base+
                                    cluster(patient_id),
                                  fitter = coxph, xtrans =
imputed_data2_first, data = BARI_first2)
summary(BARI_first2.adj.mi)

Creation of HR table with p-values
ploufrows <- names(BARI_first2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first2.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR 1st
lines.xlsx") # save in excel format

Adjusted curves with imputed data
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
```

```
                                gender+
                                seropositivity_base+
                                cluster(patient_id)+
                                strata(cohort),dummy_cox_impute_first2),
data = dummy_cox_impute_first2)


survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
dummy_cox_impute_first2, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50")
           palette = c("red2", "blue3"), # to get colors
           )

survplot_first2_adj <- survplot_first2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first2_adj
table(BARI_first2$cohort)
rm(dummy_cox_impute_first2, BARI_first2_fit)
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
```

```
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_T <- BARI_comp[cohort %in% c("TNFi")] #TNFi only
ci_TNFi <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_T)
ci_TNFi <- ci_TNFi[,-c(2,6,7,8,9)]
ci_long_TNFi <- reshape2::melt(ci_TNFi,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_TNFi$cohort <- 1
ci_long <- rbind(ci_long_BARI,ci_long_TNFi)
ci_long$cohort <- as.factor(ci_long$cohort)

plot2 <- ggplot(data = ci_long, aes(x = time,
                                    y = value,
                                    linetype =
interaction(cohort,variable),
                                        col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values
=c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
(BARI)","Other (TNFi)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
(BARI)","Other (TNFi)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
```

```
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot2
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat

imputed_data1_long <- complete(imputed_data1, action = "long") %>%
setDT()
imputed_data1_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data1_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data1_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data1_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data1$m

mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data1_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                   status = c("continue","stop_ae","stop_lae"),
                   data = as.data.frame(data_sub),
                   trans = tmat,
                   keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)
```

```
  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                                paste0(tmp_cov,collapse = " + "),
                                "+ strata(trans)")),
              data = tmp,
              method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
# estimate = Hazard ratio

summary(est, conf.int = T, exponentiate = T)

# Conclusion
# => The hazard ratio of lack of efficacy (lae) for TNFi is 65% higher
than for BARI. Significant.
# => No difference between TNFi and BARI for Adverse Event (ae)
```

Clean table with confidence intervals & p-values

```
# Hazard ratios
ploufrows <- as.character(summary(est)$term)

ploufcols  <- c("HR","95%CI","p")
coxtable_csh <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh) <- ploufrows
colnames(coxtable_csh) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_csh[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

output <- coxtable_csh
row.names(output)[1:2] <- c("TNFi Adverse Event (vs BARI)", "TNFi Lack
of Eff (vs BARI)")

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
```

```
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
output
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data1_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data1_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data1_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data1_long[stop_reasons == "CONTINUE", status := 0]

## ATTENTION levels() re-ecrit juste l'étiquette!! Change pas la
donnée !!! Donc ça re écrit les lablels

imputed_data1_long$line_of_therapy <-
as.factor(imputed_data1_long$line_of_therapy)
imputed_data1_long$seropositivity_base <-
as.factor(imputed_data1_long$seropositivity_base)

levels(imputed_data1_long$cohort) <- c("0","1")
levels(imputed_data1_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data1_long$gender) <- c("0","1")
levels(imputed_data1_long$smoker_base) <- c("2","1","0")
levels(imputed_data1_long$smoker_base)
levels(imputed_data1_long$seropositivity_base) <- c("0","1")

M <- imputed_data1$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    # subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY

mice_fit2 <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
```

```
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()

est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of adverse event between TNFi
and BARI
# Increased incidence of lack of efficacy for TNFi compared to BARI.
# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Clean tables with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae) <- ploufrows
colnames(coxtable_ae) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae[row,"95%CI"] <-  paste0(formattable(plouf[term %in% row,
`2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_ae[row,"p"] <-  writepvalue(plouf[term %in% row, p.value])}

row.names(coxtable_ae)[1] <- c("TNFi vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae) <- ploufrows
colnames(coxtable_lae) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae[row,"HR"] <-  formattable(plouf[term %in% row,
```

```
estimate])
  coxtable_lae[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae)[1] <- c("TNFi vs BARI Lack of Eff")

# output
coxtable_ae
coxtable_lae

write.xlsx(coxtable_ae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray LAE.xlsx") # saving excel file
```

(BARI vs OMA)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_O <- BARI_comp[cohort %in% c("OMA")] #OMA only
ci_OMA <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_O)
ci_OMA <- ci_OMA[,-c(2,6,7,8,9)]
ci_long_OMA <- reshape2::melt(ci_OMA,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_OMA$cohort <- 1
ci_long_2 <- rbind(ci_long_BARI,ci_long_OMA)
ci_long_2$cohort <- as.factor(ci_long_2$cohort)
```

```
plot3 <- ggplot(data = ci_long_2, aes(x = time,
                                      y = value,
                                      linetype =
interaction(cohort,variable),
                                      col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values =
c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot3
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
library(mstate)
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat
```

```
imputed_data2_long <- complete(imputed_data2, action = "long") %>%
setDT()
imputed_data2_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data2_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data2_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data2_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data2$m

mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data2_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                     status = c("continue","stop_ae","stop_lae"),
                     data = as.data.frame(data_sub),
                     trans = tmat,
                     keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)

  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                                paste0(tmp_cov,collapse = " + "),
                                "+ strata(trans)")),
             data = tmp,
             method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Transition 1 = Adverse Event
# Transition 2 = Lack of Efficacy

# Conclusion
# => No difference between OMA and BARI for Adverse Event (ae) and for
Lack of Event (lae)
```

Cleaner table with Hazard ratios with confidence intervals & p-values

```
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_csh2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh2) <- ploufrows
colnames(coxtable_csh2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_csh2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_csh2)[1:2] <- c("OMA vs BARI Adverse event", "OMA
vs BARI Lack of Eff" )
coxtable_csh2
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data2_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data2_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data2_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data2_long[stop_reasons == "CONTINUE", status := 0]

imputed_data2_long$line_of_therapy <-
as.factor(imputed_data2_long$line_of_therapy)
imputed_data2_long$seropositivity_base <-
as.factor(imputed_data2_long$seropositivity_base)
levels(imputed_data2_long$cohort) <- c("0","1")
levels(imputed_data2_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data2_long$gender) <- c("0","1")
levels(imputed_data2_long$smoker_base) <- c("2","1","0")
levels(imputed_data2_long$smoker_base)
levels(imputed_data2_long$seropositivity_base) <- c("0","1")

M <- imputed_data2$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data2_long[.imp == m]
```

```
  #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY
mice_fit2 <- lapply(1:M,function(m){

  # subset
  BARI_toto <- imputed_data2_long[.imp == m]

  # subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()
est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of "adverse event" and "lack
of efficacy" between TNFi and BARI

# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Cleaner Table with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae2) <- ploufrows
colnames(coxtable_ae2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
```

```
  coxtable_ae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_ae2)[1] <- c("OMA vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae2) <- ploufrows
colnames(coxtable_lae2) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_lae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae2)[1] <- c("OMA vs BARI Lack of Eff")

#Output
coxtable_ae2
coxtable_lae2

write.xlsx(coxtable_ae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray LAE.xlsx") # saving excel file


## 1. Saving
save.image(file="./3_clean_output/full_workspaces/workspace_1.RData")
```

2 - LDA and REM ANALYSIS

10/11/2020

```
{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)
```

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./1_datamanaged_files/datamanaged.Rdata")
```

This code aims at providing estimates for the remssion rates of the different treatments groups REM = REMmission LDA = Low Disease Activity

Both outcome are base on the CDAI CDAI = Clinical Disease Activity Index

CDAI is an index computed by the physician, which scores the severity of the disease.

1. [0] Exploration

See all available raw CDAI measures :

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

nrow(BARI_DATA)
summary(BARI_DATA[, .(CDAI0_raw, CDAI12_raw)])
```

1. [1] CARRAC (confirm covariates for confounding and for attrition)

For LDA with updated function

```
library(modules)
source_comp_eff <- modules::use("ETAPE_2_supp_code.R")

LDA_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
  seed = 123)

LDA_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
  seed = 123)

LDA_BARI_TNF
LDA_BARI_OMA
```

For REM with updated function

```
REM_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
   seed = 123)

REM_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
```

```
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
   seed = 123)

REM_BARI_TNF
REM_BARI_OMA
```

This methods was developed by Mongin et al,
https://ard.bmj.com/content/early/2022/01/12/annrheumdis-2021-221477

Pooled table

```
table <- rbind(LDA_BARI_TNF, LDA_BARI_OMA, REM_BARI_TNF, REM_BARI_OMA)

write.xlsx(table, file = "./3_clean_output/table_LDA_REM_CARRAC.xlsx",
row.names = F)
```

1. Saving

```
save.image(file="./3_clean_output/full_workspaces/workspace_2.RData")
```

2 - LDA and REM supp CODE

10/11/2020

```
{r setup, include=FALSE} import("data.table") import("plyr")
import("data.table") import("mice") import("ipw") import("survey")
import("geepack") import("futile.logger") import("emmeans")
import("stats") import("survival")
```

function to perform checks on data

```{r setup, include=FALSE} check_data = function(datain, var = “CDAI_fu”, ttt_var = “ttt”, ref_ttt = “ttt_ref”, ID_ttt = NULL, othervar = c())

{

data <- setDT(copy(datain))

vartocheck <- Reduce(union,list(var,ttt_var,othervar)) notindata <- setdiff(vartocheck,names(data))

if(length(notindata)>0){ stop(paste0(“the variables”,paste0(notindata,collapse = “,”),” are not in the dataplease correct”)) }

# force ttt as var name setnames(data,ttt_var,“ttt”)

if( data[,uniqueN(ttt)]>2){ stop(“there are more than two treatments. The analysis has been implemented only for 2 treatments”) }

if(!any(data$ttt == ref_ttt)){ stop(paste0(“The variable”,ttt_var,” does not contain any “,ttt_ref,” value”)) }

data[,ttt := relevel(as.factor(ttt),ref_ttt)] if(is.null(ID_ttt))
{ data[,ID_ttt := .I] }else{ setnames(data,ID_ttt,“ID_ttt”) data[,N := .N,by = ID_ttt] if(any(data$N>1)){ stop(“there are”,data[N>1,uniqueN(ID_ttt)],” treatment course which have more than one entry in the table. Each row should be an unique treatment”) } }
return(data) }

adjusted_model = function(data, weights = NULL, covariates = NULL){

# transform char to factor to_fact <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “character”,var]

data[,c(to_fact) := lapply(.SD,factor),.SDcols = to_fact]

#droplevels facto_vars <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “factor”,var] data[,c(facto_vars) := lapply(.SD,droplevels),.SDcols = facto_vars]
```

define forumla formula <- as.formula(paste0("LDA ~",paste0(c("ttt",covariates),collapse = " + ")))

if(!is.null(covariates)){ # fit fit <- geeglm(formula, data = data, id = ID_ttt, family = gaussian) }else{ fit <- geeglm(LDA ~ ttt , data = data, weights = weights, id = ID_ttt, family = gaussian) }

fitsummary <- summary(fit) # create table with difference between the two treatments diff <- data.table(ttt = "diff", LDA = fitsummary$coefficients[2,"Estimate"], LDA_var = fitsummary$coefficients[2,"Std.err"]^2, LDA_sup = fitsummary$coefficients[2,"Estimate"] + 1.96*fitsummary$coefficients[2,"Std.err"], LDA_inf = fitsummary$coefficients[2,"Estimate"] - 1.96*fitsummary$coefficients[2,"Std.err"], methods = "CC_adjusted")

marginal effects: margi_df <- emmeans(fit, "ttt") %>% as.data.table()

margi_df[,methods := "CC_adjusted"] setnames(margi_df,"emmean","LDA") margi_df[,LDA_inf := LDA - 1.96*SE] margi_df[,LDA_sup := LDA + 1.96*SE] margi_df[,LDA_var := SE^2]

output <- rbind(diff,margi_df[,.(ttt,LDA,LDA_sup,LDA_inf,LDA_var,methods)])

return(list(output = output,fit = fit)) }

Not adjusted complete case imputation

```{r setup, include=FALSE}

```
export("CC_raw")
CC_raw <- function(datain,
                   # data
                   var = "CDAI_fu",
                   # variable measuring effctiveness
                   thres = 10,
                   # threshold for remission or LDA
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref")
  # variable name containing the treatment
  {
  data <- check_data(datain,var,ttt,ref_ttt)
  # raw proportion
  raw_prop <- data[!is.na(get(var)),
                   .(LDA = sum(get(var)<=thres)/.N,
                     methods = "CC_raw",
                     N = .N),
                   by = ttt]
```
```

```
  # calculation of the Standard error
  raw_prop[,c("LDA_inf","LDA_sup") := lapply(c(-1.96,1.96),function(z)
{
    LDA + z*sqrt(LDA*(1-LDA)/N)
  })]

  # difference between treatments
  diff_tmp <- raw_prop[,.(ttt = "diff",
                          LDA = LDA[ttt == "ttt_1"]-LDA[ttt ==
"ttt_ref" ],
                      methods = methods[1] ,
                      SE = (sum(1/N))/2 +  1.96*sqrt(sum( LDA*(1-LDA)/N
)))]

  diff_tmp[,LDA_inf := LDA - SE]
  diff_tmp[,LDA_sup := LDA + SE]

  # bind outputs
  output <- rbind(diff_tmp[,.(ttt,LDA,LDA_inf,LDA_sup,methods)],
                  raw_prop[,-"N"])
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Adjusted complete case imputation

```{r setup, include=FALSE} export("CC_adjusted") CC_adjusted = function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0") ) # variable name containing the treatment { data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] output <- adjusted_model(data = data[!is.na(get(var))], covariates = covariates)$output

output[,methods := "CC_adjusted"] # change name back setnames(output,"ttt",ttt_var) return(output) }

```
LOCF imputation


```{r setup, include=FALSE}
export("LOCF")

LOCF <- function(datain,
                 var = "CDAI_fu",
                 var_before = "CDAI_beforefu",
```

```
                  thres = 10,
                  ttt_var = "ttt",
                  ref_ttt = "ttt_ref",
                  covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
){
  data <- copy(datain)

  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[is.na(get(var)),c(var) := get(var_before)]
  data[,LDA := get(var) <= thres]

  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  output[,methods := "LOCF"]
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Lundex imputation

```{r setup, include=FALSE} export("Lundex") Lundex <- function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", treatment_duration = "treatment_duration", stop_var = "stopany", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"), boot_num = 1000) {

data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] #### bootstrap for SE data[,tmp := 1] # replicated data for bootstrap replicateddata <- data[CJ(tmp = 1,boot = 1:boot_num),on = "tmp",allow.cartesian=TRUE] # sample with replacement for each boot sampled_idx <- replicateddata[,.I[sample(1:.N,replace = T)],by = boot]$V1 bootstrapdata <- replicateddata[sampled_idx]

# raw proportions raw_prop <- bootstrapdata[!is.na(get(var)), { adjusted_model(data = .SD)$output %>% .[ttt != "diff",.(ttt,LDA_raw = LDA)] }, by = .(boot)]

# surv analysis for each bootstraped dataset surv_formula <- as.formula(paste0("Surv(",treatment_duration,",",stop_var,")~ ttt"))

surv_coeff <- bootstrapdata[, { temp.km <- survfit(surv_formula, data = .SD) list(surv = summary(temp.km, times = 1)$surv,  ttt = gsub("ttt=","",unique(summary(temp.km) $strata))) }, by = boot]

# LDA: LDA raw * surv coeff tmp_bootstrap <- merge(raw_prop,surv_coeff,by = c("boot","ttt")) tmp_bootstrap[,LDA := LDA_raw*surv]
```

difference between treatments diff_boot <- tmp_bootstrap[,.(ttt = “diff”, LDA = LDA[ttt != ref_ttt] - LDA[ttt == ref_ttt]), by = boot]

tot_bottstrap <- rbind(diff_boot[, .(ttt, LDA, boot)], tmp_bootstrap[, .(ttt, LDA, boot)])

calculate the mean and the SE: output <- tot_bottstrap[, .(LDA = mean(LDA), LDA_sup = quantile(LDA, 0.975), LDA_inf = quantile(LDA, 0.025)), by = ttt] # change name back output[,methods := “LUNDEX”]

setnames(output,“ttt”,ttt_var) return(output) }

non-responder imputation

```{r setup, include=FALSE}
export("NRI")
NRI = function(datain,
               var="CDAI_fu",
               thres = 10,
               ttt_var = "ttt",
               ref_ttt = "ttt_ref",
               covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
)
  # variable name containing the treatment
{
  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[,LDA := get(var) <= thres]
  data[is.na(LDA),LDA := 0] # missing are non responders
  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  # change name back
  setnames(output,"ttt",ttt_var)
  output[,methods := "NRI"]
  return(output)
}
```

Inverse probability weighting imputation

```{r setup, include=FALSE} export(“IPW”) IPW <- function(datain, var = “CDAI_fu”, thres = 10, ttt_var = “ttt”, ref_ttt = “ttt_ref”, counfunders = c(“Disease_duration”,“concomitantCsDMARD”,“Prev_bDMARD3”,“CDAI0”), attrition = c(“Disease_duration”,“concomitantCsDMARD”, “Prev_bDMARD3”,“CDAI0”,“stopreason”)) {

data <- check_data(datain, var, ttt_var, ref_ttt, othervar = c(counfunders,attrition))
```

```
data[,ttt2 := as.numeric(ttt != ref_ttt)] # weight for confounding formula_coeff <-
paste0("~",paste0(counfunders,collapse = "+")) function_call <- paste0('IPWT <-
ipwpoint( exposure = ttt2 , family = "binomial", link = "logit", numerator = ~ 1,
denominator =',formula_coeff,', data = data, trunc = 0.01 )') eval(parse(text = function_call))
data$sw <- IPWT$ipw.weights

# weights for attrition formula_attr <- paste0("~",paste0(attrition,collapse = "+"))
data[,MISS := as.numeric(is.na(get(var)))] function_call <- paste0('IPCT <-
ipwpoint( exposure = MISS , family = "binomial", link = "logit", numerator = ~ 1,
denominator =',formula_attr,', data = data )') eval(parse(text = function_call)) data
$swc <- IPCT$ipw.weights

dataNoNA <- na.omit(data[,.(ttt,get(var),sw,swc,ID_ttt) %>%
setNames(c("ttt",var,"sw","swc","ID_ttt"))]) dataNoNA[,LDA := as.numeric(get(var) <=
thres)]

output <- adjusted_model(data = dataNoNA, weights = dataNoNA$sw*dataNoNA$swc)
$output

output[,methods := "IPW"]

# change name back setnames(output,"ttt",ttt_var) return(output)

}



# Confounder-Adjusted Response Rate with Attrition Correction (CARRAC)
imputation


```{r setup, include=FALSE}
export("CARRAC")
CARRAC <- function(datain,
                   var = "CDAI_fu",
                   thres = 10,
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref",
                   counfunders =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"),
                   attrition =
c("Disease_duration","concomitantCsDMARD",

"Prev_bDMARD3","CDAI0","stopreason"),
                   seed = NA) {

  data <- check_data(datain,var,ttt_var,ref_ttt)
  dataS <- data[,.SD,.SDcols =
c("ID_ttt",var,"ttt",union(counfunders,attrition))]
```
```

```
  impute_data <- mice(
    dataS,
    m = 10,
    method = "pmm",
    maxit = 5,
    printFlag = F,seed = seed
  )
  # open the data
  impute_data_complete <- setDT(complete(impute_data,action = "long"))
  # calculate LDA
  impute_data_complete[,LDA := get(var) <= thres]

  # get LDA and error for each imputation
  res_mice <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$output

  }) %>% rbindlist()

  res_mice_2 <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$fit

  })

  test <- pool(res_mice_2)
  df_pval <- summary(test)  %>% as.data.table()
  p.output <- df_pval[grepl("ttt",term),p.value]

# pooling
  pool_res <- res_mice[,.(
    LDA_mi = mean(LDA),
    w = mean(LDA_var),
    m = .N,
    b = 1/(.N-1)*sum( (LDA-mean(LDA))^2 )
              ),by = ttt]

  pool_res[,LDA_var := w + (1+1/m)*b]
  pool_res[,LDA_sd := sqrt(LDA_var)]

  # mean, 95% CI
  output <- pool_res[,.(ttt,
                        LDA_mi,
                        LDA_mi + 1.96*LDA_sd,
                        LDA_mi-1.96*LDA_sd) %>%
                       setNames(c("ttt","LDA","LDA_sup","LDA_inf"))]

  output[,methods := "CARRAC"]
```

```
  output[ttt == "diff",p := p.output]

  # change name back
  setnames(output,"ttt",ttt_var)

  return(output)
}
```

3 - FINAL FIGURES CODE

10/11/2020

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(patchwork) # package to compose multiplots !
library(ggpubr)
library(grid)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./3_clean_output/full_workspaces/workspace_1.RData")
load("./3_clean_output/full_workspaces/workspace_2.RData")
load("./3_clean_output/full_workspaces/workspace_3.RData")
```

1. Common theme

```
theme_benoit = function(){
theme_pubclean()+
  theme(panel.grid.major.x = element_line(linetype = "dotted", colour
= "grey50"),
        panel.grid.major.y = element_line(linetype = "dotted", colour
= "grey50"),
        axis.title.y = element_text(margin = margin(r = .2, unit =
"cm")),
        axis.title.x = element_text(margin = margin(t = .2, unit =
```

```
"cm")),
        plot.title = element_text(margin = margin(b = .5, unit =
"cm")))
}
```

1. [0] Mini explation

TC lenght

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

p1 <- ggplot(BARI_DATA)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/12)+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "Time of observation for all included TC")+
  ylim(-25,NA)+
  theme_benoit()
p1

p2 <- ggplot(BARI_DATA)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration
```

Saving plot

```
png("./3_clean_output/figures/PLOT_Exploration_TC_duration.png",
    width = 7,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
plot_mini_exploration
dev.off() # closing graphic device
```

TC lenght for BARI only

```
data_sub <- BARI_DATA[cohort == "BARI"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "red3")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "A - BARI")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_bari <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_bari
```

TC lenght for TNFi only

```
data_sub <- BARI_DATA[cohort == "TNFi"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "green2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "B - TNFi")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_tnfi <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_tnfi
```

TC lenght for OMA only

```
data_sub <- BARI_DATA[cohort == "OMA"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "blue2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "C - OMA")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_oma <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_oma
```

multiplot

```
multi_plot <- plot_mini_exploration_bari + plot_mini_exploration_tnfi
+ plot_mini_exploration_oma
multi_plot

median(BARI_DATA[cohort == "BARI", time_on_drug])
median(BARI_DATA[cohort == "TNFi", time_on_drug])
median(BARI_DATA[cohort == "OMA", time_on_drug])
```

Saving plot

```
png("./3_clean_output/figures/
PLOT_Exploration_TC_duration_3_groups.png",
    width = 9,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
multi_plot
dev.off() # closing graphic device
```

1. [1] Survival analysis

Forest plot BARI vs TNFi + BARI vs OMA

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("Treatment (vs BARI)", "Age (decades)", "BMI",
"Concomitant csDMARD", "Concomitant glucocorticoid", "CDAI score (10
pts)", "Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")
```

```
dfall1 <- data.table(textall, meanall, lowerall, upperall)
dfall1[,ttt := "TNFi"]

meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
dfall2 <- data.table(textall, meanall, lowerall, upperall)
dfall2[, ttt := "OMA"]

dfall <- rbind(dfall1,dfall2)
dfall$textall <- factor(dfall$textall, levels = rev(textall))

text_high <- textGrob("\u2192 Reduces \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))
text_low <- textGrob("\u2190 Improves \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))

HR_plot <- ggplot(data=dfall,
                  aes(x = textall,
                      y = meanall,
                      ymin = lowerall,
                      ymax = upperall,
                      color = ttt))+
  geom_hline(yintercept =1, linetype=2)+
  geom_point(size=2,position = position_dodge(width = .7))+
  geom_errorbar(position = position_dodge(width = .7))+
  labs(x = "",y = "",color = "")+
  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  theme(axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", color = "black"),
        legend.position="top",
        legend.key = element_blank(),
        plot.margin = unit(c(1,3,2,1),"lines"))+
  coord_flip(clip = "off")+
  annotation_custom(text_high,
           xmin=-0.64,xmax=-0.64,ymin=.2,ymax=.2)+
  annotation_custom(text_low,
           xmin=-0.64,xmax=-0.64,ymin=-.15,ymax=-.15)+
  theme_pubclean()+
  scale_color_manual(breaks = c("OMA","TNFi"),values =
c("blue3","green3"),labels = c("OMA","TNFi"))

HR_plot
```

Saving the plot in PNG file

```
png("./3_clean_output/figures/PLOT FOREST BARI vs TNFi vs OMA HR.png",

    width = 7,
```

```
    height = 5.5,
    units = "in",
    res = 300)

HR_plot

dev.off() # closing graphic device
```

BARI vs TNFi

Non-adjusted Kaplan-Meier curves

BARI vs TNFi

