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Dyslipidemia and Changes in Lipid Profiles Associated with Rheumatoid Arthritis and Initiation of Anti-TNF Therapy

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Abstract

OBJECTIVE—To investigate the frequency of lipid testing in clinical practice and explore the relationship between rheumatoid arthritis (RA), dyslipidemia, and other cardiovascular (CV) risk factors, with RA treatment.

METHODS—Patients in the retrospective database study were 18 years old and had 2 physician diagnoses for RA or osteoarthritis (OA) [comparator group] between March 2004–March 2008. Outcomes of interest included the percentage of RA and OA patients receiving lipid tests, lipid profiles (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) of RA vs. OA patients, and lipid profiles of RA patients before and after initiation with a tumor necrosis factor inhibitor (TNFi). We used multivariable regression to control potential confounders between the cohorts.

RESULTS—Over a median 2+ year follow-up, fewer RA patients than OA patients had at least one lipid test (62% [95% CI, 60–64] vs. 68% [95% CI, 65–71]). Mean TC and LDL-C were each 4 mg/dL lower in the RA cohort ($P<0.0001$); HDL-C was similar between cohorts. Across the RA cohort, 25.2% of patients had suboptimal LDL-C levels (>130 mg/dL). Among RA patients not using lipid-lowering therapy who initiated TNFi therapy ($n=96$), mean TC and LDL-C increased by 5.4 and 4.0 mg/dL, respectively.

CONCLUSION—RA patients were less likely to be tested for hyperlipidemia and had more favorable lipid profiles than OA patients. TNFi therapy modestly increased all lipid parameters. Additional studies are needed to determine the effect of traditional CV risk factors, inflammation, and the impact of biologics on CV outcomes in RA patients.

Patients with rheumatoid arthritis (RA) have higher rates of morbidity and mortality than the general population, which is highly attributed to an increased risk of cardiovascular disease (CVD) among RA patients. [1, 2] The increased risk of CVD appears to be linked to coronary atherosclerosis [3, 4] and may be directly caused by chronic inflammation or secondarily caused by physical inactivity and drugs used to treat RA [5]. Not surprisingly, RA treatment guidelines reflect this increased CV risk among RA patients. Evidence-based and expert-opinion based recommendations from the European League Against Rheumatism

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AUTHORS' CONTRIBUTIONS

JRC participated in the design of the study and provided critical review of the study results and manuscript. AJ conceived the study, participated in its design and coordination, and provided interpretation of the study results. OB participated in the design of the study, performed the statistical analysis, and provided interpretation of the results. All authors read and approved the final manuscript.

(EULAR) for the screening and management of RA patients include annual CV risk assessment, management of identified CV risk factors, and aggressive suppression of the inflammatory process to further lower the CV risk [6].

Lipid levels appear to be altered as a result of RA disease activity. Data on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels in RA patients are conflicting: some studies demonstrate similar [7] or lower [8] levels of TC, while others demonstrate increased levels of TC and LDL-C in patients with early RA [9]. Although reports on lipid profiles in RA patients vary, growing evidence suggests that patients with active untreated RA have reduced total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels [8, 10, 11]. Regardless of the TC changes in RA patients, with a decrease in HDL-C, several studies support the notion that RA leads to a more atherogenic lipid profile (TC to HDL-C ratio) which is correlated with disease activity and improves after treatment with antirheumatic medications [7-9, 12].

Inflammation is a common denominator in both RA and atherosclerosis. A growing body of evidence supports the involvement of common proinflammatory cytokines—such as macrophage migration inhibitory factor (MIF), interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF- α)—in the development and progression of both RA and atherosclerosis [3, 13]. Several studies have demonstrated that the use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents that affect these cytokines reduce inflammation in RA patients and may be associated with a reduced risk of CVD [12, 14-20].

Given that inflammation in RA patients alters the lipid profile, it is not surprising that treatment to control inflammation in RA patients may affect also lipid levels. A recent meta-analysis of 24 observational studies evaluating the effect of TNFi therapy on lipids in RA patients showed a small trend in an increase in TC, mostly due to an increase in HDL-C levels [21]. In light of uncertainties regarding the relation between RA, lipid profiles, and potent anti-inflammatory medications such as TNFi therapy, we used a large population-based database to investigate the frequency of lipid testing in clinical practice and to explore the relationship between RA, dyslipidemia, CVD risk factors, and RA treatment. The primary objective of this study was to evaluate the proportion of RA patients receiving lipid testing and the frequency of testing compared to controls (patients with osteoarthritis [OA]). We hypothesized that patients with RA would be tested less frequently than patients with OA. Secondary objectives included 1) comparing lipid levels in RA patients versus controls (OA patients) among patients tested for hyperlipidemia, and 2) describing changes in lipid levels in patients with RA who initiated therapy with a TNFi.

