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Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults: protocol of a randomized controlled trial using clinical vignettes

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Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults: protocol of a randomized controlled trial using clinical vignettes

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ABSTRACT

Introduction: Oral antithrombotic (AT) drugs are widely implicated in serious and preventable bleeding events, which justifies the implementation of risk minimization actions. Avoiding inappropriate oral AT combinations is a major concern, particularly for patients with multiple chronic conditions. The first step is to provide fast and easy access to the latest recommendations. From a systematic review of international guidelines (2012-2017), we developed a prescription support-tool synthesizing national and international guidelines on chronic management (≥ 1 month) of oral AT agents without considering in-hospital management and bridging therapy. Our main objective in this study is to evaluate the accuracy of this tool by measuring the appropriateness of oral AT prescriptions according to the most recent guidelines.

Methods and analysis: In this web-based randomized controlled trial, participating French general practitioners and cardiologists in the outpatient setting will be randomized by use or not of the prescription support-tool. They will be asked to provide the number of drugs, drug class, duration and dosage of ATs, within a time window of 10 minutes, for 3 different clinical situations presented as clinical vignettes (multiple-choice questions). The scientific committee has created and validated 30 clinical vignettes illustrating outpatient clinical situations for which the use of oral ATs (single, dual or triple therapy) is recommended or not according to the guidelines. All data will be treated anonymously.

Ethics and dissemination: If the prescription support-tool is associated with more appropriate prescription of AT combinations, its dissemination to further evaluate outcome data including haemorrhage, ischemic events, and death will be considered.

Article summary: strengths and limitations of this study

- Strengths:
  - Importance of the study: this study will evaluate a new prescription support-tool for oral antithrombotic (AT) combination. If the intervention is found to be effective, it has the potential to avoid a lot of adverse drugs events.
  - Robust intervention development: first, the prescription support-tool was developed from a systematic review of international guidelines (2012-2017). Second, a scientific committee and an expert committee have validated all clinical vignettes that we will use to evaluate the tool.
  - This is a multicentric, randomized study, with several medical specialties represented.
- Potential study limitations:
  - Bias toward selected physicians who may not be representative of general practitioners or cardiologists because they volunteered.
  - Access to the prescription support-tool in the control group cannot be avoided.
  - Generalisability: this study will be undertaken in France. Although this may limit generalisability, the prescription support-tool was developped from a systematic review of international guidelines from all over the world.

INTRODUCTION

Background

Because of multimorbidity (commonly defined as the presence of 2 or more chronic medical conditions in an individual) and medical progress, combinations of oral antithrombotic (AT) drugs, which include antiplatelet (AP) and anticoagulant (AC) therapies, are increasingly being prescribed.[1] ATs are also the most frequent drug class implicated in preventable serious and fatal adverse drug events (particularly bleeding events),[2,3] and their combination (dual or triple AT therapy) greatly increases this risk. For example, Hansen et al. reported a 3.1-fold higher risk of fatal and non-fatal bleeding with dual warfarin and clopidogrel therapy and a 3.7-fold higher risk with triple therapy (warfarin, aspirin and clopidogrel) than warfarin monotherapy in patients with non-valvular atrial fibrillation (NV-AF).[4] Data on inappropriate AT combination prescriptions are limited to a Canadian primary care cohort[5]: 15% of patients prescribed ATs had inappropriate dual or triple oral AT therapy (in terms of the type of drugs combined only), which suggests important room for improvement of AT combination prescriptions. Thus, developing efficient risk minimization actions by avoiding inappropriate combinations of ATs is necessary to improve their benefit/risk ratio.

In this perspective, from a systematic review of international guidelines (2012-2017), we developed a prescription support-tool [article under review elsewhere] synthesizing, on a double-sided page, international guidelines on chronic management (at least 1 month) of oral AT combinations (drugs, dosages and duration) in adults, without considering in-hospital management and bridging therapy. This prescription support-tool aimed at giving physicians quick access to the recommendation that fit most of their patient's clinical situation.