```
BARI1[,time_on_drug_year := time_on_drug/365.25]

surv_object1 <- Surv(time = BARI1$time_on_drug_year, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1)

survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
                         pval = T,
                         pval.method = TRUE,
                         legend.title = "Groups :",
                         legend.labs = c("BARI", "TNFi"),
                         xlab = "Time (years)",
                         xlim = c(0, 2.5),
                         censor = FALSE,
                         title = "Non-adjusted model of drug
discontinuation \nby type of treatment",
                         surv.median.line = "v",
                         linetype = 1,
                         size = 1.5,
                         #palette = c("grey78", "grey10"),
                         palette = c("red3", "green2"), # pour mettre
les couleurs
                         ggtheme = theme_benoit(),
                         risk.table = T)

values <- summary(fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.2,label =
as.character(round(values,2)))

survplot_1$plot <- survplot_1$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2"), size = 5)


print(survplot_1)
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves non adjusted
COLOR.png",
     width = 7,
       height = 7, units = "in",
       res = 300) # opening graphic device
survplot_1

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]
dummy_cox_impute1$time_on_drug_year <-
dummy_cox_impute1$time_on_drug/365.25

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
                           xlab = "Time (years)",
                           title = "A - BARI vs TNFi",
                           legend.title = "Groups :",
                           legend.labs = c("BARI", "TNFi"),
                           censor = FALSE,
                           xlim = c(0, 2.5),
```

```
                                surv.median.line = "v",
                                linetype = 1,
                                size = 1.5,
                                ggtheme = theme_benoit(),
                                # palette = c("grey78", "grey10")
                                palette = c("red2", "green3") )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,\n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding days label
values <- summary(BARI_fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_1_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green3"), size = 5)

# adding HR et p val label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI1.adj.mi$coefficients[1]), 2), "\n", "p =",
round(summary(BARI1.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)

# final print
survplot_1_adj
```

Saving the survival plot in PNG file

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves adjusted.png",

    width = 7,
    height = 5,
    units = "in",
    res = 300)

survplot_1_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression Package)

First plot to get the difference in average treatment effect in percentage

```
dt.out$time_years <- dt.out$time/365.25

plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  scale_colour_manual(values = c("red2","green3"))+
  scale_fill_manual(values = c("red2","green3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "A - BARI vs TNFi")
+
  labs(group = "Groups:")+
  theme_benoit()+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Saving Plot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves AIPTW.png",
width = 1300, height = 650, res = 120) # opening graphic device

plot.ate.diff

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
```

```
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

BARI vs OMA

Non-adjusted Kaplan-Meier curves

BARI vs OMA

```
BARI2[,time_on_drug_year := time_on_drug/365.25]

surv_object2 <- Surv(time = BARI2$time_on_drug_year, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 2.5),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           #palette = c("grey78", "grey50"),
           palette = c("red3", "blue2"), # to put colors
           risk.table = T)
survplot_2
```

Saving surplot

```
png("./3_clean_output/PLOT BARI vs OMA curves non adjusted COLOR.png",
width = 1000, height = 600, res = 100) # opening graphic device

survplot_2

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]
dummy_cox_impute2$time_on_drug_year <-
dummy_cox_impute2$time_on_drug/365.25

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (years)",
           title = "B - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           censor = FALSE,
           xlim = c(0, 2.5),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD, \n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding Days label
values <- summary(BARI_fit2)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
```

```
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_2_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"blue2"), size = 5)

# adding HR et pval label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI2.adj.mi$coefficients[1]), 2),  "\n", "p =",
round(summary(BARI2.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)



# final print
survplot_2_adj

summary(BARI_fit2, times = 1) # to see detailed surv probabilities at
given timepoints
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA curves adjusted.png", width =
1000, height = 600, res = 100) # opening graphic device

survplot_2_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression package)

First plot to get the difference in average treatment effect in percentage

```
dt.out2$time_years <- dt.out2$time/365.25

plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit() + theme(legend.spacing.x = unit(0.2, 'cm'),
```

```
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "B - BARI vs OMA")+
  labs(group = "Groups:")+

  scale_colour_manual(values = c("red2","blue3"))+
  scale_fill_manual(values = c("red2","blue3"))

plot.ate.diff2
```

Saving Plot

```
png("./3_clean_output/PLOT BARI vs OMA curves AIPTW.png", width =
1300, height = 650, res = 120) # opening graphic device

plot.ate.diff2

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

Multipanel plots

To update using patchwork

For the paper Non adjuted curves

```
# Creating list object

plots <- list()
```

```
plots[[1]] <- survplot_1
plots[[2]] <- survplot_2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)
```

Option 2 putting all data on one panel Kaplan Meier

BARI vs TNFi vs OMA

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

surv_object3 <- Surv(time = BARI_DATA$time_on_drug_year, event =
BARI_DATA$stop_DMARD)
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_DATA) # this
function creates the data for Kaplan Meyer
survplot_3 <- ggsurvplot(fit3, data = BARI_DATA,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit3)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[3,2] <- 1.72

survplot_3$plot <- survplot_3$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2", "blue2"), size = 5)

survplot_3$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_3
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA curves non
adjusted COLOR.png", width = 800, height = 600, res = 100) # opening
```

```
graphic device

survplot_3

dev.off() # closing graphic device
```

Adjusted curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1_adj
plots[[2]] <- survplot_2_adj

# Nice function

multi_plot_cox <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device

multi_plot_cox

dev.off() # closing graphic device
```

All curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1
plots[[3]] <- survplot_2
plots[[2]] <- survplot_1_adj
plots[[4]] <- survplot_2_adj

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2, nrow =
2)

# but does not display properly now.. :(
```

AIPTW absolute risk of treatment discontinuation biplot

```
plot.ate.diff + plot.ate.diff2

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA AIPTW curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device
```

```
plot.ate.diff + plot.ate.diff2

dev.off() # closing graphic device
```

Diagnostic multipanel plots

Asked by Lilly statistician to show balance in this analysis.

```
pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","green3"))+
    scale_fill_manual(values = c("red2","green3"))+

    xlab("Probability of being assigned BARI or TNFi") +
    ylab("Density") +
    labs(title = "A1 - BARI vs TNFi")

pscore_plot # overlap

pscore_plot2 <- ggplot(test.data2, aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","blue3"))+
    scale_fill_manual(values = c("red2","blue3"))+

    xlab("Probability of being assigned BARI or OMA") +
    ylab("Density") +
    labs(title = "A2 - BARI vs OMA")

pscore_plot2
# Good overlap
```

```
library(cobalt)

# BARI vs TNFi
B1 <- love.plot(COVS, treat = test.data$cohort, weights =
test.data$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B1 - BARI vs TNFi", color =
c("#FD8D3C", "#08306B"), themes = theme_pubclean() )

# BARI vs OMA
B2 <- love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B2 - BARI vs OMA", color =
c("#FD8D3C", "#08306B") , themes = theme_pubclean() )

one <- (  pscore_plot + B1)

two <- ( pscore_plot2 + B2 )

png("./3_clean_output/figures/AIPTW diagnositc COLOR.png", width =
1300, height = 900, res = 100) # opening graphic device

one / two

dev.off() # closing graphic device
```

1. [3] Fist line analysis

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])

surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "A - BARI vs TNFi",
           surv.median.line = "v",
           linetype = 1,
```

```
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50"),
            palette = c("red2", "green3"), # to get colors
            risk.table = T
            )

survplot_first1$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first1

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1

dev.off() # closing graphic device
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
            pval = T,
            pval.method = TRUE,
            legend.title = "Groups :",
            legend.labs = c("BARI", "OMA"),
            xlab = "Time (days)",
            xlim = c(0, 700),
            censor = FALSE,
            title = "B - BARI vs OMA",
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )
```

```
survplot_first2$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first2

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs OMA first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs TNFi)

```
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
```

```
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            #palette = c("grey78", "grey10")
            palette = c("red2", "green3"), # to get colors
            )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1_adj

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs OMA)

```
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first2),
data = dummy_cox_impute_first2)


survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
```

```
dummy_cox_impute_first2, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50")
           palette = c("red2", "blue3"), # to get colors
           )

survplot_first2_adj <- survplot_first2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first2_adj
table(BARI_first2$cohort)
rm(dummy_cox_impute_first2, BARI_first2_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2_adj

dev.off() # closing graphic device
```

Multipanel plots

Non adjusted curves

```
plots <- list()
plots[[1]] <- survplot_first1
plots[[2]] <- survplot_first2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA 1st Line
curves non-adjusted COLOR.png", width = 1000, height = 600, res = 100)
# opening graphic device
```

```
multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

dev.off() # closing graphic device
```

All in one BARI vs TNFi vs OMA

```
BARI_first[,time_on_drug_year := time_on_drug/365.25]

surv_object4 <- Surv(time = BARI_first$time_on_drug_year, event =
BARI_first$stop_DMARD)
fit4 <- survfit(surv_object4 ~ cohort, data = BARI_first) # this
function creates the data for Kaplan Meyer

survplot_4 <- ggsurvplot(fit4, data = BARI_first,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit4)$table[,"median"]
df <- data.frame(y = .2,x = values+.2,label =
as.character(paste(round(values*365.25,2), "\n days")))
df <- df[2,]

survplot_4$plot <- survplot_4$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("green2"),
size = 5)

survplot_4$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_4
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA first curves
non adjusted COLOR.png", width = 800, height = 600, res = 100) #
opening graphic device
```

```
survplot_4

dev.off() # closing graphic device
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
ci_long$time_months <- ci_long$time/365.25*12

plot2 <-  ggplot(data = ci_long, aes(x = time_months,
                                     y = value,
                                     linetype = variable  ,
                                     col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","green2"),
                     labels = c("BARI","TNFi"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"),
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+ # not showing the "other category"
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "A - BARI vs TNFi")

plot2

ggsave(filename = "PLOT BARI vs TNFi cumulative incidence.png",plot =
plot2, path = "./3_clean_output/", device = "png", width = 829, height
= 550, units = "px", scale = 3.2)
```

(BARI vs OMA)

Cumulative incidence function

```
ci_long_2$time_months <- ci_long_2$time/365.25*12

plot3 <-  ggplot(data = ci_long_2, aes(x = time_months,
                                       y = value,
                                       linetype = variable  ,
                                       col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","blue2"),
                     labels = c("BARI","OMA"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"), # not showing the
"other" category
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "B - BARI vs OMA")

plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs OMA
cumulative incidence.png", plot3, height = 4, width = 6, units =
"in",dpi = 300)
```

Multipanel

```
plot2_3 <- plot2 + plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs TNFi and BARI
vs OMA cumulative incidence.png", plot2_3, height = 4, width = 8,
units = "in",dpi = 300)
```

1. [6] LDA - REM

Exploration

See all available raw CDAI measures : :)

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

plot_data <- copy(BARI_long[!is.na(TC_id) & TC_id %in%
BARI_DATA$TC_id])
plot_data <- merge(plot_data, BARI_DATA[,.(TC_id, cohort)], by =
"TC_id")

CDAI_plot <- ggplot(data = plot_data,
                    aes(x = time, y = CDAI, fill = cohort) )+

  annotate("rect",xmin = 0.875,xmax = 1.125,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+
  annotate("rect",xmin = -.05,xmax = 0+1.5/12,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+

  geom_point(data = plot_data[cohort != "BARI"], alpha = 0.2, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+
  geom_point(data = plot_data[cohort == "BARI"], alpha = 0.25, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+


  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort !=
"BARI"], alpha = 0.2, size = 2, shape = 21, show.legend = F )+
  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort ==
"BARI"], alpha = 0.25, size = 2, shape = 21 , show.legend = F, )+

  geom_smooth(alpha = 0.1, size = 1, aes(color = cohort), show.legend
= F)+

  coord_cartesian(xlim = c(0,2.5))+
    labs(title = "CDAI across time type of treamtent (all TC)",
         x = "Time (years since TC initiation)",
         y = "CDAI score",
         color = "",
         fill = "")+
  theme_benoit()+
  theme(legend.position = c(1,1),
        legend.justification = c(1,1))+
  guides(color = guide_legend(override.aes = list(linetype = NA,size =
3)))

CDAI_plot
```

To me this figure is the best results to be discussed regarding REM and LDA

saving plot

```
png("./3_clean_output/figures/PLOT CDAI across time raw.png",
    width = 8,
    height = 6,
    units = "in",
    res = 120) # opening graphic device

CDAI_plot

dev.off() # closing graphic device
```

CARRAC histogram

Building large format data table from the CARRAC output

```
# Extracting LDA BARI
LDA_BARI <- rbind(LDA_BARI_TNF[2,1:4], LDA_BARI_OMA[2,1:4]) # I have
one estimation per comparison
LDA_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
LDA_BARI <- LDA_BARI[1]

# REM BARI
REM_BARI <- rbind(REM_BARI_TNF[2,1:4], REM_BARI_OMA[2,1:4]) # I have
one estimation per comparison
REM_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
REM_BARI <- REM_BARI[1]

# IDem for TNFi and OMA
LDA_TNFi <- LDA_BARI_TNF[3,1:4]
REM_TNFi <- REM_BARI_TNF[3,1:4]

LDA_OMA <- LDA_BARI_OMA[3,1:4]
REM_OMA <- REM_BARI_OMA[3,1:4]

# Binding together
LDA <- rbind(LDA_BARI, LDA_TNFi, LDA_OMA)
setnames(LDA, c("ttt", "LDA", "LDA_sup", "LDA_inf")) #putting right
labels
REM <- rbind(REM_BARI, REM_TNFi, REM_OMA)
setnames(REM, c("ttt", "REM", "REM_sup", "REM_inf"))

histo_carrac <- cbind(LDA, REM[,-1])
```

plotting

```
carrac_plot <- ggplot(data = histo_carrac, aes(x = ttt, group = ttt))
+

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +

  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "A - REM and
LDA rates \nby type of treatment \n(CARRAC)")

carrac_plot
```

also Saving CARRAC plot only

```
png("./3_clean_output/figures/PLOT BARI 3 CARRAC ONLY.png", width =
350, height = 600, res = 100) # opening graphic device

ggplot(data = histo_carrac, aes(x = ttt, group = ttt)) +

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +
```

```
  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "REM and LDA
rates \nby type of treatment \n(CARRAC)")