MATERIALS AND METHODS

Patient Identification

A retrospective analysis was conducted using data from the OptumInsight IMPACT database. This database includes medical claims, pharmacy claims, laboratory data, and patient eligibility data for 86.4 million covered lives, of which 63.7 million (74%) have pharmacy benefits and 12.6 million have laboratory results. The database includes patients 65 years of age or older, all of which are covered by standard commercial or managed care plans. The Impact database is derived from 46 health plans located across all census regions in the US (predominantly located in the North, North Central, and Atlantic regions).

Patients were included in the study if they were at least 18 years old and had at least two separate physician diagnoses (≥ 2 months apart) for RA (ICD-9-CM 714.xx) or for OA (ICD-9-CM 715.xx) between March 2004 and March 2008 (Table 1). Patients were excluded from the study if they had a diagnosis for any other autoimmune inflammatory

disease at any time during the study observation period (Appendix Table A). Patients with OA were chosen as a comparator group for RA patients because OA is a chronic condition that affects joints and may limit physical functioning, but which does not have the systemic inflammatory features more common to RA. Furthermore, OA patients were expected to be more comparable to RA patients given a higher expected prevalence of NSAID use (a recognized CV risk factor which might impact CV risk assessment) and more frequent contact with the medical system (which can motivate more use of appropriate screening tests) compared to the general population without chronic medical conditions. Additional study eligibility requirements and study design details which varied by the three study objectives are listed in Table 1.

All measures of a complete lipid panel—TC, HDL-C, LDL-C, and triglycerides (TG)—that occurred at any time during the observation period were evaluated in this study in time windows specific for each objective (Table 1). Classification of lipid levels was based on the Adult Treatment Panel III (ATP-III) cholesterol management guidelines [22]. Use of lipid-lowering medications—including niacin, fibric acid derivatives, bile acid binding resins, cholesterol absorption inhibitors, and HMG-CoA reductase inhibitors—was also evaluated in this study.

Statistical Analyses

All study variables, including baseline and outcome measures, were analyzed descriptively. Dichotomous variables were expressed as numbers and percentages and continuous variables were expressed as means (\pm standard deviation, SD), medians, or percentiles.

For dichotomous variables, p-values were calculated using the Mann-Whitney U Test, and for continuous variables, p-values were calculated using t-tests. Multivariable regression was used to control for confounders and to increase the efficiency of the estimators. The outcome variables and covariates used to control for baseline differences varied between objectives and are described in Table 1.

RESULTS

Objective 1: Frequency of Lipid Testing, Comparing RA versus OA Patients

The sample of individuals initially meeting eligibility requirements included 30,586 patients with an RA diagnosis, and 107,534 patients with an OA diagnosis (control group). Characteristics of each group at baseline, defined as six months prior to RA or OA diagnosis, are presented in Table 2. The groups were significantly different in most covariates; therefore, regression analysis was performed to control for these differences.

Over a median follow-up of 2.2 years (interquartile range, 1.6-2.8 years) for patients in the RA group and 2.5 years (interquartile range, 1.9-3.1 years) for patients in the OA group, there were somewhat fewer patients in the RA group than in the OA group who had at least one test for TC (59.1% [95% CI, 58.1-60.1] vs. 68.4% [95% CI, 64.4-70.4]), HDL-C (57.2% [95% CI, 56.0-58.4] vs. 66.4% [95% CI, 64.4-68.4]), LDL-C (58.6% [95% CI, 57.3-59.9] vs. 68.4% [95% CI, 67.1-69.7]), or TG (59.1% [95% CI, 58.2-60.0] vs. 68.4% [95% CI, 67.3-69.5]). Furthermore, the analysis of the risk-adjusted differences in the number of tests revealed that among patients who received a lipid test, slightly fewer tests were performed for RA than OA patients (TC, 2.0 [95% CI, 1.8-2.2] vs. 2.9 [95% CI, 2.6-3.2]; HDL-C, 1.8 [95% CI, 1.7-1.9] vs. 2.7 [95% CI, 2.5-2.9]; LDL-C, 1.9 [95% CI, 1.4-2.4] vs. 2.9 [95% CI, 2.5-3.3]; TG, 1.0 [95% CI, 0.8-1.2] vs. 2.9 [95% CI, 2.7-3.2]). Because follow-up time was somewhat longer for OA vs. RA patients, a subgroup analysis restricted the cohort to patients with at least 18 months of observation time after the start of follow-up and fixed the ascertainment period to these 18 months. Among this subgroup (71% of RA cohort and 68%