Study objectives and trial design

Our main hypothesis is that the prescription support-tool increases the rate of "right prescription of oral AT combinations" as defined according to the most recent guidelines.

The primary objective will be to evaluate the impact of this tool on the global appropriateness of oral AT prescriptions according to the most recent guidelines (in terms of number of drugs, drug class, duration and dosage: composite score).

Secondary objectives will be to evaluate the impact of this tool on the appropriateness of oral AT prescriptions according to the most recent guidelines in terms of the (1) number of drugs, (2) drug class, (3) dosage, (4) duration, (5) and combinations that should never be prescribed. We will also evaluate whether the impact of this tool differs by medical specialty of physicians responding. Finally, we will evaluate the degree of certainty physicians have about their AT prescriptions in line with the guidelines. In the experimental group, we will assess the use of the prescription support-tool to answer questions about clinical vignettes and the degree of the tool's perceived usefulness by physicians.

This trial is designed as a web-based, open randomized controlled trial with two parallel groups.

METHODS AND ANALYSIS

Study design

A web-based, open randomized controlled trial involving clinical vignettes will be performed in France. Clinical vignettes illustrating plausible situations will be used because they reflect clinical practice.[6,7] Such an approach has been found valid in measuring quality of care.[8,9] The randomization unit will be the physician and the unit of analysis the clinical vignette. Our study will involve a scientific committee and an expert committee. The scientific committee consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2 epidemiologists. The scientific committee designed the study protocol, created and

validated the clinical vignettes and will be responsible for data analysis and writing the manuscript. The expert committee consists of a cardiologist, a geriatrician, an internist and a general practitioner (medical specialties that often deal with patients needing chronic oral AT prescriptions). The expert committee had to review all clinical vignettes with the prescription support-tool (external validation) to confirm their agreement with clinical practice and their readability and to estimate the time needed to complete 3 clinical vignettes.

Development of clinical vignettes

Two physicians (1 cardiologist and 1 internist-geriatrician) created 30 clinical vignettes covering most outpatient clinical situations for which the long-term use of ATs (single, dual or triple therapy) is recommended or not. An example of a clinical vignette is presented in **Appendix 1.**

Prescription support tool

This tool is derived from a systematic review of guidelines (N = 63) dealing with the use of oral ATs for NV-AF, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery disease and venous thromboembolism. These pathologies were selected because most prescriptions of ATs are related to neuro-cardiovascular diseases and because we would provide a synthesis relevant for clinicians in charge of the follow-up of patients with oral AT combinations, including patients with more than one indication for AT. Indication, type of drugs combined, dosage and duration of prescription are synthesized in this easy-to-use tool, which fits on one double-sided page and can be stored in a physician's pocket. Our tool also specifies the type of ATs that should never be combined (combinations of oral anticoagulant (OAC), combinations of P2Y12 inhibitors or the combination of one OAC with one potent P2Y12 inhibitor, namely ticagrelor or prasugrel), the clinical situations in which oral AT combinations are never indicated and the contraindications of ATs. The full description of this tool is under review elsewhere.

Study setting and eligibility criteria

This study will be conducted among French practicing physicians who are involved in outpatient settings, including general practitioners and cardiologists. Physicians with an exclusive hospital practice will not be considered. Physicians will be identified and contacted for participation directly by email via physicians' associations. Each physician willing to participate will complete, after providing their consent to participate, a questionnaire via a web-based survey, including questions on age, sex, medical specialty, and years of medical practice. Physicians will be asked about the approximate proportion of patients with oral AT combinations in their practice (≤ 5%, 6–10%, 11–20% or ≥ 21%), whether they feel comfortable or not with management of oral AT prescriptions (totally, partially, rarely, never) and whether they know where to find the most recent guidelines on oral AT prescriptions.