dev.off() # closing graphic device
```

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p4-5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7 & supp p2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supp p2
Bias	9	Describe any efforts to address potential sources of bias	p16
Study size	10	Explain how the study size was arrived at	supp p9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p8-9
		(*b*) Describe any methods used to examine subgroups and interactions	supp p 5-6
		(*c*) Explain how missing data were addressed	p8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	p8-9
		(*e*) Describe any sensitivity analyses	p9 & supp p5-6

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p13-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p14-15 & supp
Discussion			
Key results	18	Summarise key results with reference to study objectives	p15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Filled in by Benoît GILBERT, 30-01-2023

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COMPARATIVE EFFECTIVENESS OF BARICITINIB AND ALTERNATIVE BIOLOGICAL DMARDs IN A SWISS COHORT STUDY OF RA PATIENTS

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COMPARATIVE EFFECTIVENESS OF BARICITINIB AND ALTERNATIVE BIOLOGICAL DMARDs IN A SWISS COHORT STUDY OF RA PATIENTS

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ABSTRACT

Objectives: This observational study compares the effectiveness of baricitinib (BARI), a targeted synthetic DMARD (tsDMARD) with alternative biological DMARDs (bDMARDs) in rheumatoid arthritis (RA) patients, from a prospective, longitudinal cohort.

Methods: We compared patients initiating a treatment course of BARI, tumor necrosis factor inhibitors (TNFi) or other mode of action bDMARDs (OMA), during a period when all these DMARDs where available in Switzerland. The primary outcome was drug-maintenance; secondary outcomes included discontinuation rates related specifically to ineffectiveness and to adverse events. We further analyzed rates of low disease activity (LDA) and remission (REM) at 12 months, and drug maintenance in b- and tsDMARD-naïve population.

Results: A total of 1053 treatment courses (TC) were included: 273 on BARI, 473 on TNFi and 307 on OMA. BARI was prescribed to older patients with longer disease duration and more previous treatment failures than TNFi. Compared to BARI, the adjusted drug maintenance was significantly shorter for TNFi (hazard ratio (HR) for discontinuation: 1.76; 95% CI [1.32-2.35]), but not compared to OMA (HR 1.27; 95% CI [0.93-1.72]). These results were similar in the b/tsDMARD-naïve population. The higher discontinuation of TNFi was mostly due to an increased discontinuation for ineffectiveness (HR = 1.49; 95% CI [1.03 – 2.15]), with no significant differences in drug discontinuation for adverse events (HR = 1.46; 95% CI [0.83 - 2.57]. The LDA and REM rates at 12 months did not differ significantly between the 3 groups.

Conclusions: BARI demonstrated a significantly higher drug maintenance compared to TNFi, mainly due to lower drug discontinuations for ineffectiveness. We found no difference in drug-maintenance between BARI and OMA. Clinical outcomes did not differ between the three groups. Our results suggest that BARI is an appropriate therapeutic alternative to bDMARDs in the management of RA.

Strengths and limitations of this study

Strengths:

- Use data derived from office-based rheumatologists
- Study period where all alternative medications were available on the market
- Several sensitivity analyses, congruent with main results

Limitations:

- Not a randomized setting
- Sub-analysis in b/tsDMARD-naïve population has limited sample size

INTRODUCTION

Rheumatoid arthritis (RA) is an auto-immune disease leading to widespread inflammation and irreversible joint damage, if insufficiently treated. New treatment paradigms have emerged in the last decades, such as “early aggressive therapy” in the so called “window of opportunity”, during which patients are more likely to reach long term remission.[1] A wide panel of biological disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been approved in the management of RA, after failure of methotrexate. In clinical-trial settings, b- and tsDMARDs have demonstrated significant reduction of joint inflammation and prevention of joint damage.[2–8]

Efficacy estimates from placebo-controlled randomized trials often differ from real-world effectiveness estimates, because of patient selection, adherence to therapy and other reasons.[9–12] Indeed, drug maintenance of many bDMARDs remains modest in observational analyses, while long term remissions are rare and secondary loss of efficacy frequent.[13] Furthermore, understanding the clinical effectiveness of bDMARDs or tsDMARDs in specific conditions, such as elderly or multi-morbid patients, may become important as we move towards personalized care. Finally, trials provide only limited data on long term effectiveness and safety because clinical-trial follow-up is typically less than 12 months.

Baricitinib (BARI) has been approved in Switzerland for the treatment of RA in 2017 as well as all around the world. Clinical trials with BARI have established efficacy and demonstrated acceptable adverse events profile, both in combination with methotrexate or in monotherapy.[14–20] However, evidence about effectiveness of BARI compared to TNFi in

real-world settings are scarce. A recently published analysis of registry data from Sweden showed that baricitinib had higher maintenance as compared to most other bDMARD.[21] Pappas et al., in the United States, also demonstrated that TNFi and non-TNFi drugs had similar outcomes when prescribed in b/tsDMARD-naïve population, an observation replicated in the RA-BE-REAL study.[22,23]

The aim of our analysis was to compare real-world drug maintenance between BARI and other approved b/tsDMARDs, using data from a European registry.

METHODS

Study population

This is a nested cohort study from a prospective, longitudinal, cohort of Swiss RA patients in a real-life setting, the Swiss Clinical Quality Management registry (SCQM). The SCQM registry was founded in 1997 with the financial support of Swiss regulatory authorities, who recommended a continuous monitoring of all patients receiving new DMARDs. Unlike many other European registries, most patients are enrolled by private office-based rheumatologists (60%), providing a population-based sample of RA patients in Switzerland. All approved RA treatments are represented in the registry. The data for this analysis was extracted from the SCQM registry on 2020-06-01.

We used “treatment courses” (TCs) as our denominator of interest, with each new treatment initiation considered as a separate “treatment course” (TC). We included all TCs with the medications of interest initiated between 2017-09-01 and 2020-06-01, with at least one follow-up visit, in adult patients with a diagnosis of RA confirmed by a rheumatologist. Thus, a given patient could potentially contribute to several TCs during the study period. To minimize the risk of confounding bias, the time window was selected to include only the period when all the therapies examined were available for prescription and reimbursed (BARI was first reimbursed on the Swiss market in September 2017). We excluded TCs with no follow-up visit at the time of data extraction.

Exposure of interest

The exposure of interest was the type of treatment used, namely BARI, TNFi, and other mode of action bDMARDs (OMA), excluding other tsDMARDs and rituximab. We decided to exclude rituximab a priori, because its long-term action impairs precise estimation of treatment discontinuation. Tofacitinib was excluded because we had insufficient TC to perform meaningful comparative effectiveness analyses against a single other specific tsDMARD agent. Included TNFi treatments were: adalimumab, etanercept, golimumab, certolizumab, infliximab. Included OMA treatments were: tocilizumab, abatacept, sarilumab, and anakinra.

Outcomes

The primary outcome of this analysis was the time to all-cause-discontinuation. This outcome, also referred to as "drug maintenance", captures both the drug's effectiveness and its tolerance.[24] The time to all-cause-discontinuation was defined as the number of days between treatment initiation and the reported date of discontinuation, or the date of initiation of a new b/tsDMARD, whatever came first. In survival analyses, death or lost-to-follow up are censored. We also report discontinuation rates at 12 months. Temporary discontinuations of less than 6 months (for instance, because of an elective surgery or a pregnancy) were not considered a permanent drug discontinuation. Discontinuation reasons are recorded by the clinician when stopping a DMARD treatment, who chooses between four options ("Adverse event", "Ineffectiveness", "Remission", or "Other").

Pre-planned secondary outcomes, were time to discontinuation due to ineffectiveness and time to discontinuation due to adverse events. Other secondary outcomes included response rates, namely the rates of low disease activity (LDA) and remission (REM), at 12 months, defined respectively as attaining a CDAI score <= 10 and CDAI score <= 2.8 (not mutually

exclusive).[25] Finally, we performed an exploratory subgroup analysis, restricting the population to b/tsDMARD-naive patients only, and re-assessing the main outcome in this setting.

Statistical analysis

Analyses were conducted and reported in accordance to EULAR recommendations for comparative effectiveness research.[9] Baseline characteristics were compared using generalized linear mixed models to account for repeated treatments within the same patients. For the primary outcomes, Kaplan-Meier survival analyses were used to assess crude drug maintenance, and groups were compared using Log-Rank tests. Subsequently, missing covariates were imputed using chained equations (see below for details). We then implemented Cox proportional hazard ratio models, to obtain adjusted estimates. Based on prior subject matter knowledge,[26] we adjusted our models for the following potential confounders: age, gender, BMI, concomitant csDMARDs use (yes/no), concomitant prednisone usage (yes/no), CDAI score at baseline, disease duration, smoking status (current-, former-, never-smoker) and line of therapy (1^{st}, 2^{nd}, 3^{rd}, 4^{th} or more), and seropositivity (yes/no). Detailed definitions for each variable are available in the supplement (Supplementary Material 1). The main analysis (survival analysis) accounted for clustering resulting from patients with multiple treatment courses, inducing correlation within the patient-level data. The cluster term is used to compute a robust variance for the model, by applying the so-called Huber sandwich estimator.[27] . All conditions of application of the Cox model were verified. One additional sensitivity analysis was conducted for the primary outcome, using augmented inverse probability of treatment weighting (AIPTW).

In secondary analyses, we used the Fine-Gray approach to assess specific reasons for drug discontinuation (i.e. ineffectiveness, or adverse event) in a competing-risk setting. The Fine-Gray method takes competing risks into account when estimating the cumulative incidence function, modelling the sub-distribution hazard without treating competing events as censoring events.[28] Other secondary outcomes included response rates (LDA and REM) at 12 months. To avoid overestimations, we computed the response rates using the 'confounder-adjusted response rate with attrition correction' (CARRAC) method.[29] The latter estimates the response rates using multiple imputations, with a model including both confounders and treatment stop reason. CARRAC thus provides reliable estimates when reasons for treatment discontinuation differ between compared groups.

For all adjusted analyses, missing baseline covariates were imputed using closest value in a window of -90 to +30 days. However, this window was reduced to -30 to +7 days when imputing baseline CDAI. If still missing after this first step, baseline CDAI values were imputed using linear mixed effect regression model with quadratic time. We imputed other baseline covariates with chained equations technique, which provides unbiased estimates if the variables are missing at random.[29] Such imputations were performed using 50 datasets with 25 iterations. Imputation was done using the whole data set, before adequately subsetting the data for each group comparison.

We also imputed data required for secondary outcomes, including disease activity. If the CDAI score at 12-month was not available, the closest value in a window of +/- 45 days was used (a 3-month-wide window). If still missing, the 12-month CDAI values were imputed using nearest neighboring value, as previously described.[30]

All analyses were conducted using R (version 4.0.3), in particular with packages "*tableone*", "*survival*", "*mice*".[31] Two tailed p-values < 0.05 were considered significant. We did not

adjust p value for multiple comparisons, as outcomes were pre-specified. Final analysis code is shown in the supplement (Supplementary Material 2).

Patient and Public Involvement

Patient involvement is central to the SCQM cohort. Several patients are part of the executive board and involved in the approval of research projects.

RESULTS

Population description

During the study period, 1053 TC were initiated in 834 different patients, including 273 TC with BARI, 473 with TNFi and 307 with OMA (Figure S1; Figure S2). TNFi were more often given as a second line therapy after methotrexate failure. Inversely, BARI was prescribed to significantly older patients, with longer disease durations and more previous treatment failures (Table 1).

Table 1: Baseline characteristics of study population, SCQM-RA registry, 2017-2020.

Variable	BARI (TC = 273; 273 pts)		TNFi (TC = 473; 408 pts)		OMA (TC = 307; 289 pts)		p values
	n % of total in group Otherwise: Mean (SD)						
Patients		*Miss.*		*Miss.*		*Miss.*	
Female	78 %	0	74 %	1	73 %	1	0.097
Age (years)	59 (14)	0	52 (15)	1	59 (13)	1	**0.021**
Disease duration (years)	13 (10)	4	8 (9)	19	11 (9)	5	**0.027**
CDAI baseline (raw data)	19 (10)	175	18 (10)	301	20 (13)	204	0.34
CDAI baseline (imputed)	15 (9)	0	14 (9)	0	16 (11)	0	0.06
Obesity (BMI > 30)	16 %	104	14 %	134	13 %	115	0.85
Smoking Current Former Never	17 % 28 % 43 %	32	18 % 26 % 41 %	69	21 % 28 % 48 %	26	Ref. 0.95 0.98
Seropositive (ACPA or RF)	75 %	1	70 %	7	77 %	5	0.92
TC		*Miss.*		*Miss.*		*Miss.*	
Concomitant csDMARD	40 %	0	61 %	0	46 %	0	**<0.01**
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	17 % 20 % 19 % 44 %	0	48 % 23 % 11 % 18 %	0	22 % 24 % 24 % 31 %	0	**Ref.** **<0.01** **<0.01** **<0.01**
Previous tsDMARD use (non-BARI)	33 %	0	1 %	0	5 %	0	**<0.01**
Concomitant glucocorticoid (at any time)	22 %	0	20 %	0	24 %	0	0.35
Mean dose of concomitant glucocorticoid (mg)	2.0 (4.6)	0	2.1 (5.4)	0	2.2 (5.1)	0	0.95
Dose of BARI (4mg)	86 %	0	-	-	-	-	-

Table 1 Legend: In Switzerland, BARI was prescribed to older patients, with longer disease duration and more previous treatment failures. Missing values for covariables are reported as absolute numbers

BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. Ref. = Reference

category for p-values (pairwise comparisons). P-values are obtained by generalized linear mixed models to account for repeated treatments within the same patients. In TFNi and OMA groups, some patients have contributed several TC, thus total number of TCs exceeds total number of patients.

Time to all-cause-discontinuation

Crude proportions of treatment discontinuation by reasons are reported in Table S1, and crude times of observation are represented on Figure S2.

At 12 months, based on the Kaplan-Meier curves (Figure 1), the estimated proportions of patients still on therapy were: 71% (95% CI [65% - 77%]) in the BARI group, 55% (95% CI [50% - 61%]) in the TNFi group, and 63% (95% CI [57% - 70%]) in the OMA group.

Overall, unadjusted time to all-cause-discontinuation was significantly longer in the BARI group compared to the TNFi group (estimated median prescription survival-time of 704 versus 448 days; Log-rank p<0.01; Figure 1). These results persisted after adjustment for confounding factors using the multivariable Cox model (HR = 1.76; 95% CI [1.32-2.35]; p<0.001; Table S2 and Figure S3; Figure S4).

BARI versus OMA time to all-cause-discontinuation was not significantly different, even after adjustment (HR 1.27; 95% CI [0.93-1.72]; p = 0.13; Table S2, Figure S3 and Figure S4).

Sensitivity analyses using AIPTW led to similar conclusions (Figure S5). Covariates significantly associated with decreased drug maintenance were high baseline CDAI scores and concomitant glucocorticoid usage (Table S2 and Figure S3).

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

In this exploratory subgroup analysis, we restricted the population to patients without prior experience of b/tsDMARDs (so-called 'bio-naïve' patients, i.e. first b/tsDMARD prescription after methotrexate failure). In this subpopulation, patient characteristics were more balanced than in the main analysis, except for age, which remained younger in TNFi population, and concomitant csDMARDs usage (more frequent in TNFi) (Table S3). Of note, the sample size was consequently reduced to 46 BARI, 225 TNFi and 66 OMA.

When analysing only these b/tsDMARD-naïve patients, both the non-adjusted (Figure 2) and the adjusted differences between BARI and TNFi became larger (HR TNFi vs BARI = 2.5; 95% CI [1.23 – 5.16]; p=0.01), but the differences between baricitinib and OMA group remained not significantly different (HR OMA vs BARI = 1.90; 95% CI [0.71 – 5.1]; p=0.2).

Time to discontinuation for adverse events or ineffectiveness

A secondary outcome was the cumulative incidence of drug discontinuation by specific reasons for discontinuation (ineffectiveness or adverse events, Figure 3). Using Fine-Gray adjusted approach, we found no difference in the incidence of adverse event comparing BARI to TNFi (HR = 1.46; 95% CI [0.83 - 2.57]; p=0.13), or BARI to OMA (HR = 1.34; 95% CI [0.74 - 2.42]; p=0.25). The incidence of drug discontinuation for ineffectiveness was more frequent in TNFi compared to BARI (HR = 1.49; 95% CI [1.03 – 2.15]; p=0.01), but similar between OMA and BARI (HR = 1.09; 95% CI [0.72 – 1.64]; p=0.69).

Remission and low disease activity at 12 months

The estimated 12-month rates of REM and LDA, estimated using CARRAC did not differ significantly between the 3 groups (Figure 4). LDA ranged from 62% to 71% and REM ranged from 17% to 26%.

DISCUSSION

In this study, the overall drug maintenance of BARI was significantly longer compared to TNFi, despite the fact that it was prescribed to older patients, with longer disease duration, and more previous treatment failures similar to what was observed in RA-BE-REAL, another real-world study.[23] However, the adjusted 12-month response rates in terms of LDA and REM did not differ significantly between BARI, TNFi and OMA groups. The difference in drug discontinuation owes mainly to more treatment discontinuations for ineffectiveness in the

TNFi group compared to the BARI group, while drug discontinuation due to adverse event did not differ significantly between the groups.

Our results are in line with previous findings comparing other JAK-inhibitors (JAKi) (i.e. tofacitinib as well as BARI) to TNFi and OMA medications,[22,32] which reported a longer drug maintenance of tsDMARD compared to TNFi, and similar maintenance to other bDMARDs. Of note, Lauper et al., using data from 19 national registers, found no difference in retention time between JAK-inhibitors and TNFi.[33] Still, Lauper et al. grouped all JAKi together in their study, thus it is not clear if these observations remain true for BARI alone, which might differ from other JAKi. For instance, Barbulescu et al. reported a higher drug maintenance for BARI as compared to tofacitinib.[21]

It was previously shown that BARI is more efficient in relieving pain as compared to adalimumab therapy [34] and some molecular mechanisms relevant to JAK-STAT signalling have been hypothesized.[35] This observation has been hypothesised to result anti-nociceptive effect independent from inflammation.[35] This faster pain relief could partially explain why BARI has increased maintenance than other medication in our study, even though having similar 12-months LDA and REM rates. An alternative hypothesis is that the more convenient oral administration encourages patients to stay on medication longer. Yet, a third possible interpretation is that patients who experienced numerous treatment failures tend to stay on their latest therapy; however, our study accounts for this potential bias, by performing a sensitivity analysis in a subgroup of b-tsDMARD naïve patients, which showed a similar result. Finally, given recent discussion regarding tofacitinib safety,[36] future research needs to clarify whether a class effect for JAKi related adverse events exist. In this analysis, we found no indication for an increased incidence of adverse-related treatment discontinuation with