of OA cohort), RA patients were less likely compared to OA patients to receive any TC testing (56% [95% CI, 53-59] vs. 67% [95% CI, 63-71]).

Objective 2: Comparison of Lipid Levels in RA versus OA Patients

From the initial sample size of 136,996 RA patients, and based upon the availability of lab data in the database, 12,319 (9.0%) were eligible for the lipid level objective analysis compared with the 29,621 patients from the 194,192 OA controls (15.3%). Similar to the study population for Objective 1, there were significant differences among eligible RA and OA patients at baseline (Table 3).

Multivariable-adjusted regression analysis was performed to assess risk-adjusted lipid levels and CVD-related comorbidity prevalence. Mean TC, LDL-C, and TG levels were significantly lower in the RA than in the OA cohort (TC, 195 mg/dL [95% CI, 191-199] vs. 199 mg/dL [95% CI, 192-205]; LDL-C, 112 mg/dL [95% CI, 111-113] vs. 116 mg/dL [95% CI, 114-118]; TG, 132 mg/dL [95% CI, 129-135] vs. 138 mg/dL [95% CI, 136-140]; $P<0.0001$ for all comparisons), while HDL-C levels were marginally higher for the RA cohort relative to the OA cohort (56.8 mg/dL vs. 56.1 mg/dL; $P=0.02$). Furthermore, significantly fewer RA patients than OA patients had borderline high or high TC and LDL-C levels, based on ATP-III lipid classification levels ($P=0.0001$; Figure 1). RA patients were significantly less likely than OA patients to have a recorded diagnosis of hyperlipidemia (33% [95% CI, 28-35] vs. 45% [95% CI, 41-48]) and hypertension (45% [95% CI, 41-49] vs. 54% [95% CI, 49-56]; $P<0.0001$ for both).

Objective 3: Comparison of Lipid Levels Before and After TNFi Therapy in RA Patients

A total of 1,393 RA patients were eligible for the analysis of changes in lipid levels after TNFi therapy initiation. Of these patients, 289 had a lipid test within 90 days preceding and following TNFi initiation, 477 patients had a lipid test within 120 days, and 766 had a test within 180 days of TNFi initiation. Lipid test results were further stratified by use or non-use of lipid-lowering medications before and after TNFi initiation. Patients were classified as consistent users (lipid-lowering medication use before and after TNFi therapy), non-users (no lipid-lowering medication use before or after TNFi therapy), or mixed users (lipid-lowering medication therapy either before or after TNFi therapy, but not both). Mixed lipid-lowering medication users' results were not reported due to an inadequate sample size to characterize the various patterns of use with these agents. Furthermore, we did not observe any patients who started TNFi therapy, then was tested for hyperlipidemia but who did not have a result available in the data, initiated a lipid-lowering medication, and then was re-tested and had lipid results available.

We identified 289 patients with paired lipid levels within ± 90 days preceding and following the start of TNFi treatment (mean 65 days between the paired lipid tests). Among non-users of lipid-lowering medications starting therapy with a TNFi ($n=96$), mean HDL-C, TC, and LDL-C levels increased modestly: HDL-C, 0.9 mg/dL [95% CI, 0.1-1.6]; TC, 5.4 mg/dL [95% CI, 2.6-18.3]; LDL-C, 4.0 mg/dL [95% CI, 0.3-7.7] (Figure 2). Mean TG levels also increased in these patients (mean change, 7.3 mg/dL, $P=0.08$). Among consistent lipid-lowering medication users ($n=21$), HDL-C levels decreased by a mean of 3.4 mg/dL [95% CI, 2.2-10.0]; no significant changes were observed in TC, LDL-C, and TG levels (Figure 2). The atherogenic index (ratio of TC to HDL) decreased in both patients consistently using and not using lipid-lowering medications (3.8 to 3.6 and 3.7 to 3.6, respectively; $P=0.08$).

The within-person analysis described above was repeated for the groups who had lipid testing within ± 120 and ± 180 days of TNFi initiation. Study results were consistent, with

adjusted LDL levels consistently higher after TNFi initiation in patients not taking lipid-lowering medications, regardless of the timing of the test (data not shown).

DISCUSSION

This real-world analysis demonstrated that patients with RA had mean TC, LDL-C, and TG levels that were lower than OA patients. Although RA patients were slightly more likely to be in a favorable ATP-III category, approximately 25% of RA patients had suboptimal lipid levels based on current ATP-III guidelines [22]. Among RA patients initiating TNFi therapy and who had their TC and LDL-C re-tested within three months, mean TC and LDL-C increased 5 and 4 mg/dL after TNFi therapy was initiated. Finally, we observed that while RA patients were only slightly less likely to receive any lipid testing than OA patients, approximately one-third of RA patients did not receive any testing during the observation period of more than 2 years.

Among RA patients not receiving lipid-lowering medications, we observed that treatment with TNFi was associated with modest increases in TC and LDL-C levels. This is consistent with results from other studies that observed increases in lipid levels after treatment with biological agents. In a recent meta-analysis of 24 observational studies evaluating the effect of TNFi therapy on lipids in RA patients, a small trend of an increase in TC was observed [21]. Of the four controlled studies which measured the atherogenic index, one study found a significant increase of 8.9% in the TNFi therapy group and a significant decrease of 10.4% in the control group [23], two studies reported non-significant decreases in the TNFi group with no changes in the control groups [24, 25], and one study reported a significant decrease in cases compared to controls, but data were not provided [26]. In our study, we found minimal changes in lipid profiles among RA patients who were treated with lipid-lowering medication prior to and during TNFi therapy. However, our results could not be compared with the meta-analysis since no similar sub-group analysis of lipid level changes among patients using lipid-lowering medication treatments was performed [21].

Aside from TNFi, other biologic agents have been shown to affect lipid profiles. Tocilizumab (TCZ), which inhibits the proinflammatory cytokine interleukin-6 (IL-6) binding to its receptors,[27] is associated with decreases in inflammatory markers [28]. TCZ is associated with increased lipid levels in RA patients (e.g. an increase in LDL of 20 mg/dL among TCZ+MTX users), but has not been associated with an increase in CV events during short-term follow-up.[29-32] In a recently completed long-term follow-up study of TCZ in RA patients (mean treatment duration of 2.4 years), TC, HDL-C, LDL-C, and TG levels increased after 6 weeks of treatment and remained relatively stable at the elevated level thereafter [31, 32].

The clinical importance of lipid levels on CVD risk in RA is not completely understood. Recent evidence suggests that there may be a paradoxical effect of lipids on the risk of CVD in RA, where lower and not higher TC and LDL-C levels are associated with increased cardiovascular risk [11]. Furthermore, although HDL-C is generally considered to be cardioprotective—both through its ability to promote cholesterol efflux from artery cell walls and anti-inflammatory properties which project LDL-C from oxidation—a growing body of evidence suggests that in inflammatory conditions such as RA and systemic lupus erythematosus, patients have non-protective “pro-inflammatory HDL” (piHDL) which promotes accumulation of oxidized phospholipids in LDL-C [33, 34].

Based upon what appears to be more favorable TC and LDL-C distributions in RA patients compared to OA patients, the results of this analysis suggest that lipid profiles in RA patients only partially explain the previously-observed excess CVD risk associated with the

systemic inflammation of RA [35]. Other inflammation-induced factors, such as increased oxidative stress, insulin resistance, endothelial dysfunction, pro-thrombotic state, and elevated homocysteine levels,[36] as well as non-inflammatory mechanisms, such as genetic polymorphism and CV toxicity associated with certain anti-rheumatic drugs (e.g., glucocorticoids) may also contribute to the increased CVD risk in RA [36].

A major strength of this study is that it is based on real-world clinical practice. The dataset closely represents the United States in terms of population age, gender, and geographic region [37]. Comparing the United States versus the Impact dataset, the age distributions are as follows: 0-20 (27% US vs. 25% Impact), 21-39 (27% vs. 24%), 40-64 (31% vs. 40%), and 65+ (13% vs. 11%). In terms of regions, the distributions are as follows: northeast (18% US vs. 29% Impact), Midwest (22% vs. 26%), South (37% vs. 37%), and West (23% vs. 11%). Similar proportions of men are in each (49% in the United States versus 51% in the Impact dataset).