BARI compared to alternative bDMARDs. Randomized controlled trials are ongoing to further compare safety profile of BARI versus TNFi (NCT04086745 and NCT03915964).

Limitations and Strengths

This work has several limitations, mostly inherent to the observational setting. First, as this is a non-randomized study, we cannot formally exclude unmeasured confounding between the groups. The available baseline variables were, in most cases, adequately balanced, except for age. When we restricted the analysis to the subgroup of b/tsDMARD naïve patients, we found largely similar results. Despite being limited by the small sample size, this exploratory subgroup analysis suggests that confounding by line of treatment was adequately accounted for in the adjusted analysis.

Secondly, the average length of follow-up was only approximatively 200 days per TC (Figure S2). Indeed, our study covers about 2 and a half years, and we only included TC newly initiated during this time-windows. Also, because of the study setting, as much as 65% of TC did not have CDAI scores recorded at the date of initiation, and many were missing at the 12-month exact timepoint (Figure S6). Hence, our analysis of response rates relied heavily on linear interpolation techniques, using other available timepoints, which results in large confidence intervals for estimated response rates.[30]

The main strength of the study is that it relies on real-world data and includes a relatively large number of patients providing adequate statistical power (Figure S7). As these patients are mostly treated by office-based rheumatologists, our study population is representative of routine clinical practice. Also, sub-group analyses and sensitivity analyses were consistent with the main results.

CONCLUSIONS

In this non-randomized cohort study, drug maintenance of BARI was significantly higher than TNFi. However, we found no difference in drug maintenance when comparing BARI with other bDMARDs. Based on available data, the estimated 12-month response rates did not significantly differ between BARI, TNFi and OMA groups. We found no difference in treatment discontinuation for adverse event between the three groups. Overall, our results are in line with findings from randomized trials..

OTHERS

Contributorship statement

Benoît GILBERT contributed to data-management, data-analysis, figures, manuscript drafting. Denis MONGIN contributed to data-management, data-analysis, figures, manuscript-revision. Romain AYMON contributed to data-analysis (in particular, sensitivity analyses), manuscript revision. Kim LAUPER took part in data-analysis and manuscript revision. Cédric LAEDERMANN was involved in the study design and manuscript revision. Clémentine PERRIER was involved in the study design and manuscript revision. Ruediger MUELLER contributed to the study design and manuscript revision. Delphine COURVOISIER was involved in the study design, data-analysis and interpretation, manuscript revision. Axel FINCKH was in charge of the study design (principal investigator), data analysis, data interpretation and manuscript revision.

Competing interests

Benoît GILBERT has been once a paid speaker (Eli Lilly) and participated in advisory board (Janssen). Clementine PERRIER is employed by Eli Lilly and holds stock options (Eli Lilly and Company). Cedric LAEDERMANN is employed by Eli Lilly and holds stock options (Eli Lilly and Novartis). Axel FINCKH has received grants or contracts (Eli-Lilly, Pfizer, Abbvie, Gilead, BMS), consulting fees (Astra-Zeneca, Abbvie, Pfizer, Gilead), honorary payments (BMIS, Abbvie, Eli Lilly, Pfizer, MSD), and participated in advisory boards (Astra-Zeneca, Gilead, Novartis, Abbvie, Eli Lilly, Pfizer, J&J, Mylan, UCB). Denis MONGIN, Romain Aymon, Rüdiger Müller and Delphine COURVOISIER have no conflicts of interest to disclose.

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Data sharing statement

Restrictions apply to the availability of these data. Data is owned by a third party, the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) foundation. Data may be obtained after approval and permission from this license holder (SCQM). Contact information for data request: scqm@hin.ch

Ethical Review and Regulatory Considerations

This observational study has been approved by the Geneva ethical review boards (ERBs) as required by local law (Project ID: 2019-00930 ; approval date 28 May 2019). Every participant has signed an information and consent form at inclusion in the SCQM registry. Hence, this study has been conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with Good Pharmacoepidemiology Practices (GPPs).

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34 Taylor PC, Lee YC, Fleischmann R, *et al.* Achieving Pain Control in Rheumatoid Arthritis with Baricitinib or Adalimumab Plus Methotrexate: Results from the RA-BEAM Trial. *JCM*. 2019;8:831.

35 Busch-Dienstfertig M, González-Rodríguez S. IL-4, JAK-STAT signaling, and pain. *JAKSTAT*. 2013;2:e27638.

36 Álvaro-Gracia JM, García-Llorente JF, Valderrama M, *et al.* Update on the Safety Profile of Tofacitinib in Rheumatoid Arthritis from Clinical Trials to Real-World Studies: A Narrative Review. *Rheumatol Ther*. 2021;8:17–40.

FIGURE LEGENDS

Figure 1 - Non-adjusted time to drug discontinuation analyses (Kaplan-Meier), SCQM, 2017-2020.

These “survival curves” represent the drug maintenance after initiation, as the estimated proportion of patients still on therapy, by treatment group. Death and loss to follow-up were censored. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : $p < 0.001$. Log-Rank BARI vs OMA: $p = 0.11$.

Figure 2 - Unadjusted time to drug discontinuation in b/tsDMARD-naïve patients, SCQM, 2017-2020.

These Kaplan-Meier curves represent the crude “survival” of drug prescription, by treatment group. Death and loss to follow-up are censored. BARI = baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : $p = 0.003$. Log-Rank BARI vs OMA : $p = 0.15$.

Figure 3 - Cumulative incidence of drug discontinuation by stop reason and by type of treatment, SCQM, 2017-2020.

This figure represents the unadjusted cumulative incidence of drug discontinuation, by group and by reason of discontinuation. BARI = baricitinib. TNFi = Tumor Necrosis Factor. OMA = Other mode of Action bDMARDs.

Figure 4 - Estimated response rates at 12-months (CARRAC), SCQM, 2017-2020.

BARI = baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other Mode of Action bDMARDs. LDA = Low Disease Activity (i.e. CDAI score <= 10), in light grey. REM = Remission

(i.e. CDAI score <= 2.8), in dark grey. 95% CI are represented. This method does not allow computing p-values. Nb: two estimates were obtained in the BARI group and averaged to display only one representative value on the plot. Actual row output was 68% (95%CI [55% ; 80%]) (BARI vs TNFi model) or 62% (95% CI [54% ; 70%]) (BARI vs OMA model) for LDA, and 23% (95% CI [14% ; 31%]) (BARI vs TNFi model) or 17 % (95% CI [10% ; 24%]) (BARI vs OMA model) for REM.

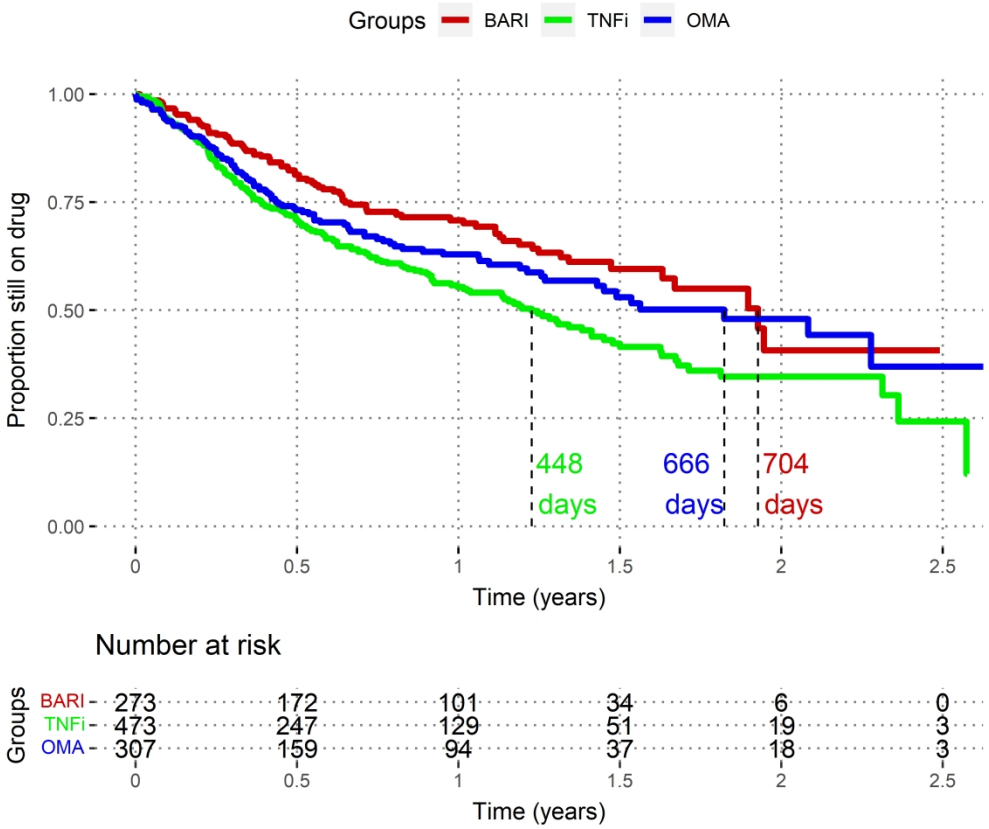

Figure 1 - Non-adjusted time to drug discontinuation analyses (Kaplan-Meier), SCQM, 2017-2020. These "survival curves" represent the drug maintenance after initiation, as the estimated proportion of patients still on therapy, by treatment group. Death and loss to follow-up were censored. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : p < 0.001. Log-Rank BARI vs OMA: p = 0.11.

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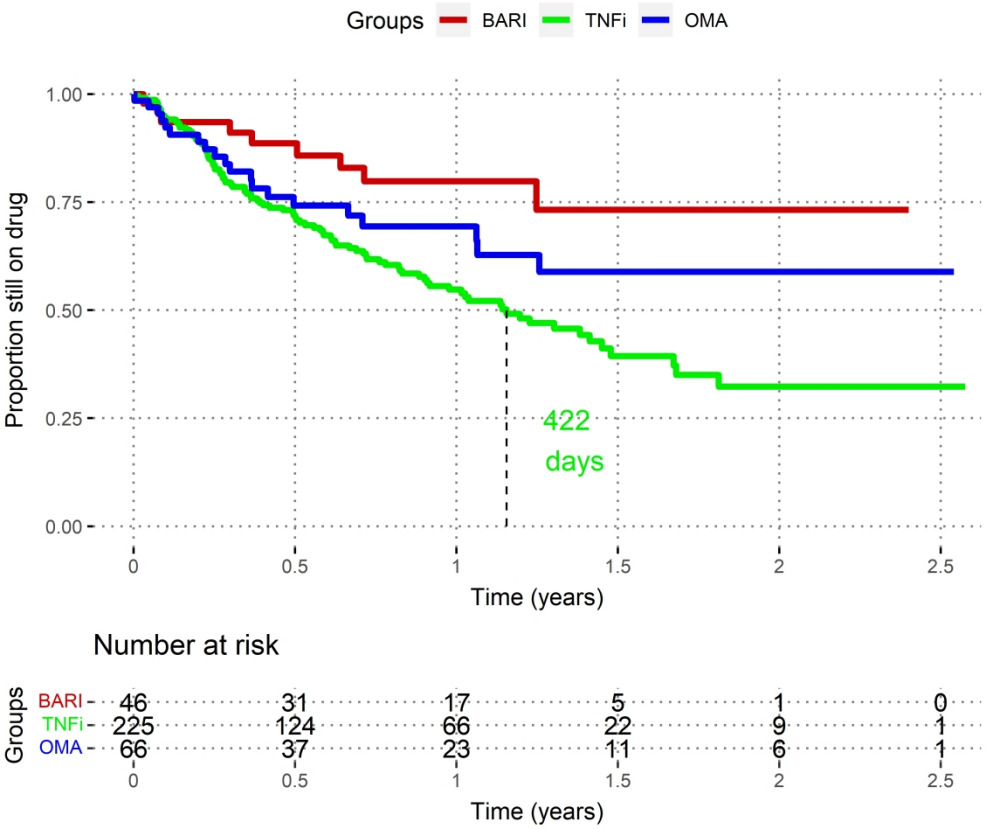

Figure 2 - Unadjusted time to drug discontinuation in b/tsDMARD-naïve patients, SCQM, 2017-2020. These Kaplan-Meier curves represent the crude "survival" of drug prescription, by treatment group. Death and loss to follow-up are censored. BARI = baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs. Log-Rank BARI vs TNFi : p = 0.003. Log-Rank BARI vs OMA : p = 0.15.

451x386mm (197 x 197 DPI)

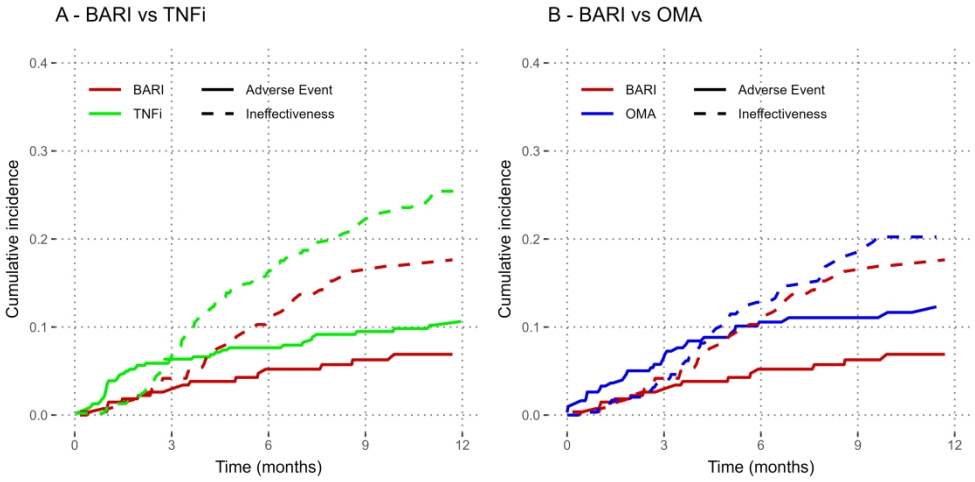

Figure 3 - Cumulative incidence of drug discontinuation by stop reason and by type of treatment, SCQM, 2017-2020.
This figure represents the unadjusted cumulative incidence of drug discontinuation, by group and by reason of discontinuation. BARI = baricitinib. TNFi = Tumor Necrosis Factor. OMA = Other mode of Action bDMARDs.

644x322mm (197 x 197 DPI)

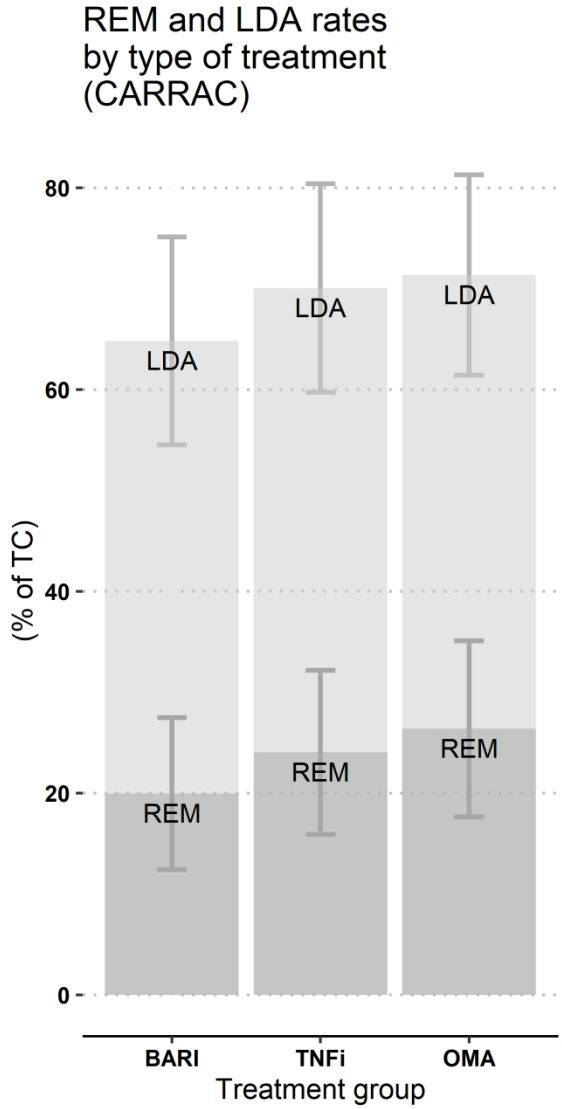

Figure 4 - Estimated response rates at 12-months (CARRAC), SCQM, 2017-2020.
BARI = baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other Mode of Action bDMARDs. LDA = Low Disease Activity (i.e. CDAI score <= 10), in light grey. REM = Remission (i.e. CDAI score <= 2.8), in dark grey. 95% CI are represented. This method does not allow computing p-values. Nb: two estimates were obtained in the BARI group and averaged to display only one representative value on the plot. Actual row output was 68% (95%CI [55% ; 80%]) (BARI vs TNFi model) or 62% (95% CI [54% ; 70%]) (BARI vs OMA model) for LDA, and 23% (95% CI [14% ; 31%]) (BARI vs TNFi model) or 17 % (95% CI [10% ; 24%]) (BARI vs OMA model) for REM.

257x451mm (197 x 197 DPI)

SUPPLEMENTARY DATA

Selection of eligible treatment courses

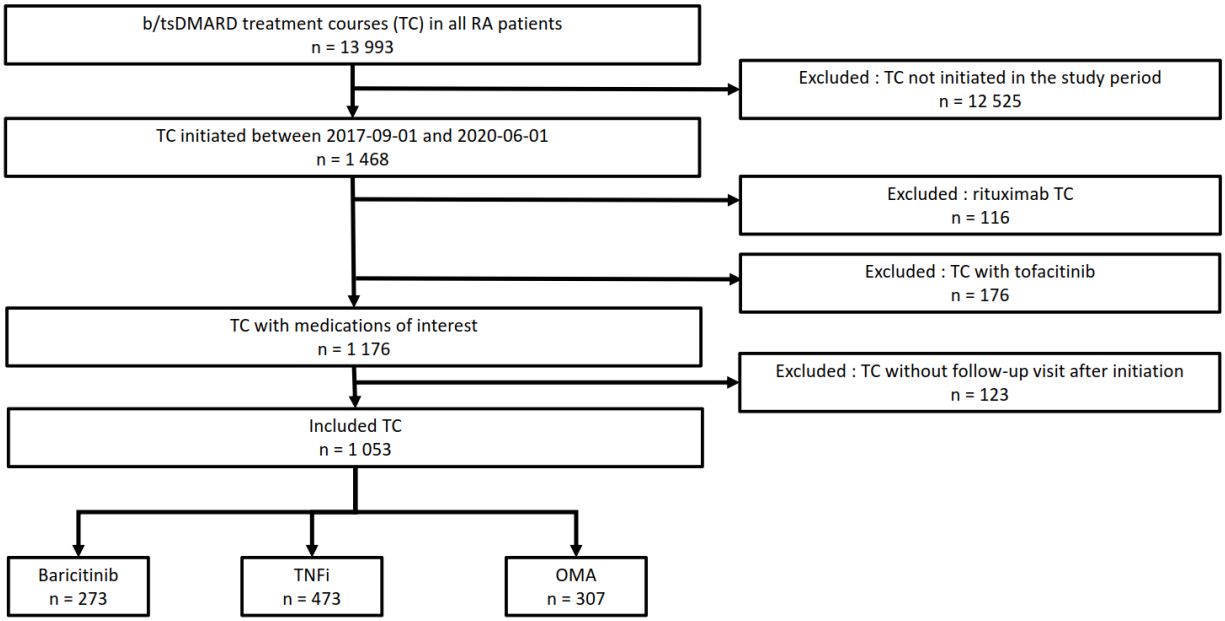

Figure S1 - Selection of eligible treatment courses, SCQM, 2017-2020.

Selection of Treatment courses included in final analysis. TC = Treatment Courses. RA = Rheumatoid Arthritis. bDMARD = biological DMARD. tsDMARD = targeted synthestic DMARD. b/tsDMARD = biological and/or targeted synthetic DMARD. TNFi = TNF inhibitors. OMA = Other Mode of Action bDMARDs.

Notice on TC duration

Due to frequent changes in medication and short study period, it has to be underlined that the median duration of a TC approximates 200 days. The proportion of TC with follow-up data of at least one year is 37% for BARI, 27% for TNFi and 31% for OMA (Figure S2) - i.e. most TC were started less than 12 months before the date of data extraction.

Notice this % is different from the % of patient still under therapy that we estimate using Kaplan-Meier or Cox model. Indeed, the latter includes a censoring of the lost-to-follow-up patients, hence the denominator is different. As a consequence, this does not contradict the reported “median prescription survival timey”, for instance of 704 days for BARI TCs. The latter is the output estimated by the Kaplan-Meier model, taking censoring into account; it does not imply that actual observations in the dataset have this duration.

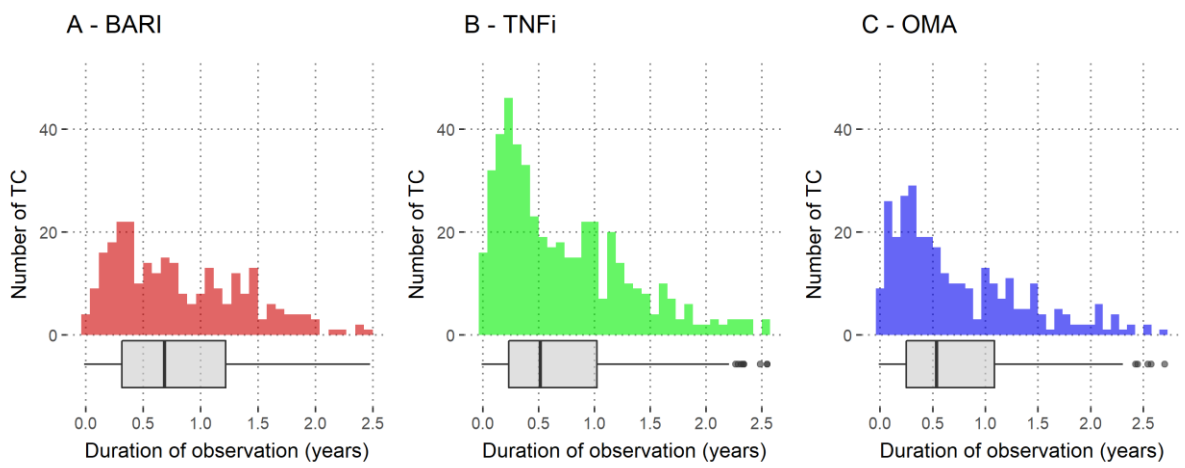

Figure S2: Distribution of the observation time for included TCs, per group, SCQM, 2017-2020. Most of the treatment courses have an actual duration and/or follow-up period of less than one year. TC = Treatment Course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs.

Variable definitions

Below we give additional detail about included covariates:

Age: age in years, at TC initiation. Continuous variable.

Gender: male or female. Categorical variable.

BMI: BMI at TC initiation. Continuous variable.

CDAI score: CDAI score at TC initiation. Continuous variable. If missing, imputed according to procedure described in methods section.

Disease duration: time interval between RA diagnosis date and TC initiation date. Continuous variable, expressed in years, but used in decades in models.

Smoking status: smoking status at TC initiation. Categorical variable (current-, former-, never-smoker).

Concomitant csDMARD: yes/no variable. A concomitant csDMARD was defined as csDMARD prescription ongoing for at least 40% of the duration of the TC. Otherwise, the TC was categorized as monotherapy. csDMARDs included: methotrexate, sulfasalazin, leflunomide, azathioprine and hydroxy-chloroquine, alone or in combination.

Concomitant glucocorticoid: Yes/no variable. Concomitant glucocorticoid usage was defined as having at least one active prescription of glucocorticoid, at any dose, at any timepoint of the TC.

Line of therapy: strictly speaking, this categorical variable is displaying: [*number of previous TC ever* + 1]. 4 or more has been grouped in the same category. Hence, it is considering all data of the SCQM registry, i.e. TCs initiated before our study period are also accounted for as previous therapies.

Seropositivity: yes/no variable. Seropositivity is defined as positivity for anti-citrullinated peptide antibodies and/or rheumatoid factor.

Time to all cause discontinuation

Table S1: Crude treatment discontinuation by group and by reason, SCQM, 2017-2020.			
	BARI (TCs = 273; 273 pts)	**TNFi (TCs = 473; 408 pts)**	**OMA (TCs = 307; 289 pts)**
Treatment discontinuation (all causes)	30 %	43 %	35 %
For adverse events	8 %	10 %	10 %
For ineffectiveness	16 %	23 %	17 %
For remission	0 %	1 %	0 %
For other reason	5 %	8 %	7 %

Table S1 legend: % are computed on total number of TCs per group, for the whole study period. BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. TC = Treatment Courses. Pts = Number of patients. Due to rounding, the sum of the percentages of the causes of discontinuation may not correspond exactly to the total treatment discontinuation percentage.

Cox model output

Table S2 contains the complete output of the two adjusted Cox models used in the main time-to-drug discontinuation analysis.

Table S2: Hazard ratio of drug discontinuation, Cox models, SCQM-RA registry, 2017-2020.

	BARI vs TNFi			**BARI vs OMA**		
	Hazard ratio	**95% CI**	**p**	**Hazard ratio**	**95% CI**	**p**
TNFi (vs baricitinib)	1.76	1.32-2.35	**<0.001**	-	-	-
OMA (vs baricitinib)	-	-	-	1.27	0.93-1.72	0.13
Adjusting variables:						
Age (decades)	1.03	0.92-1.14	0.61	0.98	0.86-1.10	0.69
BMI	1.01	0.98-1.04	0.51	0.98	0.94-1.02	0.31
TC with csDMARD	0.84	0.66-1.09	0.19	1.22	0.90-1.67	0.20
Glucocorticoid usage	1.29	0.93-1.79	0.12	1.86	1.32-2.61	**<0.001**
CDAI score	1.40	1.26-1.56	**<0.001**	1.15	1.03-1.28	**0.01**
Disease duration (decades)	0.95	0.81-1.10	0.46	0.85	0.70-1.03	0.10
Current smoker (vs non-smoker)	1.20	0.86-1.68	0.28	1.09	0.73-1.64	0.66
Ever smoker (vs non-smoker)	1.10	0.79-1.52	0.57	1.38	0.95-2.00	0.09
2nd line therapy (vs 1st)	1.11	0.80-1.53	0.52	1.37	0.81-2.33	0.24
3rd line therapy (vs 1st)	0.98	0.64-1.51	0.93	1.56	0.92-2.64	0.10
4th or later line (vs 1st)	1.06	0.75-1.51	0.73	1.57	0.93-2.63	0.09
Female gender	1.05	0.78-1.42	0.74	1.16	0.81-1.67	0.41
Seropositivity	0.77	0.59-1.01	0.055	0.94	0.67-1.31	0.71

BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. CI = Confidence Interval. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index.

Figure S3 below gives the exact same information as Table S2:

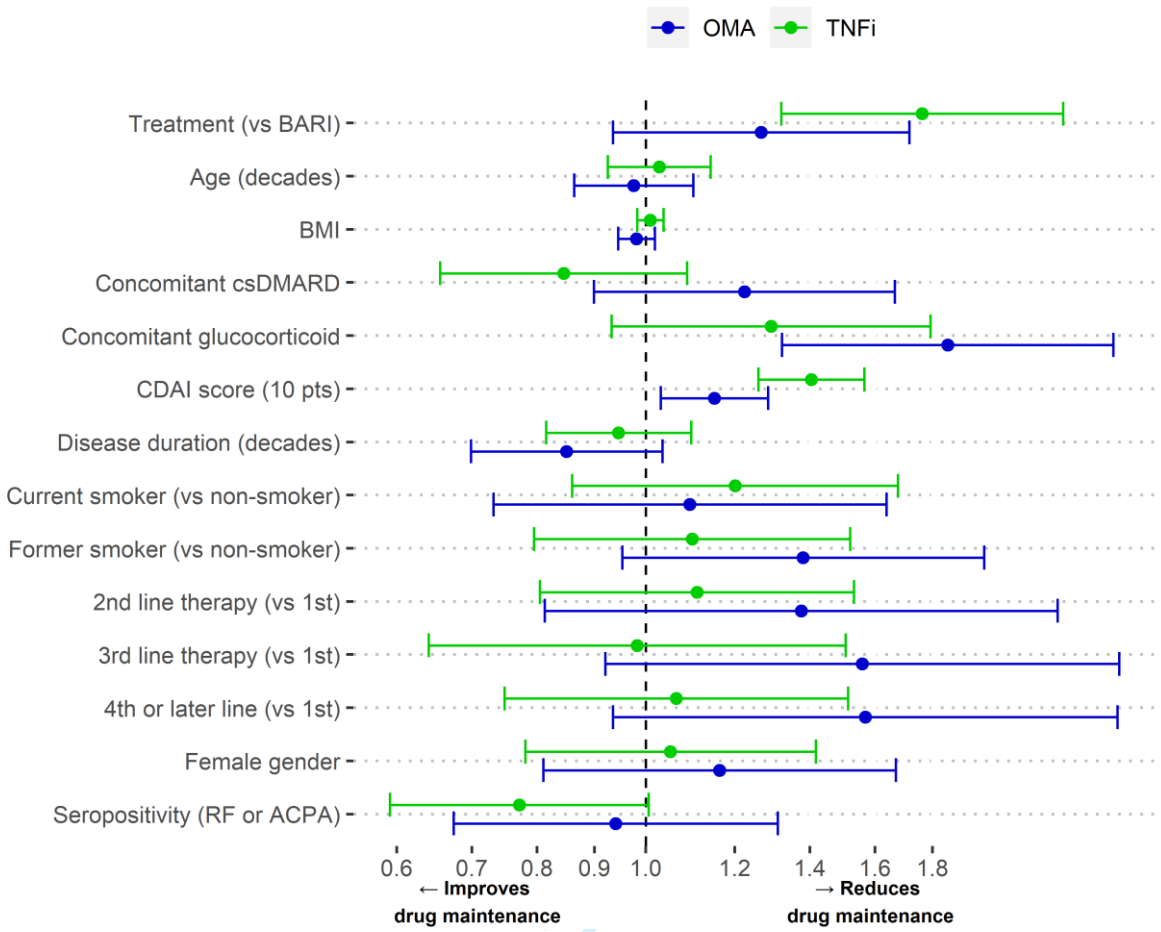

Figure S3: Hazard ratio of drug discontinuation (95% CI).

BARI = Baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other mode of Action bDMARDs. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index. RF = Rheumatoid Factor. ACPA = Anti-citrullinated Peptides Antibodies.

The corresponding cox-adjusted drug-survival curves are provided below:

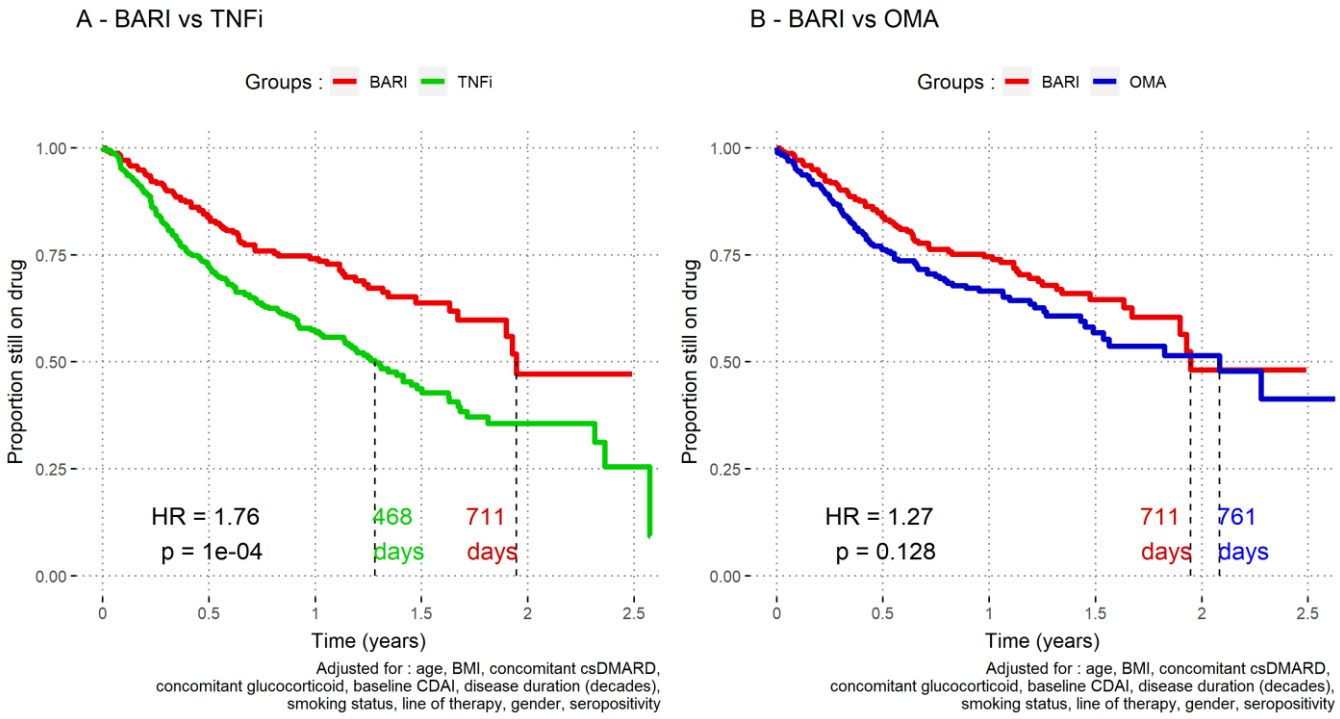

Figure S4: Multivariable Cox model of drug discontinuation by type of treatment, SCQM, 2017-2020.

These curves are merlely the visualisation of Cox models presented in Table S1 and Figure S2.

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action bDMARDs

Models are adjusted for : age, BMI, concomitant csDMARD, concomitant glucocorticoïd, baseline CDAI, disease duration, smoking status, line of therapy, gender, serpostivity.

Sensitivity analysis using AIPTW

As a sensitivity analysis, the main time to drug discontinuation was also performed using "augmented inverse probability of treatment weighting" (AIPTW), including the same covariates. In other words, we combined a propensity score using a logistic regression model and an inverse probability weighted Cox regression. We used the *RiskRegression* package in R, to obtain risk ratios.

Figure S5 represents the absolute risk of treatment discontinuation, for all included timepoints. At one year, the adjusted discontinuation risk in BARI was 19 % lower than in TNFi group (p<0.001) (Figure S5 A), with a risk ratio of 1.76 (95% CI [1.19 – 2.34]; p=0.009). Similarly, at one year, the adjusted treatment discontinuation risk in BARI was 8 % lower than in the OMA group (p=0.06) (Figure S5 B), with a risk ratio of 1.28 (95% [0.91 – 1.65]; p=0.14). Overall, this sensitivity analysis confirms the findings reported in the main body of the article.

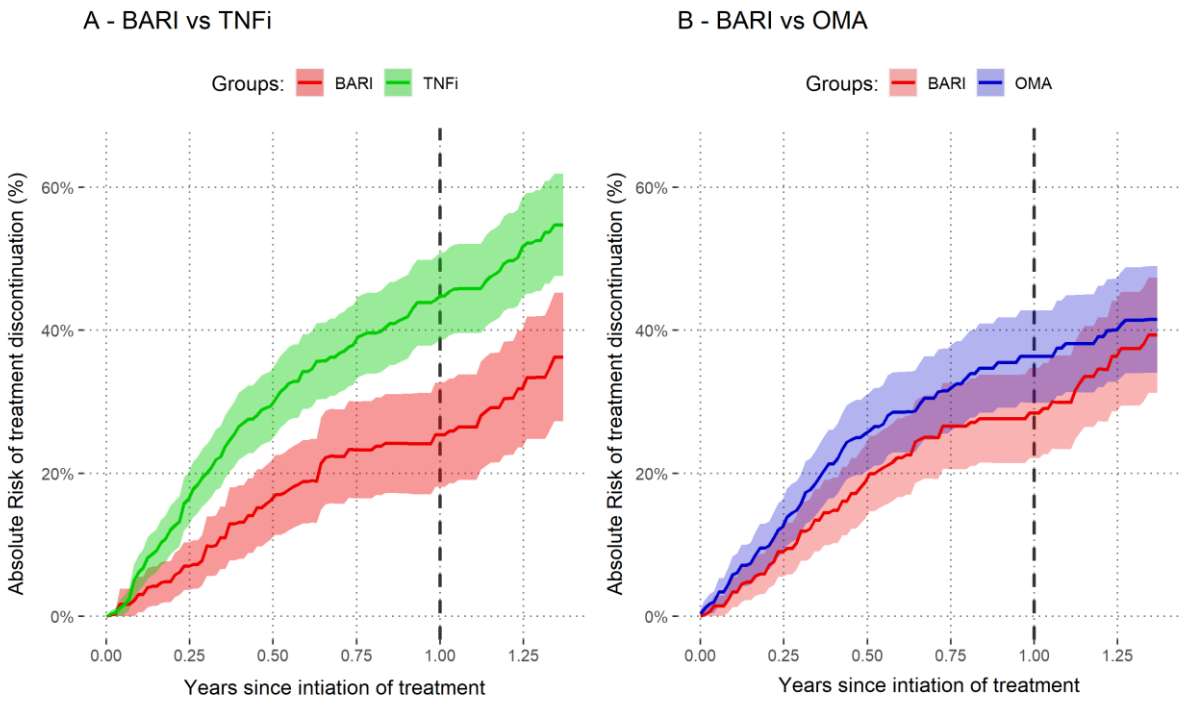

Figure S5: Absolute risk of treatment discontinuation by type of treatment (AIPTW), SCQM, 2017-2020)

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inihibitors. OMA = Other Modes of Action bDMARDs. AIPTW = Augmtented Inverse Probability of Treatment Weigthning. Adjusted for : age, bmi, concomitant csDMARDs, prednisone usage, baseline CDAI, disease duration, smoking status, line of therapy, gender, seropositivity.

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

Table S3: Baseline characteristics of study population, b/tsDMARD-naïve patients, SCQM-RA registry, 2017-2020.

	BARI (n = 46)		**TNFi (n = 225)**		**OMA (n = 66)**		**p values**
	n % Otherwise: Mean (SD)						
Patient-Variables		Miss.		Miss.		Miss.	
Female	70 %	0	71 %	1	73 %	1	0.88
Age (years)	57 (15)	0	52 (14)	1	57 (16)	1	<0.01
Disease duration (years)	6 (6)	1	5 (7)	13	7 (9)	2	0.24
CDAI baseline (raw data)	16 (8)	31	18 (10)	135	18 (14)	42	0.77
CDAI baseline (imputed)	12 (7)	0	14 (9)	0	14 (10)	0	0.61
Obesity (BMI > 30)	11 %	13	13 %	58	5 %	27	0.28
Smoking Current Former Never	 28 % 26 % 26 %	9	 18 % 24 % 39 %	42	 14 % 21 % 46 %	13	0.18
Seropositive (ACPA or RF)	80 %	1	69 %	5	76 %	2	0.20
TC variables							
Dose of BARI (4mg)	83 %	0	-	-	-	-	-
TC duration > 12-months	37 %	0	29 %	0	35 %	0	0.48
Concomitant csDMARD	41 %	0	66 %	0	50 %	0	<0.01
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	100 %	0	100 %	0	100 %	0	-
Previous tsDMARD use (non-BARI)	0 %	0	0 %	0	0 %	0	-
Concomitant glucocorticoid (at any time)	13 %	0	20 %	0	17 %	0	0.50
Mean dose of concomitant glucocorticoid (mg)	1 (4)	0	3 (6)	0	2 (6)	0	0.50

Table S3: BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. p-values are computed with either Chi^2 or ANOVA.

Response rates – raw CDAI data

Figure S6 shows the crude available values for CDAI scores, by type of treatment and time. Only a minority of CDAI scores were assessed at 0- or 12-month timepoints of TCs (i.e. 680/1053 = 65% were missing for baseline value, and 908/1053 = 86% were missing for exact 12-month value). Future research would certainly benefit having CDAI scores assessed at regular and homogenous time-intervals, based on the initiation date of biological therapies.

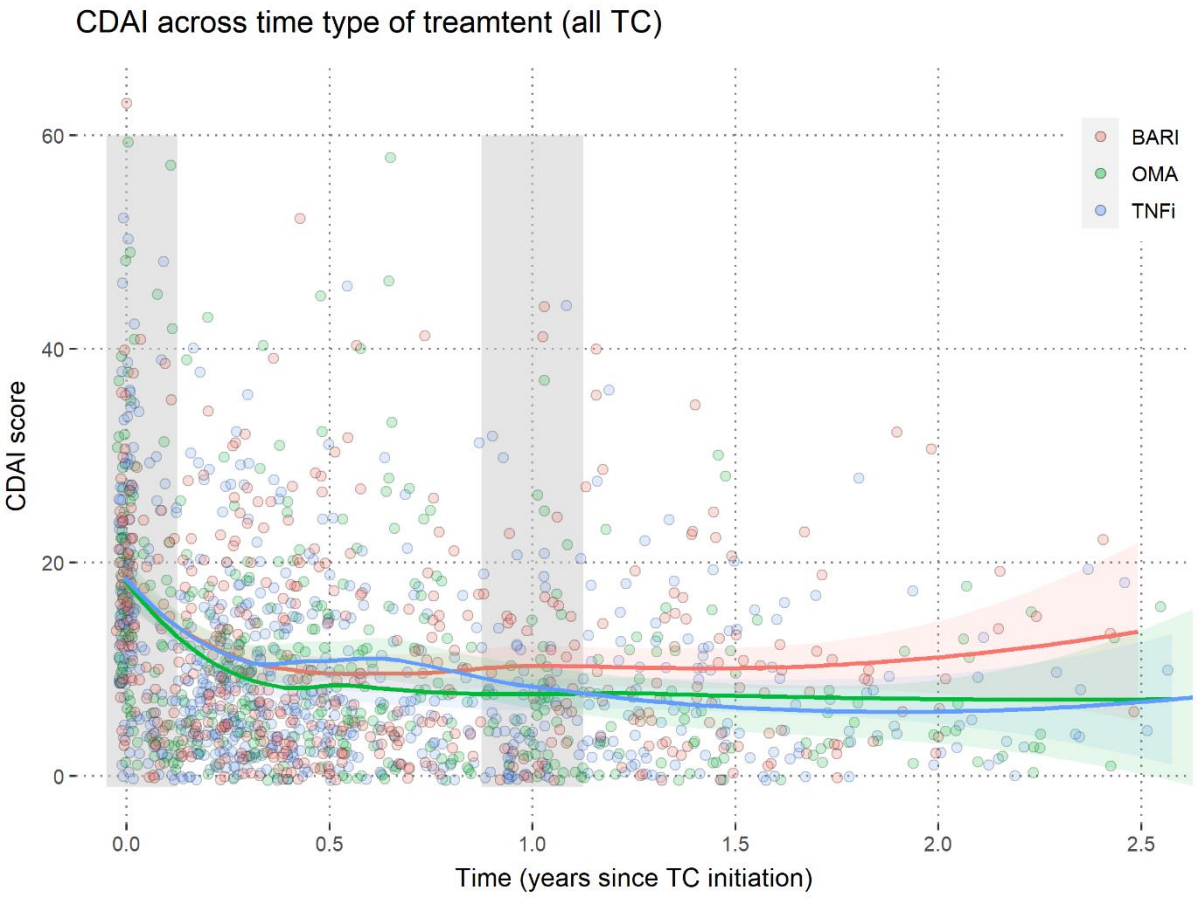

Figure S6: CDAI across time by type of treatment, raw data, SCQM, 2017-2020.

Only a minority of CDAI score were obtained sharp at 0 or 12 months of TCs. CDAI = Clinical Disease Activity Index. TC = Treatment course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action b/tsDMARDs.

Study size

Based on estimates from similar analyses with tofacitinib (TOFA) performed in this registry, we calculated the number of patients that would be needed to detect a significant decrease in time to all cause-discontinuation of treatment (hazard ratio) between treatment groups using the method described by Schoenfeld and Richter. We assumed a statistical power of 80%, a type I error probability of 0.05, a median BARI retention of 30 months, the inclusion of 3 patients on TNFi for every patient on BARI, an accrual time of 2 years, and additional follow-up of 6 months. We display below the sample size for the BARI group for a range of possible effect sizes ("hazard ratio" between 1.1 and 1.8).

If the true hazard ratio is similar to the one found with TOFA compared to TNFi after a single TNFi failure (HR 1.68), we will need to study 149 patients on BARI and 447 patients on TNFi to be able to reject the null hypothesis that the experimental and control curves are equal with probability (power) of 80%. Pragmatically, we propose to start the analysis of the data only once at least 200 patients on BARI have been included and followed for an average of at least 18 months.

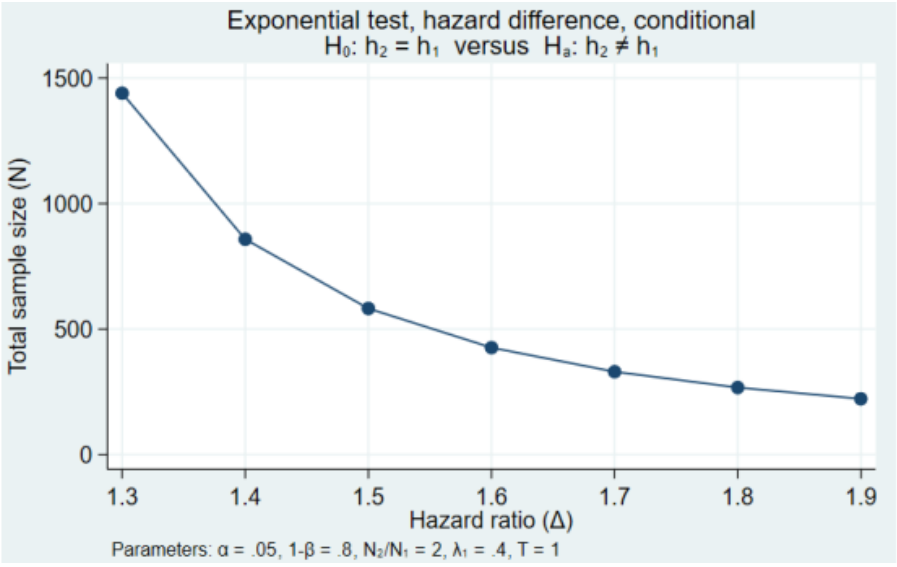

Figure S7: Estimated total sample size for two-sample comparison of survivor functions

1 - SURVIVAL ANALYSIS

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(gridExtra)
library(grid)
library(cmprsk)
library(mstate)
library(cobalt)

rm(list = ls()) # To select all loaded objects and delete them
setwd(dirname(rstudioapi::getActiveDocumentContext()$path)) # setting
up working directory in the location of the .Rmd file

load("./1_datamanaged_files/datamanaged.Rdata") # loading data.managed
data
```