Conclusions from this study need to be weighed within the confines of some limitations of this data source. Clinical data related to risk factors such as smoking, CVD history, family history of CVD, and blood pressure, as well as RA disease severity and activity, were not available in the database. Studies have shown that while some traditional risk factors (dyslipidemia, family cardiac history, hypertension, diabetes mellitus, and obesity) impart similar risk for a CV event among RA and non-RA patients, other traditional CV risk factors (male gender, smoking, and personal cardiac history) impart significantly less relative CV risk in RA versus non-RA patients [38]. Beyond traditional CV risk factors, several disease severity and disease activity markers in RA—such as extra-articular manifestations, elevated erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) seropositivity, higher joint count, and functional status—correlate with the rate of CVD and major CV events, including myocardial infarction (MI), congestive heart failure (CHF), and death [4, 39-41].

Another limitation of this study is that this analysis did not investigate longitudinal changes in lipid levels associated with TNFi therapy beyond 180 days. A study by Popa et al. (2007) showed that although short-term effects of TNFi therapy on lipids seemed beneficial and anti-atherogenic, the atherogenic index increased after six months from the start of therapy. Furthermore, changes in disease activity and inflammatory status were inversely correlated with changes in TC and HDL-C levels and positively correlated with the variation of atherogenic index [42]. When evaluated over a longer period, such as six months or beyond, infliximab treatment has been associated with significantly increased levels of TC and TG, with no change in HDL-C and LDL-C or atherogenic indices at 6 months [43]. In other studies, RA patients treated with infliximab had increased lipid levels (TC, HDL-C, LDL-C) initially, which returned to baseline by six months to one year of treatment (except for TC levels, which remained increased in one study) [26, 44]. The effect of time was partially addressed in this study by sensitivity analysis in which similar results were obtained when lipid tests were carried out before or after 120 and 180 days. However, further investigations into the long-term effect of TNFi therapy on lipid levels are needed. Finally, we excluded patients who initiated lipid-lowering therapy after initiation of TNFi therapy and before follow-up lipid testing was performed (i.e. described as ‘mixed’ lipid lowering medication users). While this may have excluded some individuals with elevated lipids, these patients initiated a lipid lowering medication prior to follow-up lipid testing, avoiding concern for a selection bias related to the effect of TNFi on lipids.

CONCLUSION

Patients with RA have a higher mortality rate than the general population. Much of this risk is due to CVD. This study showed that in clinical practice RA patients were tested for

dyslipidemia less frequently than their OA counterparts. Furthermore, although RA patients tended to have relatively lower lipid levels, more than 25% of patients had suboptimal lipid levels based on current ATP-III guidelines. Analysis of lipid levels in RA patients before and after TNFi therapy initiation showed modest increases in TC, LDL-C, and HDL-C levels among patients not using lipid-lowering medications. Due to the increased risk of CVD and mortality among RA patients, more aggressive and early lipid management, including greater use of statin therapy may be appropriate to reduce CVD among RA patients who have elevated lipid and CRP levels. Additional prospective, long-term studies are needed to comprehensively determine the role of inflammation and the impact of biologics on lipid levels and CV outcomes in patients with RA.

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APPENDIX

Table A
Autoimmune Inflammatory Diseases for which Patients were Excluded

Condition	ICD-9-CM Code(s)
Acute disseminated encephalomyelitis (ADEM)	323.61
Addison's disease	255.4
Ankylosing spondylitis	720
Antiphospholipid antibody syndrome (APS)	279.8
Autoimmune hemolytic anemia	283
Autoimmune hepatitis	571.42
Bullous pemphigoid	694.5
Celiac disease	579
Cushing's disease	255
Dermatomyositis	710.3
Diabetes mellitus type 1	250.01, 250.03
Goodpasture's syndrome	446.21
Graves' disease	242
Guillain-Barre syndrome	357
Hashimoto's disease	245.2
Idiopathic thrombocytopenia purpura (ITP)	287.31
Inflammatory bowel disease	555, 556
Inflammatory myopathy	359
Lupus erythematosus	695.4

Condition	ICD-9-CM Code(s)
Multiple sclerosis	340
Myasthenia gravis	358, 258.01
Pemphigus	694.4, 694.5, 694.6
Pernicious anemia	281
Polymyalgia	725
Polyomyositis	710.4
Primary biliary cirrhosis	571.6
Psoriasis	696.1
Psoriatic arthritis	696
Reactive arthritis	99.3
Sjögren's syndrome	410.2
Systemic lupus erythematosus	710
Temporal arteritis	446.5
Vasculitis	362.18
Wegener's granulomatosis	446.4

Patients with the above ICD-9-CM codes recorded in the database at any time during the study observation period were excluded from the study.

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SIGNIFICANCE AND INNOVATION

- Our retrospective analysis of a representative US database demonstrated RA patients are significantly less likely to be tested for hyperlipidemia than controls (patients with osteoarthritis).
- Approximately 25% of patients with RA have suboptimal LDL-C levels according to the ATP-III cholesterol management guidelines.
- Initiation of anti-TNF therapy increased total cholesterol levels by approximately 5mg/dL among RA patients not on treatment with lipid lowering agents

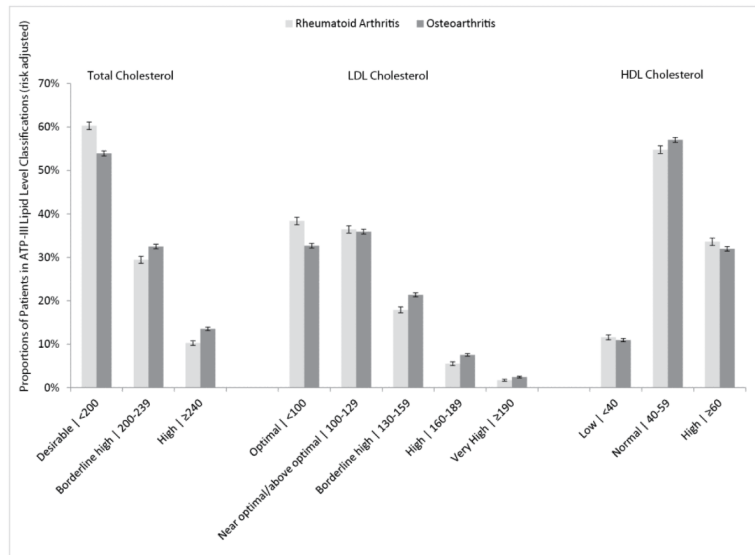


Figure 1. Proportions of RA and OA Patients in Various Lipid Categories Based On ATP-III Classifications

RA and OA cohorts were adjusted using multivariable regression based on factors listed in Table 1. Error bars indicate the 95% confidence interval of the mean.

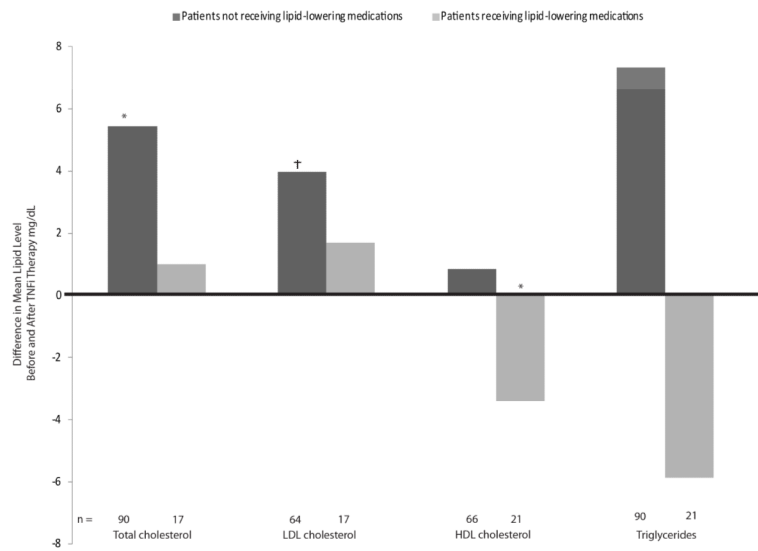


Figure 2. Changes in Lipid Levels after TNFi Initiation in Patients with RA

Includes patients who underwent lipid testing within 90 days before and after TNFi initiation. Not all patients underwent the complete set of lipid tests (e.g., patients might have undergone only TC testing but not HDL or LDL testing). A linear regression model was used to control for the factors listed in Table 1. * $p < 0.0001$; † $p < 0.01$ for the null hypothesis that there was no change in lipid values after TNFi initiation