Loading fonctions

```
# home-made function to force writing with two decimals
formattable = function(nbr){return(formatC(nbr,format = "f",digits =
nombreapresvirgule))}
nombreapresvirgule <- 2

# Home-made Fonction to write the p value (by denis)
writepvalue = function(pvalue) {
  if (is.na(pvalue)) {result <- NA} else {
    if(pvalue < 0.001) {
```

```
      result <- "<0.001"
    } else if (pvalue <0.01) {
      result <- formatC( pvalue ,format = "f",digits = 3)
    }
    else {
      (result <- formatC( pvalue ,format = "f",digits = 2) )
      i = 1
      while(result == 0.05) {
        result <- formatC( pvalue ,format = "f",digits = 2 + i)
        i = i + 1
      }}
    return(result)
  }
}
options(scipen = 999)
```

Mini Exploration

```
uniqueN(BARI_DATA[]$patient_id) # number of patients (< than number of
TC)
uniqueN(BARI_DATA[]$TC_id) # unmber of TC

plot <- qplot(x = BARI_DATA[]$time_on_drug)+
  geom_vline(xintercept = 365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 365 + 40, label="1 Year", y=20), colour="white",
angle=0)+

  geom_vline(xintercept = 2*365, size = 1.2, alpha = 0.5)+
  geom_text(aes(x = 2*365 + 40, label="2 Year", y=20), colour="black",
angle=0)+

  geom_vline(xintercept = mean(BARI_DATA$time_on_drug), color = "red",
size = 1.2)+
  geom_text(aes(x = mean(BARI_DATA$time_on_drug) + 40, label="Mean",
y=20), colour="red", angle=0)+

  geom_vline(xintercept = median(BARI_DATA$time_on_drug), color =
"green", size = 1.2)+
  geom_text(aes(x = median(BARI_DATA$time_on_drug) - 40,
label="Median", y=20), colour="green", angle=0)+

  labs(x = "Duration of TC (days)", y = "Number of TC", title =
"Repartition of the duration of included TC (all groups)")+

  theme_pubclean()

plot

mean(BARI_DATA$time_on_drug)
```

```
median(BARI_DATA$time_on_drug)

# Nb : Research protocol said we wanted a follow-up duration of
"average of 18 months"
mean(BARI_DATA[cohort == "BARI"]$time_on_drug)/30
mean(BARI_DATA[cohort == "TNFi"]$time_on_drug)/30
mean(BARI_DATA[cohort == "OMA"]$time_on_drug)/30 # looks more like 9
months..

# ok, 24-month follow-up will be complicated
uniqueN(BARI_DATA[time_on_drug > 2*365, TC_id]) # number if TC with
duration > 24 months
```

1. [0] Table 1 BARI vs TNFi et OMA bDMARDs

Common table with all the data

Showing NA to have complete counts and accurate % in each category

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving table 1 NA

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1_NA.xlsx")
```

Without NA to obtain adequate p values

```
BARI_DATA[,time_on_drugDiff0 := as.numeric(time_on_drug > 0)] # time
in drug < 0
```

```
BARI_DATA[,time_on_drug365 := as.numeric(time_on_drug > 365.25)]

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars2 <- c()
tab2 <- CreateTableOne(vars = myVars2, data = BARI_DATA, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp2 <- print(tab2, nonnormal= nonnormalVars2, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving table 1

```
write.xlsx(tab1exp2, file =
"./3_clean_output/BARI_3_groups_table1.xlsx")
```

But BMJ-Open reviewer 2 aksed for p-values in Table 1 that account for patients providing multiple TCs. Here is how to proceed (it is a bit less conservative):

```
library(lme4)
library(lmerTest)

# Two glmer() models have to be compared, to assess the impact of
grouping, for each baseline variable).

# gender
gender.tab1 <- glmer(gender ~ cohort + (1|patient_id), data =
BARI_DATA , family = "binomial")
gender.null <- glmer(gender ~ (1|patient_id), data = BARI_DATA ,
family = "binomial")
anova(gender.tab1, gender.null)

# Age_base
age_base.tab1 <- lmer(age_base ~ cohort + (1|patient_id), data =
BARI_DATA )
age_base.null <- lmer(age_base ~ (1|patient_id), data = BARI_DATA)
anova(age_base.tab1, age_base.null)

# Disease duration
disease_duration_base_years.tab1 <- lmer(disease_duration_base_years ~
cohort + (1|patient_id), data = BARI_DATA )
```

```
disease_duration_base_years.null <- lmer(disease_duration_base_years ~
(1|patient_id), data = BARI_DATA)
anova(disease_duration_base_years.tab1,
disease_duration_base_years.null)


# CDAI raw
CDAI0_raw.tab1 <- lmer(CDAI0_raw ~ cohort + (1|patient_id), data =
BARI_DATA )
CDAI0_raw.null <- lmer(CDAI0_raw ~ (1|patient_id), data = BARI_DATA)
anova(CDAI0_raw.tab1, CDAI0_raw.null)


# CDAI (imputed)
CDAI0.tab1 <- lmer(CDAI0 ~ cohort + (1|patient_id), data = BARI_DATA )
CDAI0.null <- lmer(CDAI0 ~ (1|patient_id), data = BARI_DATA)
anova(CDAI0.tab1, CDAI0.null)


# obesity
obese_base.tab1 <- glmer(obese_base ~ cohort + (1|patient_id), data =
BARI_DATA , family = "binomial")
obese_base.null <- glmer(obese_base ~ (1|patient_id), data = BARI_DATA
, family = "binomial")
anova(obese_base.tab1, obese_base.null)


# smoker base - 1st level vs second level
smoker_base.tab1 <- glmer(smoker_base ~ cohort + (1|patient_id), data
= BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "FORMER_SMOKER")]  ,
family = "binomial")
smoker_base.null <- glmer(smoker_base ~ (1|patient_id), data =
BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "FORMER_SMOKER")]  ,
family = "binomial")
anova(smoker_base.tab1, smoker_base.null)


# smoker base - 2nd level versus third
smoker_base.tab1 <- glmer(smoker_base ~ cohort + (1|patient_id), data
= BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "NEVER_SMOKER")]  ,
family = "binomial")
smoker_base.null <- glmer(smoker_base ~ (1|patient_id), data =
BARI_DATA[smoker_base %in% c("CURRENT_SMOKER", "NEVER_SMOKER")]  ,
family = "binomial")
anova(smoker_base.tab1, smoker_base.null)


# seropositivity
seropositivity_base.tab1 <- glmer(seropositivity_base ~ cohort + (1|
```

```
patient_id), data = BARI_DATA , family = "binomial")
seropositivity_base.null <- glmer(seropositivity_base ~ (1|
patient_id), data = BARI_DATA , family = "binomial")
anova(seropositivity_base.tab1, seropositivity_base.null)


# Concomittant csDMARD
TC_with_csDMARD.tab1 <- glmer(TC_with_csDMARD ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
TC_with_csDMARD.null <- glmer(TC_with_csDMARD ~ (1|patient_id), data =
BARI_DATA , family = "binomial")
anova(TC_with_csDMARD.tab1, TC_with_csDMARD.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "2nd")]
, family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "2nd")] ,
family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "3rd")]
, family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st", "3rd")] ,
family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# Line of therapy
line_of_therapy.tab1 <- glmer(as.factor(line_of_therapy) ~ cohort +
(1|patient_id), data = BARI_DATA[line_of_therapy %in% c("1st",
"4th_or_later")] , family = "binomial")
line_of_therapy.null <- glmer(as.factor(line_of_therapy) ~ (1|
patient_id), data = BARI_DATA[line_of_therapy %in% c("1st",
"4th_or_later")] , family = "binomial")
anova(line_of_therapy.tab1, line_of_therapy.null)


# N_prev_tsDMARD
N_prev_tsDMARD.tab1 <- glmer(as.factor(N_prev_tsDMARD) ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
N_prev_tsDMARD.null <- glmer(as.factor(N_prev_tsDMARD) ~ (1|
patient_id), data = BARI_DATA , family = "binomial")
```

```
anova(N_prev_tsDMARD.tab1, N_prev_tsDMARD.null)


# Concomittant prednisone
PREDNISON_STEROID.tab1 <- glmer(PREDNISON_STEROID ~ cohort + (1|
patient_id), data = BARI_DATA , family = "binomial")
PREDNISON_STEROID.null <- glmer(PREDNISON_STEROID ~ (1|patient_id),
data = BARI_DATA , family = "binomial")
anova(PREDNISON_STEROID.tab1, PREDNISON_STEROID.null)


# Dose of PREDNISONE
PREDNISON_STEROID_dose.tab1 <- lmer(PREDNISON_STEROID_dose ~ cohort +
(1|patient_id), data = BARI_DATA )
PREDNISON_STEROID_dose.null <- lmer(PREDNISON_STEROID_dose ~ (1|
patient_id), data = BARI_DATA)
anova(PREDNISON_STEROID_dose.tab1, PREDNISON_STEROID_dose.null)
```

Other various computations for Table 1 —-

```
uniqueN(BARI_DATA$patient_id)

mean(BARI_DATA[, time_on_drug])

median(BARI_DATA[cohort == "Bari" , time_on_drug])
median(BARI_DATA[cohort == "OMA" , time_on_drug])
median(BARI_DATA[cohort == "TNFi" , time_on_drug])

median(BARI_DATA[cohort == "OMA"]$time_on_drug)

mean(BARI_DATA[,disease_duration_base_years], na.rm = T)

table(is.na(BARI_DATA$CDAI0_raw), BARI_DATA$cohort) # number of
missing CDAI0_raw...
table(is.na(BARI_DATA$CDAI0), BARI_DATA$cohort) # number of missing
CDAI0... (after imputation)

table(is.na(BARI_DATA$CDAI12_raw), BARI_DATA$cohort) # number of
missing CDAI12_raw...
table(is.na(BARI_DATA$CDAI12), BARI_DATA$cohort) # number of missing
CDAI12 after imputation

hist(BARI_DATA$CDAI0_raw)
hist(BARI_DATA$CDAI0)

summary(BARI_DATA[cohort=="BARI", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
```

```
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="TNFi", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID",  "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

summary(BARI_DATA[cohort=="OMA", c("gender",
"age_base","disease_duration_base_years", "CDAI0_raw", "CDAI0",
"obese_base", "smoker_base", "seropositivity_base", "time_on_drug365",
"TC_with_csDMARD", "line_of_therapy", "N_prev_tsDMARD",
"PREDNISON_STEROID", "PREDNISON_STEROID_dose", "dose",
"initiation_year", "time_on_drug","HAQ_score_base")]) # to see NA
values for all variables

table(is.na(BARI_DATA$disease_duration_base_years), BARI_DATA$cohort)
# number of missing disease duration...

table(is.na(BARI_DATA$age_base), BARI_DATA$cohort) # number of steroid
doses missing

table(is.na(BARI_DATA$PREDNISON_STEROID_dose), BARI_DATA$cohort) #
number of missing baseline steroids
```

Imputation using MICE —- BARI vs TNFi et OMA bDMARDs —-

Common imputation step with all data

```
BARI <- BARI_DATA[,c("TC_id", "patient_id", "stop_DMARD",
"stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0", "disease_duration_base_years", "time_on_drug", "bmi_base",
"smoker_base", "line_of_therapy", "obese_base", "gender", "cohort",
"adverse_event_reported", "seropositivity_base")] # choose variables
of interest

BARI$smoker_base <- as.factor(BARI$smoker_base) # put labels as factor
BARI$line_of_therapy <- as.factor(BARI$line_of_therapy)
BARI$gender <- as.factor(BARI$gender)
BARI$concomitant_csDMARD <- as.factor(BARI$concomitant_csDMARD)
BARI$PREDNISON_STEROID <- as.factor(BARI$PREDNISON_STEROID)
BARI$cohort <- as.factor(BARI$cohort)

# Imputation

if(!file.exists("./2_cached_files/imputed_data")){ # to avoid re-
```

```
computing if alsready done
  imputed_data <- mice(BARI, m=50, method="pmm", maxit=25, seed=500)
  save(imputed_data, file = "./2_cached_files/imputed_data")
} else {
  load("./2_cached_files/imputed_data")
}

# Subsettings

BARI1 <- BARI[cohort %in% c("BARI", "TNFi")] # creating subset for
BARI vs TNFi comparaison
BARI1[,cohort := as.factor(as.character(cohort))]

imputed_data1 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data1 <- imputed_data1[imputed_data1$cohort %in% c("BARI",
"TNFi"),] # to keep only BARI and TNFi rows
imputed_data1$cohort <- as.factor(as.character(imputed_data1$cohort))
imputed_data1 <- as.mids(imputed_data1) # re concateneting in previous
format, to use fit.mult.impute


BARI2 <- BARI[cohort %in% c("BARI", "OMA")] # creating subset for BARI
vs OMA comparaison
BARI2[,cohort := as.factor(as.character(cohort))]

imputed_data2 <- complete(imputed_data,"long", include=T) # to put in
long format and categorize variables
imputed_data2 <- imputed_data2[imputed_data2$cohort %in% c("BARI",
"OMA"),] # to keep only BARI and OMA rows
imputed_data2$cohort <- as.factor(as.character(imputed_data2$cohort))
imputed_data2 <- as.mids(imputed_data2) # re concateneting in previous
format, to use fit.mult.impute
```

1. [1] SURVIVAL ANALYSIS (drug discontinuation)

Exploration

```
table(BARI_DATA$cohort, BARI_DATA$stop_DMARD)
table(BARI_DATA$cohort, BARI_DATA$stop_reasons)
```

Checking adequacy of COX models —-

For BARI vs TNFi

```
# categorization for linearity checking
test1 <- complete(imputed_data1,"long", include=T) # to put in long
format and categorize variables
```

```
test1$agecat <- cut(test1$age_base, 4)
test1$bmicat <- cut(test1$bmi_base, 4)
test1$cdaicat <- cut(test1$CDAI0, 4)
test1$duracat <- cut(test1$disease_duration_base_years, 4)

test1 <- as.mids(test1, .imp=1, .id=2) # re concateneting in previous
format, to use fit.mult.impute

# linearity checking

BARI1.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                       I(agecat)+
                                       I(bmicat)+
                                       TC_with_csDMARD+
                                       PREDNISON_STEROID+
                                       I(cdaicat)+
                                       I(duracat)+
                                       C(smoker_base, base=3)+
                                       line_of_therapy+
                                       gender+
                                       seropositivity_base+
                                       cluster(patient_id),
                                     fitter = coxph, xtrans = test1,
data = BARI1)

summary(BARI1.adj.mi.test)
rm(BARI1.adj.mi.test)

# Log-linearity of coefficients ?

# Coefs age are between 0.15 and 0.25, let's assume it's ok
# Hum bmi coefs are not so log-linear, rather close to 0
# For CDAI also
# Looks ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test1ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                         data= BARI1)
cox.zph(test1ph) # it's ok

# Hazard proportionality test on imputed data sets

test1 <- complete(test1,"long",include=T) # To reset the charges to
```

```
long format
test1 <- test1[test1$.imp==1 | test1$.imp==2 |  test1$.imp==3 |
test1$.imp==4 | test1$.imp==5 ,] # To select only 5 data sets

test1ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
~ as.factor(cohort)+
                          I(age_base/10)+
                          bmi_base+
                          TC_with_csDMARD+
                          PREDNISON_STEROID+
                          CDAI0+
                          I(disease_duration_base_years/10)+
                          C(smoker_base, base=3)+
                          line_of_therapy+
                          gender+
                          seropositivity_base+
                          cluster(patient_id),
                        data = test1)

cox.zph(test1ph.adj.mi)

schonfeldall <- cox.zph(test1ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test1ph.adj.mi, test1)
```

For BARI vs OMA

```
# categorization for linearity checking
test2 <- complete(imputed_data2,"long", include=T) # to put in long
format and categorize variables

test2$agecat <- cut(test2$age_base, 4)
test2$bmicat <- cut(test2$bmi_base, 4)
test2$cdaicat <- cut(test2$CDAI0, 4)
test2$duracat <- cut(test2$disease_duration_base_years, 4)

test2 <- as.mids(test2, .imp=1, .id=2) # re concateneting in previous
format, to use fit.mult.impute

# linearity checking

BARI2.adj.mi.test <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
as.factor(cohort)+
                                       I(agecat)+
                                       I(bmicat)+
```

```
                                        TC_with_csDMARD+
                                        PREDNISON_STEROID+
                                        I(cdaicat)+
                                        I(duracat)+
                                        C(smoker_base, base=3)+
                                        line_of_therapy+
                                        gender+
                                        seropositivity_base+
                                        cluster(patient_id),
                                      fitter = coxph, xtrans = test2,
data = BARI2)

summary(BARI2.adj.mi.test)
rm(BARI2.adj.mi.test)

# Log-linearity of coeficients ?

# Coefs age are around -0.4, let's assume it's ok
# Hum bmi coefs are discusable
# For CDAI it's ok
# More or less ok for disease_duration_base_years.

# --> Let's keep all variable in the continuous format

# Proportionality test of hazards on raw data

test2ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                         data= BARI2)
cox.zph(test2ph) # it's ok


# Hazard proportionality test on imputed data sets

test2 <- complete(test2,"long",include=T) # To put imputed data in
ling format
test2 <- test2[test2$.imp==1 | test2$.imp==2 |  test2$.imp==3 |
test2$.imp==4 | test2$.imp==5 ,] # To select only 5 datasets

test2ph.adj.mi <- coxph(Surv(time = time_on_drug, event = stop_DMARD)
~ as.factor(cohort)+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
```

```
                              line_of_therapy+
                              gender+
                              seropositivity_base+
                              cluster(patient_id),
                            data=test2)

cox.zph(test2ph.adj.mi)

schonfeldall <- cox.zph(test2ph.adj.mi) # Test cox.zph may not be ok,
but it's because of the multiple imputation (often the case with a lot
of data)
for (i in 1:11){
    plot(schonfeldall[i]) # so we should go to a visual testing --> ok
  }

rm(schonfeldall, test2ph.adj.mi, test2)
```

BARI vs TNFi —-

COX model

Final Cox Model

```
BARI1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort +
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data1,
data = BARI1)

summary(BARI1.adj.mi)
```

Creation of HR table and p-values

```
ploufrows <- names(BARI1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI1.adj.mi)
```

```
for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",
formattable(plouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("TNFi (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid", "CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_1 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs TNFi")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
```

```
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_1

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R

BARI vs TNFi

```
surv_object1 <- Surv(time = BARI1$time_on_drug, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
summary(coxph(surv_object1 ~ cohort, data=BARI1))
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1) # this function
creates the data for Kaplan Meyer
fit1
survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib","TNFi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10"),
           palette = c("red2", "green3"), # specify colors
           risk.table = T)
survplot_1
summary(fit1, times = 365)
summary(fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs TNFi",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib","TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey10")
           palette = c("red2", "green3") # to change colors
           )

# adding some legends
survplot_1_adj <- survplot_1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_1_adj
# summary(BARI_fit1) # to see detailed surv probabilities at given
timepoints
```

```
summary(BARI_fit1, times = 365)
summary(BARI_fit1, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data_adj <- survplot_1_adj$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA
library(riskRegression)

# I select only one imputed dataset. Would be even better to find a
way to pool/average the results from the 50 imputed datasets, but it
does not seem doable by default
test.data <- complete(imputed_data1, 1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment <- glm(cohort~I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
```

```
                                    seropositivity_base,
                                    data = test.data, x = TRUE, y =
TRUE)

m.censor <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base
                                    , x =TRUE, y = TRUE,
                                    data = test.data)


# And we measure the average treatment effect using function "ate",
specifying the time at which we want to compute the ATE

out <- ate(event = m.event ,
             treatment = m.treatment,
             censor = m.censor,
             data = test.data,
             cause = 1,
             estimator = "AIPTW",
             times = seq(from = 0, to = 500, by = 5))

dt.out <- as.data.table(out)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data$pscores <- m.treatment$fitted.values
test.data %>% setDT()

pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
```

```
          axis.title.x = element_text(hjust = 0.2, size = 16))
pscore_plot # overlap


## Computing the weights
test.data$weights <- ifelse(test.data$cohort == "TNFi",
1/test.data$pscores, 1/(1-test.data$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS <- subset(test.data, select = c(cohort,age_base,
                                     bmi_base,
                                     TC_with_csDMARD,
                                     PREDNISON_STEROID,
                                     CDAI0,
                                     disease_duration_base_years,
                                     smoker_base,
                                     line_of_therapy,
                                     gender,
                                     seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS, treat = test.data$cohort, thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
thresholds = 0.1)
# bal.tab(COVS, treat = test.data$cohort,  v.threshold = 2)
# bal.tab(COVS, treat = test.data$cohort, weights = test.data$weights,
v.threshold = 2)


# But plotting is clearer:
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("mean.diffs"), thresholds = c(m = .1), var.order =
"adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS, treat = test.data$cohort, weights = test.data$weights,
stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
```

```
  geom_line(aes(y = estimate, color = level), size = 1)+
  #geom_vline(xintercept = 90)+

  scale_colour_manual(values = c("lightblue","darkseagreen3"))+
  scale_fill_manual(values = c("lightblue","darkseagreen3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:")+
  labs(group = "Groups:")+
  theme_bw(base_size = 14)+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

We can also consider the AIPTW estimate at a specific time point. For example at365-day.

```
r.one <- dt.out[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
```

```
table <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(table) <- ploufrows
colnames(table) <- ploufcols

library(formattable)
table[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
table[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
table[1,"p"] <-  writepvalue(r.one$p.value)
table[2,"Estimate"] <-  paste0(r.two$estimate)
table[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
table[2,"p"] <-  writepvalue(r.two$p.value)

table

# Interpretation: If every patient had received BARI, the 365-day risk
of treatment discontinuation would have been 19.34% (points) lower
compared to when every patient had received TNFi.
```