Table 1

Patient Eligibility Requirements by Objective

Objective	Time Period ^d	Continuous Eligibility Requirement	Lipid Test Requirement	Index Date Definition	Variables Controlled for in the Regression Analysis
1) Comparison of Frequency of Lipid Testing [RA patients vs. OA patients]	Apr 2005 – Mar 2008	Medical and pharmacy benefits for 18 months [6 months before and 12 months after RA/OA diagnosis]	None	Date of 2nd physician RA/OA diagnosis	Baseline: Demographics ^b Insurance type ^c Comorbidities, comorbidity scores ^d RA medication use ^e Lipid-lowering medication use ^f Healthcare utilization ^g
2) Comparison of Lipid Levels [RA patients vs. OA patients]	Mar 2004 – Mar 2008	Medical and pharmacy benefits for 12 months	1 lipid test result (TC, HDL-C, LDL-C, or TG) after 2 nd RA/OA diagnosis	Date of lipid test	Baseline: Demographics ^b Insurance type ^c Comorbidities, comorbidity scores ^d RA medication use ^e Lipid-lowering medication use ^f Healthcare utilization ^g
3) Comparison of Changes in Lipid Levels in RA patients [90 days before / after starting TNFi therapy]	Mar 2004 – Mar 2008	Medical and pharmacy benefits for 6 months before TNFi initiation	1 lipid test before and another 6 weeks after TNFi initiation	Date of TNFi (etanercept, adalimumab, infliximab) initiation	Baseline: Demographics ^b Comorbidities, comorbidity scores ^d RA medication use ^e Lipid-lowering medication use ^f Healthcare utilization ^g Lipid tests (HDL-C, LDL-C, TC, TG) Days from diagnosis to lipid test

^a All objectives had a 6 month baseline period which occurred prior to the index date;

^b Age, gender, geographic location;

^c Capitated or not capitated;

^d Individual comorbidities adjusted for include those listed in the clinical characteristics table for each cohort; comorbidity scores include the Charlson Comorbidity Index, Chronic Disease Score;

^e TNF inhibitors, DMARDs, corticosteroids, NSAIDs;

^f Bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, statins, niacin;

^gInpatient, physician visits, outpatient visits, ER visits; hSensitivity analyses widened the windows before and after initiating TNFi therapy to \pm 120 days and \pm 180 days

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Table 2a
Demographic Characteristics of Patients Included in the Lipid Testing Sample (Objective 1) Measured during the 6-month Baseline Period

Parameter	RA Patients	OA Patients
	N=30,586	N=107,534
	N (%) or Mean (SD)	N (%) or Mean (SD)
Female Gender	22,658 (74.1%)	62,689 (58.3%)
Age Group		
18-49	13,883 (45.4%)	27,430 (25.5%)
50-64	13,560 (44.3%)	58,716 (54.6%)
65-74	2,124 (6.9%)	12,289 (11.4%)
75-84	1,019 (3.3%)	9,099 (8.5%)
Age (years)	50.2 (12.0)	56.1 (10.6)
Insurance Type		
Capitated	7,683 (25.1%)	40,499 (37.7%)
Census Region		
Midwest	4,389 (14.4%)	14,208 (13.2%)
Northeast	10,846 (35.5%)	52,408 (48.7%)
South	11,778 (38.5%)	30,069 (28.0%)
West	3,569 (11.7%)	10,815 (10.1%)

Table 2b
Clinical Characteristics of Patients Included in the Lipid Testing Sample (Objective 1)
Measured during the 6-month Baseline Period

Parameter	RA Patients	OA Patients
	N=30,586	N=107,534
	N (%) or Mean (SD)	N (%) or Mean (SD)
Comorbidities and Scores		
CCI Score [48]	1.1 (0.9)	0.4 (0.9)
Chronic Disease Score [49]	2.5 (3.0)	2.8 (2.9)
Fibromyalgia	2,593 (8.5%)	5,336 (5.0%)
Respiratory Infections	7,844 (25.7%)	32,472 (30.2%)
Diabetes	1,880 (6.2%)	10,385 (9.7%)
Obesity	664 (2.2%)	4,445 (4.1%)
Hypertension	7,077 (23.1%)	41,259 (38.4%)
Healthcare Utilization		
Inpatient	0.1 (0.3)	0.1 (0.3)
Physician visits	4.4 (6.2)	5.9 (6.6)
Outpatient visits	1.2 (2.8)	1.7 (3.4)
ER visits	0.2 (1.3)	0.3 (1.3)
RA-related Medications		
Non-cytotoxic DMARDs ^a	3,498 (11.4%)	399 (0.4%)
Cytotoxic DMARDs ^b	795 (2.6%)	680 (0.6%)
Methotrexate	3,764 (12.3%)	118 (0.1%)
Corticosteroids	7,421 (24.3%)	16,772 (15.6%)
NSAIDs	13,047 (42.7%)	50,215 (46.7%)
Lipid-lowering Medications	3,570 (11.7%)	26,896 (25.0%)

CCI, Charlson Comorbidity Index; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal antiinflammatory drug

^a gold compounds, penicillamine, chloroquine, hydroxychloroquine, sulfasalazine;

^b azathioprine, cyclosporine, cyclophosphamide, leflunomide

Table 3a
Demographic Characteristics of Patients Included in the Lipid Level Sample (Objective 2)
Measured during the 6-month Baseline Period

Parameter	RA Patients	OA Patients
	N=12,319	N=29,621
	N (%) or Mean (SD)	N (%) or Mean (SD)
Gender		
Female	9,357 (76.0%)	18,410 (62.8%)
Age Group		
18-49	3,895 (31.6%)	5,216 (17.8%)
50-64	6,565 (53.3%)	16,429 (56.0%)
65-74	1,287 (10.5%)	4,291 (14.63%)
75-84	572 (4.6%)	3,400 (11.6%)
Age (years)	54.2 (11.0)	58.7 (10.3)
Insurance Type		
Capitated	4,208 (34.2%)	11,953 (40.8%)
Census Region		
Midwest	1,165 (9.5%)	3,100 (10.6%)
Northeast	4,872 (39.6%)	10,809 (36.9%)
South	5,595 (45.4%)	13,981 (47.7%)
West	685 (5.6%)	1,439 (4.9%)

Table 3b
Clinical Characteristics of Patients Included in the Lipid Level Sample (Objective 2)
Measured during the 6-month Baseline Period

Parameter	RA Patients	OA Patients
	N=12,319	N=29,621
	N (%) or Mean (SD)	N (%) or Mean (SD)
Comorbidities and Scores		
CCI Score [48]	1.2 (1.1)	0.5 (1.0)
Chronic Disease Score [49]	4.5 (3.5)	3.1 (3.0)
Fibromyalgia	912 (7.4%)	1,262 (4.3%)
Respiratory Infections	4,367 (35.5%)	9,944 (33.9%)
Diabetes	1,599 (13.0%)	4,242 (14.5%)
Obesity	330 (2.7%)	1,295 (4.4%)
Hypertension	5,379 (43.7%)	15,603 (53.2%)
Polycystic Ovarian Disease	18 (0.2%)	12 (0.0%)
Coronary Artery Disease	943 (7.7%)	2,538 (8.7%)
Heart Failure	236 (1.9%)	632 (2.2%)
Hyperlipidemia	6,073 (49.3%)	16,635 (56.7%)
Lipid Levels		
Total Cholesterol	196.2 (36.4)	198.7 (37.8)
HDL Cholesterol	56.6 (15.9)	55.2 (16.1)
LDL Cholesterol	113.0 (31.7)	115.9 (33.3)
Triglycerides	133.1 (66.8)	138.5 (68.8%)
Healthcare Utilization		
Inpatient	0.0 (0.2)	0.1 (0.3)
Physician visits	4.2 (6.0)	5.8 (6.5)
Outpatient visits	1.3 (2.2)	1.8 (3.5)
ER visits	0.2 (1.2)	0.3 (1.2)
RA-related Medications		
DMARD only	4,439 (36.0%)	0 (0.0%)
Non-TNFi only	3 (0.0%)	1 (0.0%)
Non-TNFi and DMARDs	13 (0.1%)	0 (0.0%)
TNFi only	819 (6.7%)	0 (0.0%)
TNFi and DMARDs	1,231 (10.0%)	0 (0.0%)
Corticosteroids	4,166 (33.8%)	4,587 (15.6%)
NSAIDs	6,639 (53.9%)	12,849 (43.8%)
Lipid-lowering Medications	3,294 (26.7%)	8,678 (29.6%)

DMARD, disease-modifying antirheumatic drug; ER, emergency room; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumor necrosis factor inhibitor