BARI vs OMA —-

COX model

```
BARI2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                  I(age_base/10)+
                                  bmi_base+
                                  TC_with_csDMARD+
                                  PREDNISON_STEROID+
                                  I(CDAI0/10)+
                                  I(disease_duration_base_years/10)+
                                  C(smoker_base, base=3)+
                                  line_of_therapy+
                                  gender+
                                  seropositivity_base+
                                  cluster(patient_id),
                                fitter = coxph, xtrans = imputed_data2,
data = BARI2)

summary(BARI2.adj.mi)
```

Creation of HR table and p-values (denis)

```
ploufrows <- names(BARI2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI2.adj.mi)
```

```
for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR.xlsx") #
saving excel file
```

Forest plot

```
meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("OMA (vs BARI)", "Age (decades)", "BMI", "Concomitant
csDMARD", "Concomitant glucocorticoid", "CDAI score (10 pts)",
"Disease duration (decades)", "Current smoker (vs non-smoker)",
            "Former smoker (vs non-smoker)", "2nd line therapy (vs
1st)", "3rd line therapy (vs 1st)", "4th or later line (vs 1st)",
"Female gender", "Seropositivity (RF or ACPA)")

dfall <- data.frame(textall, meanall, lowerall, upperall)
dfall$textall <- factor(dfall$textall,
                        levels = textall)

HR_plot_2 <- ggplot(data=dfall, aes(x=textall, y= meanall, ymin =
lowerall, ymax = upperall))+

  geom_pointrange(size=0.5)+
  geom_errorbar(aes(ymin=lowerall, ymax=upperall),width=0.5)+
  geom_hline(yintercept =1, linetype=2)+

  xlab('')+ ylab(" ")+
  ggtitle("BARI vs OMA")+

  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  facet_wrap(~textall,nrow=16, strip.position= "right", scales =
"free_y") +

  theme_pubclean()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
```

```
unit(c(1,3,2,1),"lines"))+

    coord_flip()

HR_plot_2

# adding some manual annotation
grid.text("Improves drug maintenance", x = unit(0.3, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
grid.text("Reduces drug maintenance", x = unit(0.87, "npc"), y =
unit(0.05, "npc"), gp = gpar(fontface = "bold"))
```

Non-adjusted Kaplan-Meier curves

based on mini-tutorial found on datacamp.com/community/tutorials/survival-analysis-R)

BARI vs OMA

```
surv_object2 <- Surv(time = BARI2$time_on_drug, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50"),
           palette = c("red2", "blue3"), # to put colors
           risk.table = T)
survplot_2
summary(fit2, times = 365)
summary(fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib","OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )

# adding some legends
survplot_2_adj <- survplot_2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_2_adj
summary(BARI_fit2, times = 365) # to see detailed surv probabilities
at given timepoints
summary(BARI_fit2, times = 730)
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data_adj <- survplot_2_adj$data.survplot
write.xlsx(plot_BARI_vs_OMA_data_adj, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_adj.xlsx",
row.names = F)
```

Sensitivity analysis with package RiskRegression (AIPTW)

```
# I select only one imputed dataset. Would be good to find a way to
pool the results from the 50 datasets imputed.
test.data2 <- complete(imputed_data2,1)

# First, we specify the treatment model (propensity score model)
# Logistic regression where the treatment group is the dependent
variable.

m.treatment2 <- glm(cohort~I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data2, family =
"binomial" )

# Then we specify both the "event model" and the "censoring model".
Both are cox model

m.event2 <- coxph(Surv(time_on_drug, stop_DMARD) ~ cohort+
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base,
                                    data = test.data2, x = TRUE, y =
TRUE)

m.censor2 <- coxph(Surv(time_on_drug,stop_DMARD==0) ~ cohort +
                                    I(age_base/10)+
                                    bmi_base+
                                    TC_with_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
```

```
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base
                                    , x =TRUE, y = TRUE,
                                    data = test.data2)

# And we measure the average treatment effect using function "ate",
specifying the times at which we want to compute the ATE

out2 <- ate(event = m.event2 ,
            treatment = m.treatment2,
            censor = m.censor2,
            data = test.data2,
            cause = 1,
            estimator = "AIPTW",
            times = seq(from = 0, to = 500, by = 5))

dt.out2 <- as.data.table(out2)
```

Diagnostics asked by Lily statistician

```
library(cobalt)

# First, the distribution of propensity scores
test.data2$pscores <- m.treatment2$fitted.values
test.data2 %>% setDT()

pscore_plot2 <- ggplot(test.data2,aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +
  xlab("Estimated Probability of being assigned BARI") +
  ylab("Density") +
    theme_minimal()+
    theme(axis.ticks.y=element_blank(),
          panel.grid.minor=element_blank(),
          legend.title=element_blank(),
          text = element_text(size = 16),
          axis.title.x =element_text(hjust = 0.2, size = 16))
pscore_plot2
# Good overlap

## Computing the weights
test.data2$weights <- ifelse(test.data2$cohort == "OMA",
1/test.data2$pscores, 1/(1-test.data2$pscores))

# Selecting only our covariates of interest (the ones in the ps model)
COVS_2 <- subset(test.data2, select = c(cohort,age_base,
                                    bmi_base,
```

```
                                        TC_with_csDMARD,
                                        PREDNISON_STEROID,
                                        CDAI0,
                                        disease_duration_base_years,
                                        smoker_base,
                                        line_of_therapy,
                                        gender,
                                        seropositivity_base))

# To get the SMD & variance ratios before/after weighting
# bal.tab(COVS_2, treat = test.data2$cohort, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, thresholds = 0.1)
# bal.tab(COVS_2, treat = test.data2$cohort,  v.threshold = 2)
# bal.tab(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, v.threshold = 2)
#

#But plotting it is better:
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted")

# We can also plot variance ratios for continuous variables
love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights,stats =  c("variance.ratios"))

# propensity scores enhance the balance overall, except for the CDAI0.
However, this is the reason we use the AIPTW. The remaining imbalance
is accounted for by the outcome model (outcome model is the cox
regression), and the misspecification of the outcome model is
mitigated by the balancing done by propensity score.
```

First plot to get the difference in average treatment effect in percentage

```
plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,500,50)) + scale_y_continuous(labels
= scales::percent)+

  xlab("Days since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "Absolute risk of
treatment discontinuation by type of treatment - BARI vs TNFi")+
```

```
  labs(group = "Groups:")

plot.ate.diff2
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_minimal()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

We can also consider the AIPTW estimate at a specific time point. For example at 365-day.

```
r.one <- dt.out2[type == "diffRisk" & time == 365, .
(estimate,lower,upper,p.value)]
r.two <- dt.out2[type == "ratioRisk" & time == 365, .
(estimate,lower,upper,p.value)]

ploufrows <- c("Difference in average treatment effect","Ratio in
average treatment effect")
ploufcols  <- c("Estimate","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols

library(formattable)
coxtable[1,"Estimate"] <-  paste0(formattable(r.one$estimate*100),"%")
coxtable[1,"95%CI"] <-
paste0(formattable(r.one$lower),"-",formattable(r.one$upper))
coxtable[1,"p"] <-  writepvalue(r.one$p.value)
coxtable[2,"Estimate"] <-  paste0(r.two$estimate)
coxtable[2,"95%CI"] <-  paste0(r.two$lower,"-",r.two$upper)
coxtable[2,"p"] <-  writepvalue(r.two$p.value)

coxtable

# Interpretation: If every patient had received BARI, the 365-day risk
```

of treatment discontinuation would have been xx% (points) lower compared to when every patient had received TNFi.

.

[3] 1st LINE vs 1st LINE analysis

Common Table 1

Table 1 with NA, to have exact counts and proportions

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection of TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = F, includeNA = T)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1 NA.xlsx")
```

Table 1 without NA to have adequate p values to interpret

```
BARI_first <- BARI_DATA
BARI_first <- BARI_first[line_of_therapy == "1st"] # selection TC
first line

myVars2 <- c("gender", "age_base","disease_duration_base_years",
"CDAI0_raw", "CDAI0", "obese_base", "smoker_base",
"seropositivity_base", "time_on_drug365", "TC_with_csDMARD",
```

```
"line_of_therapy", "N_prev_tsDMARD", "PREDNISON_STEROID",
"PREDNISON_STEROID_dose", "dose", "initiation_year",
"time_on_drug","HAQ_score_base")

catVars2 <- c("PREDNISON_STEROID", "TC_with_csDMARD", "gender",
"obese_base", "smoker_base", "line_of_therapy", "time_on_drugDiff0",
"time_on_drug365", "N_prev_tsDMARD", "dose", "initiation_year",
"seropositivity_base")

nonnormalVars <- c()

tab1 <- CreateTableOne(vars = myVars2, data = BARI_first, factorVars =
catVars2, strata = "cohort", test = T, includeNA = F)
tab1exp <- print(tab1, nonnormal= nonnormalVars, catDigits = 1,
contDigits=1, pDigits=2, quote = FALSE, noSpaces = TRUE)
```

Saving

```
write.xlsx(tab1exp, file = "./3_clean_output/BARI 3 groups first line
table1.xlsx")

summary(BARI_first[cohort=="BARI", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="TNFi", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables

summary(BARI_first[cohort=="OMA", c("TC_id", "patient_id",
"stop_DMARD", "stop_reasons", "age_base", "concomitant_csDMARD",
"concomitant_csDMARD_type", "TC_with_csDMARD",  "PREDNISON_STEROID",
"CDAI0","CDAI0_raw", "disease_duration_base_years", "time_on_drug",
"bmi_base", "smoker_base", "line_of_therapy", "obese_base", "gender",
"cohort", "adverse_event_reported", "seropositivity_base", "dose")]) #
to see NA values for all variables
```

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])
```

```
surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           # palette = c("grey78", "grey50", "grey10"),
           palette = c("red2", "green3"), # to get colors
           risk.table = T
           )

survplot_first1
table(BARI_first1$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
```

```
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )

survplot_first2
table(BARI_first2$cohort)
summary(fit3)

rm(surv_object3, fit3)
```

Adjusted survival analyses

BARI vs TNFi

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                              cluster(patient_id),
                       data= BARI_first1)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data1_first <- complete(imputed_data1,"long",include=T) # to
put in the long format
imputed_data1_first <- filter(imputed_data1_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data1_first <- as.mids(imputed_data1_first) # put back in
previous format, to use fit.mult.impute

BARI_first1.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                    I(age_base/10)+
                                    bmi_base+
                                    concomitant_csDMARD+
                                    PREDNISON_STEROID+
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base+
                                    cluster(patient_id),
                                  fitter = coxph, xtrans =
```

```
imputed_data1_first, data = BARI_first1)
summary(BARI_first1.adj.mi)

Creation of HR table with p-values
ploufrows <- names(BARI_first1.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first1.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs TNFi HR 1st
lines.xlsx") # save in excel format

Adjusted curves with imputed data
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
```

```
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey10")
           palette = c("red2", "green3"), # to get colors
           )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

BARI vs OMA

Verification (quick)

```
# Test of proportionality of hazards on raw data
test_first_ph <- coxph(Surv(time = time_on_drug, event = stop_DMARD) ~
as.factor(cohort)+
                            cluster(patient_id),
                       data= BARI_first2)
cox.zph(test_first_ph)
```

Adjusted Cox-model

```
imputed_data2_first <- complete(imputed_data2,"long",include=T) # to
put in the long format
imputed_data2_first <- filter(imputed_data2_first, line_of_therapy ==
"1st")  # only keep 1st line imputed TC
imputed_data2_first <- as.mids(imputed_data2_first) # put back in
previous format, to use fit.mult.impute

BARI_first2.adj.mi <- fit.mult.impute(Surv(time_on_drug, stop_DMARD) ~
cohort+
                                      I(age_base/10)+
                                      bmi_base+
                                      concomitant_csDMARD+
                                      PREDNISON_STEROID+
```

```
                                    I(CDAI0/10)+
                                    I(disease_duration_base_years/10)+
                                    C(smoker_base, base=3)+
                                    line_of_therapy+
                                    gender+
                                    seropositivity_base+
                                    cluster(patient_id),
                                  fitter = coxph, xtrans =
imputed_data2_first, data = BARI_first2)
summary(BARI_first2.adj.mi)

Creation of HR table with p-values
ploufrows <- names(BARI_first2.adj.mi$coefficients)
ploufcols  <- c("HR","95%CI","p")
coxtable <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable) <- ploufrows
colnames(coxtable) <- ploufcols
plouf <- summary(BARI_first2.adj.mi)

for(row in ploufrows)
{
  coxtable[row,"HR"] <-
formattable(plouf$coefficients[row,"exp(coef)"])
  coxtable[row,"95%CI"] <-
paste0(formattable(plouf$conf.int[row,"lower .95"]),"-",formattable(pl
ouf$conf.int[row,"upper .95"]))
  coxtable[row,"p"] <-  writepvalue(plouf$coefficients[row,"Pr(>|
z|)"])
}

write.xlsx(coxtable, file="./3_clean_output/BARI vs OMA HR 1st
lines.xlsx") # save in excel format

Adjusted curves with imputed data
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
```

```
                                gender+
                                seropositivity_base+
                                cluster(patient_id)+
                                strata(cohort),dummy_cox_impute_first2),
data = dummy_cox_impute_first2)


survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
dummy_cox_impute_first2, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50")
           palette = c("red2", "blue3"), # to get colors
           )

survplot_first2_adj <- survplot_first2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first2_adj
table(BARI_first2$cohort)
rm(dummy_cox_impute_first2, BARI_first2_fit)
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
```

```
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_T <- BARI_comp[cohort %in% c("TNFi")] #TNFi only
ci_TNFi <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_T)
ci_TNFi <- ci_TNFi[,-c(2,6,7,8,9)]
ci_long_TNFi <- reshape2::melt(ci_TNFi,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_TNFi$cohort <- 1
ci_long <- rbind(ci_long_BARI,ci_long_TNFi)
ci_long$cohort <- as.factor(ci_long$cohort)

plot2 <- ggplot(data = ci_long, aes(x = time,
                                    y = value,
                                    linetype =
interaction(cohort,variable),
                                        col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values
=c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
(BARI)","Other (TNFi)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (TNFi)","Ineffectiveness (BARI)","Inefectiveness (TNFi)","Other
(BARI)","Other (TNFi)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
```

```
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot2
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat

imputed_data1_long <- complete(imputed_data1, action = "long") %>%
setDT()
imputed_data1_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data1_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data1_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data1_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data1$m

mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data1_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                   status = c("continue","stop_ae","stop_lae"),
                   data = as.data.frame(data_sub),
                   trans = tmat,
                   keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)
```

```
  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                                paste0(tmp_cov,collapse = " + "),
                                "+ strata(trans)")),
              data = tmp,
              method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
# estimate = Hazard ratio

summary(est, conf.int = T, exponentiate = T)

# Conclusion
# => The hazard ratio of lack of efficacy (lae) for TNFi is 65% higher
than for BARI. Significant.
# => No difference between TNFi and BARI for Adverse Event (ae)
```

Clean table with confidence intervals & p-values

```
# Hazard ratios
ploufrows <- as.character(summary(est)$term)

ploufcols  <- c("HR","95%CI","p")
coxtable_csh <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh) <- ploufrows
colnames(coxtable_csh) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_csh[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

output <- coxtable_csh
row.names(output)[1:2] <- c("TNFi Adverse Event (vs BARI)", "TNFi Lack
of Eff (vs BARI)")

# Transition 1 = Adverse Event. Hazard Ratio vs VARI
```

```
# Transition 2 = Lack of Efficacy. Hazard Ratio vs VARI
output
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data1_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data1_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data1_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data1_long[stop_reasons == "CONTINUE", status := 0]

## ATTENTION levels() re-ecrit juste l'étiquette!! Change pas la
donnée !!! Donc ça re écrit les lablels

imputed_data1_long$line_of_therapy <-
as.factor(imputed_data1_long$line_of_therapy)
imputed_data1_long$seropositivity_base <-
as.factor(imputed_data1_long$seropositivity_base)

levels(imputed_data1_long$cohort) <- c("0","1")
levels(imputed_data1_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data1_long$gender) <- c("0","1")
levels(imputed_data1_long$smoker_base) <- c("2","1","0")
levels(imputed_data1_long$smoker_base)
levels(imputed_data1_long$seropositivity_base) <- c("0","1")

M <- imputed_data1$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    # subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY

mice_fit2 <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data1_long[.imp == m]
    #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
```

```
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()

est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of adverse event between TNFi
and BARI
# Increased incidence of lack of efficacy for TNFi compared to BARI.
# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Clean tables with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae) <- ploufrows
colnames(coxtable_ae) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae[row,"95%CI"] <-  paste0(formattable(plouf[term %in% row,
`2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_ae[row,"p"] <-  writepvalue(plouf[term %in% row, p.value])}

row.names(coxtable_ae)[1] <- c("TNFi vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae) <- ploufrows
colnames(coxtable_lae) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae[row,"HR"] <-  formattable(plouf[term %in% row,
```

```
estimate])
  coxtable_lae[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae)[1] <- c("TNFi vs BARI Lack of Eff")

# output
coxtable_ae
coxtable_lae

write.xlsx(coxtable_ae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae, file="./3_clean_output/BARI vs TNFi HR
competing risk Fine-Gray LAE.xlsx") # saving excel file
```

(BARI vs OMA)

Cumulative incidence function

```
BARI_comp <- copy(BARI_DATA)

#General

BARI_comp[stop_reasons == "ADVERSE_EVENT",status := 1]
BARI_comp[stop_reasons == "NOT_EFFECTIVE", status := 2]
BARI_comp[stop_reasons == "OTHER" | stop_reasons == "REMISSION",
status := 3]
BARI_comp[stop_reasons == "CONTINUE", status := 0]
BARI_comp$cohort <- as.factor(BARI_comp$cohort)

library(reshape)

BARI_comp_B <- BARI_comp[cohort %in% c("BARI")] #BARI only
ci_BARI <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_B)
ci_BARI <- ci_BARI[,-c(2,6,7,8,9)]
ci_long_BARI <- reshape2::melt(ci_BARI,id.vars = "time")

BARI_comp_O <- BARI_comp[cohort %in% c("OMA")] #OMA only
ci_OMA <- Cuminc(time = "time_on_drug",status = "status", data =
BARI_comp_O)
ci_OMA <- ci_OMA[,-c(2,6,7,8,9)]
ci_long_OMA <- reshape2::melt(ci_OMA,id.vars = "time")

ci_long_BARI$cohort <- 0
ci_long_OMA$cohort <- 1
ci_long_2 <- rbind(ci_long_BARI,ci_long_OMA)
ci_long_2$cohort <- as.factor(ci_long_2$cohort)
```

```
plot3 <- ggplot(data = ci_long_2, aes(x = time,
                                      y = value,
                                      linetype =
interaction(cohort,variable),
                                      col =
interaction(cohort,variable))) +
  geom_line(size = 0.75) +
  scale_color_manual(name = "",
                     values =
c("#08306B","#08306B","#238B45","#238B45","#FD8D3C","#FD8D3C"),
                     labels = c("Adverse Event (BARI)","Adverse Event
(OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_linetype_manual(name="",
                        values = c(1,3,1,3,1,3),
                        labels = c("Adverse Event (BARI)","Adverse
Event (OMA)","Ineffectiveness (BARI)","Inefectiveness (OMA)","Other
(BARI)","Other (OMA)"))+
  scale_x_continuous(name = "Time", limits = c(1,365)) +
  scale_y_continuous(name = "Cumulative incidence", limits =
c(0.0,0.3)) +
  theme_bw()+
  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="right", plot.margin =
unit(c(1,3,2,1),"lines"))+
  #ggtitle("Cumulative incidence functions")+
  theme(plot.title = element_text(hjust = 0.5))

plot3
```

Adjusting variables

```
# Covariates of interest for Cox

covs <-
c("cohort","age_base","bmi_base","TC_with_csDMARD","PREDNISON_STEROID"
,"CDAI0","disease_duration_base_years","smoker_base","line_of_therapy"
,"gender","seropositivity_base")
```

Cause-specific hazard model

```
# Rappel: imputed_data1 = BARI vs TNFi
#         imputed_data2 = BARI vs OMA

# Transition matrix definition
library(mstate)
tmat <- trans.comprisk(2, names = c("event-free","ae","lae"))
tmat
```

```
imputed_data2_long <- complete(imputed_data2, action = "long") %>%
setDT()
imputed_data2_long[,stop_ae := fifelse(stop_reasons ==
"ADVERSE_EVENT",1,0)]
imputed_data2_long[,stop_lae := fifelse(stop_reasons ==
"NOT_EFFECTIVE",1,0)]
imputed_data2_long[,stop_other := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION",1,0)]
#[,continue := fifelse(stop_reasons == "CONTINUE",1,0)]
imputed_data2_long[,continue := fifelse(stop_reasons == "OTHER" |
stop_reasons == "REMISSION" | stop_reasons == "CONTINUE",1,0)]

M <- imputed_data2$m

mice_fit <- lapply(1:M,function(m){

  # subset
  data_sub <- imputed_data2_long[.imp == m]

  mst_hosp <- msprep(time =
c("time_on_drug","time_on_drug","time_on_drug"),
                     status = c("continue","stop_ae","stop_lae"),
                     data = as.data.frame(data_sub),
                     trans = tmat,
                     keep = covs)
  # get covariates
tmp <- expand.covs(mst_hosp,covs, append = TRUE, longnames = T)
tmp_cov <- grep(paste0(covs,".",collapse = "|"),names(tmp),value = T)

  # fit
coxph(as.formula(paste0("Surv(Tstart, Tstop, status) ~",
                                paste0(tmp_cov,collapse = " + "),
                                "+ strata(trans)")),
             data = tmp,
             method = "breslow")

}) %>%
  as.mira()

est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Transition 1 = Adverse Event
# Transition 2 = Lack of Efficacy

# Conclusion
# => No difference between OMA and BARI for Adverse Event (ae) and for
Lack of Event (lae)
```

Cleaner table with Hazard ratios with confidence intervals & p-values

```
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_csh2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_csh2) <- ploufrows
colnames(coxtable_csh2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_csh2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_csh2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_csh2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_csh2)[1:2] <- c("OMA vs BARI Adverse event", "OMA
vs BARI Lack of Eff" )
coxtable_csh2
```

Subdistribution hazard model (Fine-Gray)

```
# Status variable
imputed_data2_long[stop_reasons == "ADVERSE_EVENT",status := 1]
imputed_data2_long[stop_reasons == "NOT_EFFECTIVE", status := 2]
imputed_data2_long[stop_reasons == "OTHER" | stop_reasons ==
"REMISSION", status := 3]
imputed_data2_long[stop_reasons == "CONTINUE", status := 0]

imputed_data2_long$line_of_therapy <-
as.factor(imputed_data2_long$line_of_therapy)
imputed_data2_long$seropositivity_base <-
as.factor(imputed_data2_long$seropositivity_base)
levels(imputed_data2_long$cohort) <- c("0","1")
levels(imputed_data2_long$line_of_therapy) <- c("0","1","2","3")
levels(imputed_data2_long$gender) <- c("0","1")
levels(imputed_data2_long$smoker_base) <- c("2","1","0")
levels(imputed_data2_long$smoker_base)
levels(imputed_data2_long$seropositivity_base) <- c("0","1")

M <- imputed_data2$m

# First loop to get estimates for event = 1: ADVERSE EVENT

mice_fit <- lapply(1:M,function(m){
    # subset
  BARI_toto <- imputed_data2_long[.imp == m]
```

```
  #subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 1,cencode = 0)

}) %>%
  as.mira()
est <- pool(mice_fit)
summary(est, conf.int = T, exponentiate = T)

# Second loop to get estimates for event = 2: LACK OF EFFICACY
mice_fit2 <- lapply(1:M,function(m){

  # subset
  BARI_toto <- imputed_data2_long[.imp == m]

  # subdistribution hazard model
  shm <- crr(BARI_toto$time_on_drug,BARI_toto$status,cov1 =
BARI_toto[,..covs],failcode = 2,cencode = 0)

}) %>%
  as.mira()
est2 <- pool(mice_fit2)
summary(est2, conf.int = T, exponentiate = T)

# Conclusions:
# No significant difference in incidence of "adverse event" and "lack
of efficacy" between TNFi and BARI

# CAREFUL: using a Fine-Gray model allows us to make claim about the
association between a covariate and the direction of the increase in
incidence, but we can't quantify the magnitude of the increase in
incidence.
```

Cleaner Table with Hazard ratios with confidence intervals & p-values

```
# Adverse event
ploufrows <- as.character(summary(est)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_ae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_ae2) <- ploufrows
colnames(coxtable_ae2) <- ploufcols
plouf <- summary(est, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_ae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_ae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
```

```
  coxtable_ae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_ae2)[1] <- c("OMA vs BARI Advsere Events")

# Lack of efficacy
ploufrows <- as.character(summary(est2)$term)
ploufcols  <- c("HR","95%CI","p")
coxtable_lae2 <- matrix(data = NA, nrow = length(ploufrows), ncol =
length(ploufcols))
rownames(coxtable_lae2) <- ploufrows
colnames(coxtable_lae2) <- ploufcols
plouf <- summary(est2, conf.int = T, exponentiate = T) %>% setDT()

for(row in ploufrows)
{
  coxtable_lae2[row,"HR"] <-  formattable(plouf[term %in% row,
estimate])
  coxtable_lae2[row,"95%CI"] <-  paste0(formattable(plouf[term %in%
row, `2.5 %`]),"-",formattable(plouf[term %in% row, `97.5 %`]))
  coxtable_lae2[row,"p"] <-  writepvalue(plouf[term %in% row,
p.value])}

row.names(coxtable_lae2)[1] <- c("OMA vs BARI Lack of Eff")

#Output
coxtable_ae2
coxtable_lae2

write.xlsx(coxtable_ae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray AE.xlsx") # saving excel file
write.xlsx(coxtable_lae2, file="./3_clean_output/BARI vs OMA HR
competing risk Fine-Gray LAE.xlsx") # saving excel file


## 1. Saving
save.image(file="./3_clean_output/full_workspaces/workspace_1.RData")
```

2 - LDA and REM ANALYSIS

10/11/2020

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./1_datamanaged_files/datamanaged.Rdata")
```

This code aims at providing estimates for the remssion rates of the different treatments groups REM = REMmission LDA = Low Disease Activity

Both outcome are base on the CDAI CDAI = Clinical Disease Activity Index

CDAI is an index computed by the physician, which scores the severity of the disease.

1. [0] Exploration

See all available raw CDAI measures :

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

nrow(BARI_DATA)
summary(BARI_DATA[, .(CDAI0_raw, CDAI12_raw)])
```

1. [1] CARRAC (confirm covariates for confounding and for attrition)

For LDA with updated function

```
library(modules)
source_comp_eff <- modules::use("ETAPE_2_supp_code.R")

LDA_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
  seed = 123)

LDA_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
  var = "CDAI12",
  thres = 10,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
  seed = 123)

LDA_BARI_TNF
LDA_BARI_OMA
```

For REM with updated function

```
REM_BARI_TNF <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "TNFi")],
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons" ),
   seed = 123)

REM_BARI_OMA <- source_comp_eff$CARRAC(
  datain = BARI_DATA[cohort %in% c("BARI", "OMA")],
```

```
  var = "CDAI12",
  thres = 2.8,
  ttt_var = "cohort",
  ref_ttt = "BARI",
  counfunders = c("TC_with_csDMARD","PREDNISON_STEROID",
                  "line_of_therapy","CDAI0"),
  attrition = c("TC_with_csDMARD","PREDNISON_STEROID",
                "line_of_therapy","CDAI0", "stop_reasons"),
   seed = 123)

REM_BARI_TNF
REM_BARI_OMA
```

This methods was developed by Mongin et al,
https://ard.bmj.com/content/early/2022/01/12/annrheumdis-2021-221477

Pooled table

```
table <- rbind(LDA_BARI_TNF, LDA_BARI_OMA, REM_BARI_TNF, REM_BARI_OMA)

write.xlsx(table, file = "./3_clean_output/table_LDA_REM_CARRAC.xlsx",
row.names = F)
```

1. Saving

```
save.image(file="./3_clean_output/full_workspaces/workspace_2.RData")
```

2 - LDA and REM supp CODE

10/11/2020

```
{r setup, include=FALSE} import("data.table") import("plyr")
import("data.table") import("mice") import("ipw") import("survey")
import("geepack") import("futile.logger") import("emmeans")
import("stats") import("survival")
```

function to perform checks on data

```{r setup, include=FALSE} check_data = function(datain, var = “CDAI_fu”, ttt_var = “ttt”, ref_ttt = “ttt_ref”, ID_ttt = NULL, othervar = c())

{

data <- setDT(copy(datain))

vartocheck <- Reduce(union,list(var,ttt_var,othervar)) notindata <- setdiff(vartocheck,names(data))

if(length(notindata)>0){ stop(paste0(“the variables”,paste0(notindata,collapse = “,”),” are not in the dataplease correct”)) }

# force ttt as var name setnames(data,ttt_var,“ttt”)

if( data[,uniqueN(ttt)]>2){ stop(“there are more than two treatments. The analysis has been implemented only for 2 treatments”) }

if(!any(data$ttt == ref_ttt)){ stop(paste0(“The variable”,ttt_var,” does not contain any “,ttt_ref,” value”)) }

data[,ttt := relevel(as.factor(ttt),ref_ttt)] if(is.null(ID_ttt))
{ data[,ID_ttt := .I] }else{ setnames(data,ID_ttt,“ID_ttt”) data[,N := .N,by = ID_ttt] if(any(data$N>1)){ stop(“there are”,data[N>1,uniqueN(ID_ttt)],” treatment course which have more than one entry in the table. Each row should be an unique treatment”) } }
return(data) }

adjusted_model = function(data, weights = NULL, covariates = NULL){

# transform char to factor to_fact <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “character”,var]

data[,c(to_fact) := lapply(.SD,factor),.SDcols = to_fact]

#droplevels facto_vars <- data[,lapply(.SD,class)] %>% transpose(keep.names = “var”) %>% .[V1 == “factor”,var] data[,c(facto_vars) := lapply(.SD,droplevels),.SDcols = facto_vars]
```

define forumla formula <- as.formula(paste0("LDA ~",paste0(c("ttt",covariates),collapse = " + ")))

if(!is.null(covariates)){ # fit fit <- geeglm(formula, data = data, id = ID_ttt, family = gaussian) }else{ fit <- geeglm(LDA ~ ttt , data = data, weights = weights, id = ID_ttt, family = gaussian) }

fitsummary <- summary(fit) # create table with difference between the two treatments diff <- data.table(ttt = "diff", LDA = fitsummary$coefficients[2,"Estimate"], LDA_var = fitsummary$coefficients[2,"Std.err"]^2, LDA_sup = fitsummary$coefficients[2,"Estimate"] + 1.96*fitsummary$coefficients[2,"Std.err"], LDA_inf = fitsummary$coefficients[2,"Estimate"] - 1.96*fitsummary$coefficients[2,"Std.err"], methods = "CC_adjusted")

marginal effects: margi_df <- emmeans(fit, "ttt") %>% as.data.table()

margi_df[,methods := "CC_adjusted"] setnames(margi_df,"emmean","LDA") margi_df[,LDA_inf := LDA - 1.96*SE] margi_df[,LDA_sup := LDA + 1.96*SE] margi_df[,LDA_var := SE^2]

output <- rbind(diff,margi_df[,.(ttt,LDA,LDA_sup,LDA_inf,LDA_var,methods)])

return(list(output = output,fit = fit)) }

Not adjusted complete case imputation

```{r setup, include=FALSE}

```
export("CC_raw")
CC_raw <- function(datain,
                   # data
                   var = "CDAI_fu",
                   # variable measuring effctiveness
                   thres = 10,
                   # threshold for remission or LDA
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref")
  # variable name containing the treatment
  {
  data <- check_data(datain,var,ttt,ref_ttt)
  # raw proportion
  raw_prop <- data[!is.na(get(var)),
                   .(LDA = sum(get(var)<=thres)/.N,
                     methods = "CC_raw",
                     N = .N),
                   by = ttt]
```
```

```
  # calculation of the Standard error
  raw_prop[,c("LDA_inf","LDA_sup") := lapply(c(-1.96,1.96),function(z)
{
    LDA + z*sqrt(LDA*(1-LDA)/N)
  })]

  # difference between treatments
  diff_tmp <- raw_prop[,.(ttt = "diff",
                          LDA = LDA[ttt == "ttt_1"]-LDA[ttt ==
"ttt_ref" ],
                      methods = methods[1] ,
                      SE = (sum(1/N))/2 +  1.96*sqrt(sum( LDA*(1-LDA)/N
)))]

  diff_tmp[,LDA_inf := LDA - SE]
  diff_tmp[,LDA_sup := LDA + SE]

  # bind outputs
  output <- rbind(diff_tmp[,.(ttt,LDA,LDA_inf,LDA_sup,methods)],
                  raw_prop[,-"N"])
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Adjusted complete case imputation

```{r setup, include=FALSE} export("CC_adjusted") CC_adjusted = function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0") ) # variable name containing the treatment { data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] output <- adjusted_model(data = data[!is.na(get(var))], covariates = covariates)$output

output[,methods := "CC_adjusted"] # change name back setnames(output,"ttt",ttt_var) return(output) }

```
LOCF imputation


```{r setup, include=FALSE}
export("LOCF")

LOCF <- function(datain,
                 var = "CDAI_fu",
                 var_before = "CDAI_beforefu",
```

```
                thres = 10,
                ttt_var = "ttt",
                ref_ttt = "ttt_ref",
                covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
){
  data <- copy(datain)

  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[is.na(get(var)),c(var) := get(var_before)]
  data[,LDA := get(var) <= thres]

  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  output[,methods := "LOCF"]
  # change name back
  setnames(output,"ttt",ttt_var)
  return(output)
}
```

Lundex imputation

```{r setup, include=FALSE} export("Lundex") Lundex <- function(datain, var = "CDAI_fu", thres = 10, ttt_var = "ttt", ref_ttt = "ttt_ref", treatment_duration = "treatment_duration", stop_var = "stopany", covariates = c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"), boot_num = 1000) {

data <- check_data(datain,var,ttt_var,ref_ttt) data[,LDA := get(var) <= thres] #### bootstrap for SE data[,tmp := 1] # replicated data for bootstrap replicateddata <- data[CJ(tmp = 1,boot = 1:boot_num),on = "tmp",allow.cartesian=TRUE] # sample with replacement for each boot sampled_idx <- replicateddata[,.I[sample(1:.N,replace = T)],by = boot]$V1 bootstrapdata <- replicateddata[sampled_idx]

# raw proportions raw_prop <- bootstrapdata[!is.na(get(var)), { adjusted_model(data = .SD)$output %>% .[ttt != "diff",.(ttt,LDA_raw = LDA)] }, by = .(boot)]

# surv analysis for each bootstraped dataset surv_formula <- as.formula(paste0("Surv(",treatment_duration,",",stop_var,")~ ttt"))

surv_coeff <- bootstrapdata[, { temp.km <- survfit(surv_formula, data = .SD) list(surv = summary(temp.km, times = 1)$surv,  ttt = gsub("ttt=","",unique(summary(temp.km)$strata))) }, by = boot]

# LDA: LDA raw * surv coeff tmp_bootstrap <- merge(raw_prop,surv_coeff,by = c("boot","ttt")) tmp_bootstrap[,LDA := LDA_raw*surv]
```

difference between treatments diff_boot <- tmp_bootstrap[,.(ttt = “diff”, LDA = LDA[ttt != ref_ttt] - LDA[ttt == ref_ttt]), by = boot]

tot_bottstrap <- rbind(diff_boot[, .(ttt, LDA, boot)], tmp_bootstrap[, .(ttt, LDA, boot)])

calculate the mean and the SE: output <- tot_bottstrap[, .(LDA = mean(LDA), LDA_sup = quantile(LDA, 0.975), LDA_inf = quantile(LDA, 0.025)), by = ttt] # change name back output[,methods := “LUNDEX”]

setnames(output,“ttt”,ttt_var) return(output) }

non-responder imputation

```{r setup, include=FALSE}
export("NRI")
NRI = function(datain,
               var="CDAI_fu",
               thres = 10,
               ttt_var = "ttt",
               ref_ttt = "ttt_ref",
               covariates =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0")
)
  # variable name containing the treatment
{
  data <- check_data(datain,var,ttt_var,ref_ttt)
  data[,LDA := get(var) <= thres]
  data[is.na(LDA),LDA := 0] # missing are non responders
  output <- adjusted_model(data = data,
                           covariates = covariates)$output

  # change name back
  setnames(output,"ttt",ttt_var)
  output[,methods := "NRI"]
  return(output)
}
```

Inverse probability weighting imputation

```{r setup, include=FALSE} export(“IPW”) IPW <- function(datain, var = “CDAI_fu”, thres = 10, ttt_var = “ttt”, ref_ttt = “ttt_ref”, counfunders = c(“Disease_duration”,“concomitantCsDMARD”,“Prev_bDMARD3”,“CDAI0”), attrition = c(“Disease_duration”,“concomitantCsDMARD”, “Prev_bDMARD3”,“CDAI0”,“stopreason”)) {

data <- check_data(datain, var, ttt_var, ref_ttt, othervar = c(counfunders,attrition))
```

data[,ttt2 := as.numeric(ttt != ref_ttt)] # weight for confounding formula_coeff <- paste0("~",paste0(counfunders,collapse = "+")) function_call <- paste0('IPWT <- ipwpoint(exposure = ttt2 , family = "binomial", link = "logit", numerator = ~ 1, denominator =',formula_coeff,', data = data, trunc = 0.01)') eval(parse(text = function_call)) data$sw <- IPWT$ipw.weights

weights for attrition formula_attr <- paste0("~",paste0(attrition,collapse = "+")) data[,MISS := as.numeric(is.na(get(var)))] function_call <- paste0('IPCT <- ipwpoint(exposure = MISS , family = "binomial", link = "logit", numerator = ~ 1, denominator =',formula_attr,', data = data)') eval(parse(text = function_call)) data $swc <- IPCT$ipw.weights

dataNoNA <- na.omit(data[,.(ttt,get(var),sw,swc,ID_ttt) %>% setNames(c("ttt",var,"sw","swc","ID_ttt"))]) dataNoNA[,LDA := as.numeric(get(var) <= thres)]

output <- adjusted_model(data = dataNoNA, weights = dataNoNA$sw*dataNoNA$swc) $output

output[,methods := "IPW"]

change name back setnames(output,"ttt",ttt_var) return(output)

}

Confounder-Adjusted Response Rate with Attrition Correction (CARRAC) imputation

```{r setup, include=FALSE}
export("CARRAC")
CARRAC <- function(datain,
                   var = "CDAI_fu",
                   thres = 10,
                   ttt_var = "ttt",
                   ref_ttt = "ttt_ref",
                   counfunders =
c("Disease_duration","concomitantCsDMARD","Prev_bDMARD3","CDAI0"),
                   attrition =
c("Disease_duration","concomitantCsDMARD",

"Prev_bDMARD3","CDAI0","stopreason"),
                   seed = NA) {

  data <- check_data(datain,var,ttt_var,ref_ttt)
  dataS <- data[,.SD,.SDcols =
c("ID_ttt",var,"ttt",union(counfunders,attrition))]
```

```
  impute_data <- mice(
    dataS,
    m = 10,
    method = "pmm",
    maxit = 5,
    printFlag = F,seed = seed
  )
  # open the data
  impute_data_complete <- setDT(complete(impute_data,action = "long"))
  # calculate LDA
  impute_data_complete[,LDA := get(var) <= thres]

  # get LDA and error for each imputation
  res_mice <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$output

  }) %>% rbindlist()

  res_mice_2 <- lapply(seq(1:impute_data$m),function(imp){

    adjusted_model(data = impute_data_complete[.imp == imp],
                   covariates = counfunders)$fit

  })

  test <- pool(res_mice_2)
  df_pval <- summary(test)  %>% as.data.table()
  p.output <- df_pval[grepl("ttt",term),p.value]

# pooling
  pool_res <- res_mice[,.(
    LDA_mi = mean(LDA),
    w = mean(LDA_var),
    m = .N,
    b = 1/(.N-1)*sum( (LDA-mean(LDA))^2 )
              ),by = ttt]

  pool_res[,LDA_var := w + (1+1/m)*b]
  pool_res[,LDA_sd := sqrt(LDA_var)]

  # mean, 95% CI
  output <- pool_res[,.(ttt,
                        LDA_mi,
                        LDA_mi + 1.96*LDA_sd,
                        LDA_mi-1.96*LDA_sd) %>%
                       setNames(c("ttt","LDA","LDA_sup","LDA_inf"))]

  output[,methods := "CARRAC"]
```

```
  output[ttt == "diff",p := p.output]

  # change name back
  setnames(output,"ttt",ttt_var)

  return(output)
}
```

3 - FINAL FIGURES CODE

10/11/2020

{r setup, include=FALSE} knitr::opts_chunk$set(echo = TRUE)

Libraries, Loading data and function

```
library(psych)
library(dplyr)
library(lme4)
library(lmerTest)
library(survival)
library(latticeExtra)
library(Hmisc)
library(mice)
library(car)
library(ggplot2)
library(survminer)
library(xlsx)
library(lubridate)
library(tableone)
library(data.table)
library(stringr)
library(zoo)
library(patchwork) # package to compose multiplots !
library(ggpubr)
library(grid)

rm(list = ls())
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))

load("./3_clean_output/full_workspaces/workspace_1.RData")
load("./3_clean_output/full_workspaces/workspace_2.RData")
load("./3_clean_output/full_workspaces/workspace_3.RData")
```

1. Common theme

```
theme_benoit = function(){
theme_pubclean()+
  theme(panel.grid.major.x = element_line(linetype = "dotted", colour
= "grey50"),
        panel.grid.major.y = element_line(linetype = "dotted", colour
= "grey50"),
        axis.title.y = element_text(margin = margin(r = .2, unit =
"cm")),
        axis.title.x = element_text(margin = margin(t = .2, unit =
```

```
"cm")),
        plot.title = element_text(margin = margin(b = .5, unit =
"cm")))
}
```

1. [0] Mini explation

TC lenght

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

p1 <- ggplot(BARI_DATA)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/12)+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "Time of observation for all included TC")+
  ylim(-25,NA)+
  theme_benoit()
p1

p2 <- ggplot(BARI_DATA)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration
```

Saving plot

```
png("./3_clean_output/figures/PLOT_Exploration_TC_duration.png",
    width = 7,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
plot_mini_exploration
dev.off() # closing graphic device
```

TC lenght for BARI only

```
data_sub <- BARI_DATA[cohort == "BARI"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "red3")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "A - BARI")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_bari <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_bari
```

TC lenght for TNFi only

```
data_sub <- BARI_DATA[cohort == "TNFi"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "green2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "B - TNFi")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_tnfi <- p1 +
inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_tnfi
```

TC lenght for OMA only

```
data_sub <- BARI_DATA[cohort == "OMA"]

p1 <- ggplot(data_sub)+
  geom_histogram(aes(x = time_on_drug_year), alpha = .6, binwidth =
1/13, fill = "blue2")+

  scale_x_continuous(breaks = c(0,0.5,1,1.5,2,2.5))+
```

```
  labs(x = "Duration of observation (years)",
       y = "Number of TC",
       title = "C - OMA")+
  ylim(-11,50)+
  theme_benoit()
p1

p2 <- ggplot(data_sub)+
    geom_boxplot(aes(x = time_on_drug_year), alpha = .6, fill =
"grey80")+
    theme_void()

plot_mini_exploration_oma <- p1 + inset_element(p2,0.01,0.05,0.99,0.2)
plot_mini_exploration_oma
```

multiplot

```
multi_plot <- plot_mini_exploration_bari + plot_mini_exploration_tnfi
+ plot_mini_exploration_oma
multi_plot

median(BARI_DATA[cohort == "BARI", time_on_drug])
median(BARI_DATA[cohort == "TNFi", time_on_drug])
median(BARI_DATA[cohort == "OMA", time_on_drug])
```

Saving plot

```
png("./3_clean_output/figures/
PLOT_Exploration_TC_duration_3_groups.png",
    width = 9,
    height = 5,
    units = "in",
    res = 300) # opening graphic device
multi_plot
dev.off() # closing graphic device
```

1. [1] Survival analysis

Forest plot BARI vs TNFi + BARI vs OMA

```
meanall  <- summary(BARI1.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI1.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI1.adj.mi)$conf.int[1:14,"upper .95"]
textall <- c("Treatment (vs BARI)", "Age (decades)", "BMI",
"Concomitant csDMARD", "Concomitant glucocorticoid", "CDAI score (10
pts)", "Disease duration (decades)", "Current smoker (vs non-smoker)",
"Former smoker (vs non-smoker)", "2nd line therapy (vs 1st)", "3rd
line therapy (vs 1st)", "4th or later line (vs 1st)", "Female gender",
"Seropositivity (RF or ACPA)")
```

```
dfall1 <- data.table(textall, meanall, lowerall, upperall)
dfall1[,ttt := "TNFi"]

meanall  <- summary(BARI2.adj.mi)$coefficients[1:14,"exp(coef)"]
lowerall <- summary(BARI2.adj.mi)$conf.int[1:14,"lower .95"]
upperall <- summary(BARI2.adj.mi)$conf.int[1:14,"upper .95"]
dfall2 <- data.table(textall, meanall, lowerall, upperall)
dfall2[, ttt := "OMA"]

dfall <- rbind(dfall1,dfall2)
dfall$textall <- factor(dfall$textall, levels = rev(textall))

text_high <- textGrob("\u2192 Reduces \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))
text_low <- textGrob("\u2190 Improves \ndrug maintenance",
gp=gpar(fontsize=8, fontface="bold"))

HR_plot <- ggplot(data=dfall,
                  aes(x = textall,
                      y = meanall,
                      ymin = lowerall,
                      ymax = upperall,
                      color = ttt))+
  geom_hline(yintercept =1, linetype=2)+
  geom_point(size=2,position = position_dodge(width = .7))+
  geom_errorbar(position = position_dodge(width = .7))+
  labs(x = "",y = "",color = "")+
  scale_y_log10(breaks=c(0.5,0.6, 0.7, 0.8, 0.9,1,1.2, 1.4, 1.6, 1.8))
+
  theme(axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", color = "black"),
        legend.position="top",
        legend.key = element_blank(),
        plot.margin = unit(c(1,3,2,1),"lines"))+
  coord_flip(clip = "off")+
  annotation_custom(text_high,
           xmin=-0.64,xmax=-0.64,ymin=.2,ymax=.2)+
  annotation_custom(text_low,
           xmin=-0.64,xmax=-0.64,ymin=-.15,ymax=-.15)+
  theme_pubclean()+
  scale_color_manual(breaks = c("OMA","TNFi"),values =
c("blue3","green3"),labels = c("OMA","TNFi"))

HR_plot
```

Saving the plot in PNG file

```
png("./3_clean_output/figures/PLOT FOREST BARI vs TNFi vs OMA HR.png",

    width = 7,
```

```
    height = 5.5,
    units = "in",
    res = 300)

HR_plot

dev.off() # closing graphic device
```

BARI vs TNFi

Non-adjusted Kaplan-Meier curves

BARI vs TNFi

```
BARI1[,time_on_drug_year := time_on_drug/365.25]

surv_object1 <- Surv(time = BARI1$time_on_drug_year, event =
BARI1$stop_DMARD) # indiquate time on drug and stop variable
fit1 <- survfit(surv_object1 ~ cohort, data = BARI1)

survplot_1 <- ggsurvplot(fit1, data = BARI1,  # plot
                         pval = T,
                         pval.method = TRUE,
                         legend.title = "Groups :",
                         legend.labs = c("BARI", "TNFi"),
                         xlab = "Time (years)",
                         xlim = c(0, 2.5),
                         censor = FALSE,
                         title = "Non-adjusted model of drug
discontinuation \nby type of treatment",
                         surv.median.line = "v",
                         linetype = 1,
                         size = 1.5,
                         #palette = c("grey78", "grey10"),
                         palette = c("red3", "green2"), # pour mettre
les couleurs
                         ggtheme = theme_benoit(),
                         risk.table = T)

values <- summary(fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.2,label =
as.character(round(values,2)))

survplot_1$plot <- survplot_1$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2"), size = 5)


print(survplot_1)
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves non adjusted
COLOR.png",
     width = 7,
       height = 7, units = "in",
       res = 300) # opening graphic device
survplot_1

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_TNFi_data <- survplot_1$data.survplot
write.xlsx(plot_BARI_vs_TNFi_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_TNFi_data_non_adjust
ed.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted curves based on imputed data

```
dummy_cox_impute1 <- mice::complete(imputed_data1, "long", include =
T)
dummy_cox_impute1 <- dummy_cox_impute1[dummy_cox_impute1$.imp != 0,]
dummy_cox_impute1$time_on_drug_year <-
dummy_cox_impute1$time_on_drug/365.25

BARI_fit1 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute1), data =
dummy_cox_impute1)


survplot_1_adj <- ggsurvplot(BARI_fit1, data = dummy_cox_impute1,
variable = "cohort",
                           xlab = "Time (years)",
                           title = "A - BARI vs TNFi",
                           legend.title = "Groups :",
                           legend.labs = c("BARI", "TNFi"),
                           censor = FALSE,
                           xlim = c(0, 2.5),
```

```
                                surv.median.line = "v",
                                linetype = 1,
                                size = 1.5,
                                ggtheme = theme_benoit(),
                                # palette = c("grey78", "grey10")
                                palette = c("red2", "green3") )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,\n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding days label
values <- summary(BARI_fit1)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_1_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green3"), size = 5)

# adding HR et p val label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI1.adj.mi$coefficients[1]), 2), "\n", "p =",
round(summary(BARI1.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_1_adj$plot <- survplot_1_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)

# final print
survplot_1_adj
```

Saving the survival plot in PNG file

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves adjusted.png",

    width = 7,
    height = 5,
    units = "in",
    res = 300)

survplot_1_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression Package)

First plot to get the difference in average treatment effect in percentage

```
dt.out$time_years <- dt.out$time/365.25

plot.ate.diff <- ggplot(dt.out[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  scale_colour_manual(values = c("red2","green3"))+
  scale_fill_manual(values = c("red2","green3"))+
  theme_minimal() + theme(legend.spacing.x = unit(0.2, 'cm'),
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "A - BARI vs TNFi")
+
  labs(group = "Groups:")+
  theme_benoit()+
  theme(axis.title.x = element_text(margin = margin(t = .3,unit =
"cm")),
        axis.title.y = element_text(margin = margin(r = .3,unit =
"cm")))

plot.ate.diff
```

Saving Plot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi curves AIPTW.png",
width = 1300, height = 650, res = 120) # opening graphic device

plot.ate.diff

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio <- ggplot(dt.out[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.4)+
  geom_line(aes(y = estimate, color = level), size = 2)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(0,500,50))+
```

```
  scale_y_continuous(limits = c(0.9,4.5))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio
```

BARI vs OMA

Non-adjusted Kaplan-Meier curves

BARI vs OMA

```
BARI2[,time_on_drug_year := time_on_drug/365.25]

surv_object2 <- Surv(time = BARI2$time_on_drug_year, event =
BARI2$stop_DMARD)
fit2 <- survfit(surv_object2 ~ cohort, data = BARI2) # this function
creates the data for Kaplan Meyer
survplot_2 <- ggsurvplot(fit2, data = BARI2,  # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           xlab = "Time (days)",
           xlim = c(0, 2.5),
           censor = FALSE,
           title = "Non-adjusted model of drug discontinuation by type
of treatment",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           #palette = c("grey78", "grey50"),
           palette = c("red3", "blue2"), # to put colors
           risk.table = T)
survplot_2
```

Saving surplot

```
png("./3_clean_output/PLOT BARI vs OMA curves non adjusted COLOR.png",
width = 1000, height = 600, res = 100) # opening graphic device

survplot_2

dev.off() # closing graphic device
```

Saving the plot curv object for Lilly

```
plot_BARI_vs_OMA_data <- survplot_2$data.survplot
write.xlsx(plot_BARI_vs_OMA_data, file =
"./3_clean_output/Lilly_curves_excel/plot_BARI_vs_OMA_data_non_adjuste
d.xlsx", row.names = F)
```

Home-made attempt to obtain adjusted cuves based on imputed data :

```
dummy_cox_impute2 <- mice::complete(imputed_data2, "long", include =
T)
dummy_cox_impute2 <- dummy_cox_impute2[dummy_cox_impute2$.imp != 0,]
dummy_cox_impute2$time_on_drug_year <-
dummy_cox_impute2$time_on_drug/365.25

BARI_fit2 <- survfit(coxph(Surv(time = time_on_drug_year, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           TC_with_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute2), data =
dummy_cox_impute2)

survplot_2_adj <- ggsurvplot(BARI_fit2, data = dummy_cox_impute2,
variable = "cohort",
           xlab = "Time (years)",
           title = "B - BARI vs OMA",
           legend.title = "Groups :",
           legend.labs = c("BARI", "OMA"),
           censor = FALSE,
           xlim = c(0, 2.5),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           # palette = c("grey78", "grey50")
           palette = c("red2", "blue3") # to change colors
           )+
  labs(caption = "Adjusted for : age, BMI, concomitant csDMARD, \n
concomitant glucocorticoid, baseline CDAI, disease duration
(decades),\n smoking status, line of therapy, gender, seropositivity")

# adding Days label
values <- summary(BARI_fit2)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
```

```
as.character(paste(round(values*365.25,2), "\n days")))
df[1,2] <- 1.82

survplot_2_adj$plot$labels$y <- "Proportion still on drug" # to change
the label

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"blue2"), size = 5)

# adding HR et pval label
HR <- data.frame(y = 0.1, x = 0.5, label = paste("HR =",
round(exp(BARI2.adj.mi$coefficients[1]), 2),  "\n", "p =",
round(summary(BARI2.adj.mi)$coefficients[1,"Pr(>|z|)"], 4)  ) )

survplot_2_adj$plot <- survplot_2_adj$plot +
  geom_text(data = HR,aes(x,y,label = label) , size = 5)



# final print
survplot_2_adj

summary(BARI_fit2, times = 1) # to see detailed surv probabilities at
given timepoints
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA curves adjusted.png", width =
1000, height = 600, res = 100) # opening graphic device

survplot_2_adj

dev.off() # closing graphic device
```

Sensitivity analysis (RiskRegression package)

First plot to get the difference in average treatment effect in percentage

```
dt.out2$time_years <- dt.out2$time/365.25

plot.ate.diff2 <- ggplot(dt.out2[type == "meanRisk"], aes(x =
time_years, group = level))+
  geom_vline(xintercept = 1, linetype = 2, size = 1, color = "grey20")
+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit() + theme(legend.spacing.x = unit(0.2, 'cm'),
```

```
legend.position="top" )+
  scale_x_continuous(breaks=seq(0,2.5,0.25)) +
scale_y_continuous(labels = scales::percent, limits = c(0,0.65))+

  xlab("Years since intiation of treatment")+
  ylab("Absolute Risk of treatment discontinuation (%)")+
  labs(colour="Groups:", fill = "Groups:", title = "B - BARI vs OMA")+
  labs(group = "Groups:")+

  scale_colour_manual(values = c("red2","blue3"))+
  scale_fill_manual(values = c("red2","blue3"))

plot.ate.diff2
```

Saving Plot

```
png("./3_clean_output/PLOT BARI vs OMA curves AIPTW.png", width =
1300, height = 650, res = 120) # opening graphic device

plot.ate.diff2

dev.off() # closing graphic device
```

Second plot to get the ratio in average treatment effect

```
plot.ate.ratio2 <- ggplot(dt.out2[type == "ratioRisk"], aes(x = time,
group = level))+
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = level), alpha =
0.3)+
  geom_line(aes(y = estimate, color = level), size = 1)+

  theme_benoit()+
  theme(legend.spacing.x = unit(0.2, 'cm'), legend.position="top")+
  scale_x_continuous(breaks=seq(100,400,50))+
  scale_y_continuous(limits = c(0.8,3))+

  xlab("Days since intiation of treatment")+
  ylab("Ratio in Average Treatment Effect")+
  labs(colour="treatment", fill = "treatment")

plot.ate.ratio2
```

Multipanel plots

To update using patchwork

For the paper Non adjuted curves

```
# Creating list object

plots <- list()
```

```
plots[[1]] <- survplot_1
plots[[2]] <- survplot_2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)
```

Option 2 putting all data on one panel Kaplan Meier

BARI vs TNFi vs OMA

```
BARI_DATA[,time_on_drug_year := time_on_drug/365.25]

surv_object3 <- Surv(time = BARI_DATA$time_on_drug_year, event =
BARI_DATA$stop_DMARD)
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_DATA) # this
function creates the data for Kaplan Meyer
survplot_3 <- ggsurvplot(fit3, data = BARI_DATA,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit3)$table[,"median"]
df <- data.frame(y = .1,x = values+.1,label =
as.character(paste(round(values*365.25,2), "\n days")))
df[3,2] <- 1.72

survplot_3$plot <- survplot_3$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("red3",
"green2", "blue2"), size = 5)

survplot_3$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_3
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA curves non
adjusted COLOR.png", width = 800, height = 600, res = 100) # opening
```

```
graphic device

survplot_3

dev.off() # closing graphic device
```

Adjusted curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1_adj
plots[[2]] <- survplot_2_adj

# Nice function

multi_plot_cox <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device

multi_plot_cox

dev.off() # closing graphic device
```

All curves

```
# Creating list object

plots <- list()
plots[[1]] <- survplot_1
plots[[3]] <- survplot_2
plots[[2]] <- survplot_1_adj
plots[[4]] <- survplot_2_adj

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2, nrow =
2)

# but does not display properly now.. :(
```

AIPTW absolute risk of treatment discontinuation biplot

```
plot.ate.diff + plot.ate.diff2

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA AIPTW curves
adjusted COLOR.png", width = 1000, height = 600, res = 100) # opening
graphic device
```

```
plot.ate.diff + plot.ate.diff2

dev.off() # closing graphic device
```

Diagnostic multipanel plots

Asked by Lilly statistician to show balance in this analysis.

```
pscore_plot <- ggplot(test.data, aes(x = pscores, color = cohort, fill
= cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","green3"))+
    scale_fill_manual(values = c("red2","green3"))+

    xlab("Probability of being assigned BARI or TNFi") +
    ylab("Density") +
    labs(title = "A1 - BARI vs TNFi")

pscore_plot # overlap

pscore_plot2 <- ggplot(test.data2, aes(x = pscores, color = cohort,
fill = cohort)) +
  geom_density(alpha = .47) +

    theme_minimal()+
    theme(axis.ticks.y = element_blank(),
          panel.grid.minor = element_blank(),
          legend.title = element_blank(),
          text = element_text(size = 16),
          axis.title.x = element_text(hjust = 0.2, size = 16))+

    scale_colour_manual(values = c("red2","blue3"))+
    scale_fill_manual(values = c("red2","blue3"))+

    xlab("Probability of being assigned BARI or OMA") +
    ylab("Density") +
    labs(title = "A2 - BARI vs OMA")

pscore_plot2
# Good overlap
```

```
library(cobalt)

# BARI vs TNFi
B1 <- love.plot(COVS, treat = test.data$cohort, weights =
test.data$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B1 - BARI vs TNFi", color =
c("#FD8D3C", "#08306B"), themes = theme_pubclean() )

# BARI vs OMA
B2 <- love.plot(COVS_2, treat = test.data2$cohort, weights =
test.data2$weights, stats =  c("mean.diffs"), thresholds = c(m = .1),
var.order = "adjusted", title = "B2 - BARI vs OMA", color =
c("#FD8D3C", "#08306B") , themes = theme_pubclean() )

one <- (  pscore_plot + B1)

two <- ( pscore_plot2 + B2 )

png("./3_clean_output/figures/AIPTW diagnositc COLOR.png", width =
1300, height = 900, res = 100) # opening graphic device

one / two

dev.off() # closing graphic device
```

1. [3] Fist line analysis

Non-adjusted Survival curves

BARI vs TNFi

```
BARI_first1 <- copy(BARI_first[cohort %in% c("BARI", "TNFi")])

surv_object3 <- Surv(time = BARI_first1$time_on_drug, event =
BARI_first1$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first1))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first1) # function
which creates Kaplan-meier data
survplot_first1 <- ggsurvplot(fit3, data = BARI_first1,   # plot
           pval = T,
           pval.method = TRUE,
           legend.title = "Groups :",
           legend.labs = c("BARI", "TFNi"),
           xlab = "Time (days)",
           xlim = c(0, 700),
           censor = FALSE,
           title = "A - BARI vs TNFi",
           surv.median.line = "v",
           linetype = 1,
```

```
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50"),
            palette = c("red2", "green3"), # to get colors
            risk.table = T
            )

survplot_first1$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first1

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1

dev.off() # closing graphic device
```

BARI vs OMA

```
BARI_first2 <- BARI_first[line_of_therapy == "1st" & cohort %in%
c("BARI", "OMA")] # selection des TC TNFi

surv_object3 <- Surv(time = BARI_first2$time_on_drug, event =
BARI_first2$stop_DMARD) # indiquate stop variable and time_on_drug
summary(coxph(surv_object3 ~ cohort, data = BARI_first2))
fit3 <- survfit(surv_object3 ~ cohort, data = BARI_first2) # function
which creates Kaplan-meier data
survplot_first2 <- ggsurvplot(fit3, data = BARI_first2,   # plot
            pval = T,
            pval.method = TRUE,
            legend.title = "Groups :",
            legend.labs = c("BARI", "OMA"),
            xlab = "Time (days)",
            xlim = c(0, 700),
            censor = FALSE,
            title = "B - BARI vs OMA",
            surv.median.line = "v",
            linetype = 1,
            size = 1.5,
            ggtheme = theme_benoit(),
            # palette = c("grey78", "grey50", "grey10"),
            palette = c("red2", "blue3"), # to get colors
            risk.table = T
            )
```

```
survplot_first2$plot$labels$y <- "Proportion still on drug" # to
change the label
survplot_first2

rm(surv_object3, fit3)
```

saving plot curves

```
png("./3_clean_output/PLOT BARI vs OMA first line curves non adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs TNFi)

```
dummy_cox_impute_first1 <- mice::complete(imputed_data1_first, "long",
include = T)
dummy_cox_impute_first1 <-
dummy_cox_impute_first1[dummy_cox_impute_first1$.imp != 0,]

BARI_first1_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                             I(age_base/10)+
                             bmi_base+
                             concomitant_csDMARD+
                             PREDNISON_STEROID+
                             CDAI0+
                             I(disease_duration_base_years/10)+
                             C(smoker_base, base=3)+
                             line_of_therapy+
                             gender+
                             seropositivity_base+
                             cluster(patient_id)+
                             strata(cohort),dummy_cox_impute_first1),
data = dummy_cox_impute_first1)


survplot_first1_adj <- ggsurvplot(BARI_first1_fit, data =
dummy_cox_impute_first1, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "TNFi"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
```

```
            linetype = 1,
            size = 1.5,
            ggtheme = theme_minimal(),
            #palette = c("grey78", "grey10")
            palette = c("red2", "green3"), # to get colors
            )

survplot_first1_adj <- survplot_first1_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first1_adj
table(BARI_first1$cohort)
rm(dummy_cox_impute_first1, BARI_first1_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs TNFi first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first1_adj

dev.off() # closing graphic device
```

Adjusted curves with imputed data (BARI vs OMA)

```
dummy_cox_impute_first2 <- mice::complete(imputed_data2_first, "long",
include = T)
dummy_cox_impute_first2 <-
dummy_cox_impute_first2[dummy_cox_impute_first2$.imp != 0,]

BARI_first2_fit <- survfit(coxph(Surv(time = time_on_drug, event =
stop_DMARD) ~ cohort+
                           I(age_base/10)+
                           bmi_base+
                           concomitant_csDMARD+
                           PREDNISON_STEROID+
                           CDAI0+
                           I(disease_duration_base_years/10)+
                           C(smoker_base, base=3)+
                           line_of_therapy+
                           gender+
                           seropositivity_base+
                           cluster(patient_id)+
                           strata(cohort),dummy_cox_impute_first2),
data = dummy_cox_impute_first2)


survplot_first2_adj <- ggsurvplot(BARI_first2_fit, data =
```

```
dummy_cox_impute_first2, variable = "cohort",
           xlab = "Time (days)",
           title = "Multivariable Cox model of drug discontinuation by
type of treatment - 1st line vs 1st line",
           legend.title = "Groups :",
           legend.labs = c("Baricitinib", "OMA bDMARDs"),
           censor = FALSE,
           xlim = c(0, 700),
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_minimal(),
           #palette = c("grey78", "grey50")
           palette = c("red2", "blue3"), # to get colors
           )

survplot_first2_adj <- survplot_first2_adj +
    labs(caption = "Adjusted for : age, BMI, concomitant csDMARD,
concomitant glucocorticoid, baseline CDAI, disease duration (decades),
smoking status, line of therapy, gender, seropositivity")

survplot_first2_adj
table(BARI_first2$cohort)
rm(dummy_cox_impute_first2, BARI_first2_fit)
```

Saving the survival plot in PNG file

```
png("./3_clean_output/PLOT BARI vs OMA first line curves adjusted
COLOR.png", width = 1000, height = 600, res = 100) # opening graphic
device

survplot_first2_adj

dev.off() # closing graphic device
```

Multipanel plots

Non adjusted curves

```
plots <- list()
plots[[1]] <- survplot_first1
plots[[2]] <- survplot_first2

# Nice function

multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

png("./3_clean_output/figures/BIPLOT BARI vs TNFi vs OMA 1st Line
curves non-adjusted COLOR.png", width = 1000, height = 600, res = 100)
# opening graphic device
```

```
multi_plot <- arrange_ggsurvplots(plots, print = T, ncol = 2)

dev.off() # closing graphic device
```

All in one BARI vs TNFi vs OMA

```
BARI_first[,time_on_drug_year := time_on_drug/365.25]

surv_object4 <- Surv(time = BARI_first$time_on_drug_year, event =
BARI_first$stop_DMARD)
fit4 <- survfit(surv_object4 ~ cohort, data = BARI_first) # this
function creates the data for Kaplan Meyer

survplot_4 <- ggsurvplot(fit4, data = BARI_first,  # plot
           pval = F,
           pval.method = F,
           legend.title = "Groups",
           legend.labs = c("BARI", "TNFi", "OMA"),
           xlab = "Time (years)",
           xlim = c(0, 2.5),
           censor = FALSE,
          # title = "Non-adjusted drug discontinuation by type of
treatment (Kaplan-Meier)",
           surv.median.line = "v",
           linetype = 1,
           size = 1.5,
           ggtheme = theme_benoit(),
           palette = c("red3", "green2", "blue2"), # to put colors
           risk.table = T)

values <- summary(fit4)$table[,"median"]
df <- data.frame(y = .2,x = values+.2,label =
as.character(paste(round(values*365.25,2), "\n days")))
df <- df[2,]

survplot_4$plot <- survplot_4$plot +
  geom_text(data = df,aes(x,y,label = label), color = c("green2"),
size = 5)

survplot_4$plot$labels$y <- "Proportion still on drug" # to change the
label
survplot_4
```

Saving surplot

```
png("./3_clean_output/figures/PLOT BARI vs TNFi vs OMA first curves
non adjusted COLOR.png", width = 800, height = 600, res = 100) #
opening graphic device
```

```
survplot_4

dev.off() # closing graphic device
```

1. [4] LACK of EFFICACYY and ADVERSE EVENTS

Analysis by stop_reasons in competing risk

(BARI vs TNFi)

Cumulative incidence function

```
ci_long$time_months <- ci_long$time/365.25*12

plot2 <-  ggplot(data = ci_long, aes(x = time_months,
                                     y = value,
                                     linetype = variable  ,
                                     col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","green2"),
                     labels = c("BARI","TNFi"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"),
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+ # not showing the "other category"
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "A - BARI vs TNFi")

plot2

ggsave(filename = "PLOT BARI vs TNFi cumulative incidence.png",plot =
plot2, path = "./3_clean_output/", device = "png", width = 829, height
= 550, units = "px", scale = 3.2)
```

(BARI vs OMA)

Cumulative incidence function

```
ci_long_2$time_months <- ci_long_2$time/365.25*12

plot3 <-  ggplot(data = ci_long_2, aes(x = time_months,
                                       y = value,
                                       linetype = variable  ,
                                       col = cohort )) +
  geom_line(size = 0.75)+

  scale_color_manual(breaks = c(0,1),
                     values = c("red3","blue2"),
                     labels = c("BARI","OMA"))+
  scale_linetype_manual(breaks = c("CI.1","CI.2"), # not showing the
"other" category
                        values = c("solid","dashed", "dotted"),
                        labels = c("Adverse Event","Ineffectiveness"))
+
  scale_x_continuous(name = "Time (months)",
                     breaks = c(0,3,6,9,12),
                     limits = c(0,12)) +
  scale_y_continuous(name = "Cumulative incidence", limits = c(0,0.4))
+
  theme_benoit()+
  theme(legend.box = "horizontal",
        legend.position = c(0.05,1),
        legend.justification = c(0,1),
        legend.background = element_blank(),
        legend.key = element_blank(), #no legend key background
        legend.key.width = grid::unit(2, "lines"))+ # longer line in
legend, to see properly the dashed
  labs(color = "", linetype = "", title = "B - BARI vs OMA")

plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs OMA
cumulative incidence.png", plot3, height = 4, width = 6, units =
"in",dpi = 300)
```

Multipanel

```
plot2_3 <- plot2 + plot3

ggsave(filename = "./3_clean_output/figures/PLOT BARI vs TNFi and BARI
vs OMA cumulative incidence.png", plot2_3, height = 4, width = 8,
units = "in",dpi = 300)
```

1. [6] LDA - REM

Exploration

See all available raw CDAI measures : :)

```
BARI_long[, group := "non-BARI"]
BARI_long[drug == "BIOLOGIC_BARICITINIB", group := "BARI"]

plot_data <- copy(BARI_long[!is.na(TC_id) & TC_id %in%
BARI_DATA$TC_id])
plot_data <- merge(plot_data, BARI_DATA[,.(TC_id, cohort)], by =
"TC_id")

CDAI_plot <- ggplot(data = plot_data,
                    aes(x = time, y = CDAI, fill = cohort) )+

  annotate("rect",xmin = 0.875,xmax = 1.125,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+
  annotate("rect",xmin = -.05,xmax = 0+1.5/12,
                  ymin = -1,ymax = 60,alpha = .5,fill = "grey80")+

  geom_point(data = plot_data[cohort != "BARI"], alpha = 0.2, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+
  geom_point(data = plot_data[cohort == "BARI"], alpha = 0.25, size =
2, shape = 21, position = position_jitter(width = 0.02, seed = 123) )+


  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort !=
"BARI"], alpha = 0.2, size = 2, shape = 21, show.legend = F )+
  #geom_jitter(width = 0.01, height = 0.01, data = plot_data[cohort ==
"BARI"], alpha = 0.25, size = 2, shape = 21 , show.legend = F, )+

  geom_smooth(alpha = 0.1, size = 1, aes(color = cohort), show.legend
= F)+

  coord_cartesian(xlim = c(0,2.5))+
    labs(title = "CDAI across time type of treamtent (all TC)",
         x = "Time (years since TC initiation)",
         y = "CDAI score",
         color = "",
         fill = "")+
  theme_benoit()+
  theme(legend.position = c(1,1),
        legend.justification = c(1,1))+
  guides(color = guide_legend(override.aes = list(linetype = NA,size =
3)))

CDAI_plot
```

To me this figure is the best results to be discussed regarding REM and LDA

saving plot

```
png("./3_clean_output/figures/PLOT CDAI across time raw.png",
    width = 8,
    height = 6,
    units = "in",
    res = 120) # opening graphic device

CDAI_plot

dev.off() # closing graphic device
```

CARRAC histogram

Building large format data table from the CARRAC output

```
# Extracting LDA BARI
LDA_BARI <- rbind(LDA_BARI_TNF[2,1:4], LDA_BARI_OMA[2,1:4]) # I have
one estimation per comparison
LDA_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
LDA_BARI <- LDA_BARI[1]

# REM BARI
REM_BARI <- rbind(REM_BARI_TNF[2,1:4], REM_BARI_OMA[2,1:4]) # I have
one estimation per comparison
REM_BARI[, LDA := mean(LDA)][, LDA_sup := mean(LDA_sup)][, LDA_inf :=
mean(LDA_inf)] # averaging
REM_BARI <- REM_BARI[1]

# IDem for TNFi and OMA
LDA_TNFi <- LDA_BARI_TNF[3,1:4]
REM_TNFi <- REM_BARI_TNF[3,1:4]

LDA_OMA <- LDA_BARI_OMA[3,1:4]
REM_OMA <- REM_BARI_OMA[3,1:4]

# Binding together
LDA <- rbind(LDA_BARI, LDA_TNFi, LDA_OMA)
setnames(LDA, c("ttt", "LDA", "LDA_sup", "LDA_inf")) #putting right
labels
REM <- rbind(REM_BARI, REM_TNFi, REM_OMA)
setnames(REM, c("ttt", "REM", "REM_sup", "REM_inf"))

histo_carrac <- cbind(LDA, REM[,-1])
```

plotting

```
carrac_plot <- ggplot(data = histo_carrac, aes(x = ttt, group = ttt))
+

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +

  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "A - REM and
LDA rates \nby type of treatment \n(CARRAC)")

carrac_plot
```

also Saving CARRAC plot only

```
png("./3_clean_output/figures/PLOT BARI 3 CARRAC ONLY.png", width =
350, height = 600, res = 100) # opening graphic device

ggplot(data = histo_carrac, aes(x = ttt, group = ttt)) +

  theme_pubclean()+

  geom_errorbar( mapping=aes(x=ttt, ymin=LDA_inf*100,
ymax=LDA_sup*100), width=0.2, size=1, color="grey70")+
  geom_errorbar( mapping=aes(x=ttt, ymin=REM_inf*100,
ymax=REM_sup*100), width=0.2, size=1, color="grey50")+

  geom_bar(aes(y = LDA*100), stat = "identity", fill = "grey80", alpha
= 0.5)+
  geom_text(aes(y = LDA*100, label = "LDA"), vjust = 1.5) +
```

```
  geom_bar(aes(x = ttt, y = REM*100), stat = "identity", fill =
"grey65", alpha = 0.5)+
  geom_text(aes(x= ttt, y = REM*100, label = "REM"), vjust=1.5) +

  theme(strip.text.y = element_blank(),
        strip.background = element_blank(),
        axis.line.x = element_line(size = 0.5),
        axis.text = element_text(face = "bold", colour = "black"),
        legend.position="bottom", plot.margin =
unit(c(1,3,2,1),"lines"))+

  scale_y_continuous(limits = c(0,82))+

  labs(y = "(% of TC)", x = "Treatment group", title = "REM and LDA
rates \nby type of treatment \n(CARRAC)")

dev.off() # closing graphic device
```

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p4-5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7 & supp p2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supp p2
Bias	9	Describe any efforts to address potential sources of bias	p16
Study size	10	Explain how the study size was arrived at	supp p9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p8-9
		(*b*) Describe any methods used to examine subgroups and interactions	supp p 5-6
		(*c*) Explain how missing data were addressed	p8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	p8-9
		(*e*) Describe any sensitivity analyses	p9 & supp p5-6

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p13-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p14-15 & supp
Discussion			
Key results	18	Summarise key results with reference to study objectives	p15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Filled in by Benoît GILBERT, 30-01-2023