Intervention

Selected physicians will be randomized to 2 groups by use or not of the prescription support-tool. In the control group, no tool will be provided. In the experimental group, the tool will be provided with an explanatory guide. All selected physicians will receive 3 different clinical vignettes, each corresponding to a specific situation for which the physician will have to indicate the "right prescription" of ATs by answering a multiple-choice question, with the number, type, duration and dosage of AT provided. They will have to state their degree of certainty with the prescription. The total completion time will be approximately 10 minutes and physicians will be able to stop and continue at any time. Physicians from the control group will receive the prescription support-tool once they have completed their answers for the 3 clinical vignettes. To maximize the participation rate, after being selected, physicians will be sent reminders every 20 days.

Outcomes

The primary outcome measure is the rate of the "right prescription of oral ATs" as defined according to the guidelines in terms of number, class, duration and dosage between the two groups.

Secondary outcomes are (1) the primary outcome by physicians' specialty and (2) the difference between the control and intervention groups in the degree of confidence physicians have in their AT prescriptions in line with the guidelines. The prescription support-tool, synthesizing national and international guidelines on chronic management of oral AT prescriptions, will be the reference.

Randomization

Concealment and balance between trial arms will be achieved by using a computer-generated randomization scheme, stratified by whether the physician is a general practitioner or a cardiologist, in blocks of 4. The clinical vignettes assignment will be randomized in blocks of 30. Physicians allocated to receive the prescription support-tool will be asked to comment on the overall usefulness of the tool.

Data collection methods and data management

The dedicated website was designed by an engineer. Data from physicians' answers will be automatically integrated in a database for statistical analysis. The data will be completely anonymous. In particular, neither the physician's name nor email address will be collected. There is no planned follow-up in this trial.

Patient and Public Involvement

Patients and / or the public have not been involved in the development of the research or in the study design because the randomization unit will be the physicians and the unit of analysis the clinical vignette. The main objective of this study is to evaluate a tool for physicians to help them with their prescriptions of ATs.

Sample size and statistical considerations

In considering that 85% of AT prescriptions is appropriate[5] in the control group and hoping to demonstrate an increase in this proportion up to 90% with the support-tool as well as that each physician will complete 3 clinical vignettes, we will need to include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per group. To obtain a multiple of 10 for the randomization (because each physician will complete 3 vignettes), we hope to include at least 230 physicians per group. If more physicians are willing to participate, all collected data will be considered. A generalized mixed model with a clinical-vignette effect and a physician-effect nested in the arm of the study will be used. All analyses will involve use of R v3.4.0 (www.cran.r-project.org).

ETHICS AND DISSEMINATION

Results of this study will be disseminated in a paper submitted to a peer-reviewed journal and presentations at relevant conferences. If the use of the prescription support-tool is associated with an increased rate of appropriate prescribing of oral AT combinations, we will further consider wide dissemination of the support-tool among physicians and evaluate the impact of this diffusion on patients' clinical outcomes (bleeding events, ischemic events, death).

ACKNOWLEDGMENTS

Authors' contributions: LZ, DBZ, AD and FT designed the study. LZ and MH designed the clinical vignettes and all authors reviewed and validated them. LZ drafted and prepared the manuscript for publication. All authors re-read and corrected the manuscript. All authors approved the final manuscript.

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Competing interests: None.

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Ethics approval: The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) has reviewed and approved our research project on 06/12/2018: number 18-492.

Trial registration: submitted to ClinicalTrials.gov (Protocol version 06/21/2018).

The study start date is summer 2018.

REFERENCES

1. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet. 2015;386(9990):281–91. doi:10.1016/S0140-6736(15)60243-4.

2. Patel NS, Patel TK, Patel PB, Naik VN, Tripathi CB. Hospitalizations due to preventable adverse reactions—a systematic review. Eur J Clin Pharmacol. 2017;73(4):385–98. doi:10.1007/s00228-016-2170-6.

3. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. Brit J Clin Pharmaco. 2008;65(4):573–9. doi:10.1111/j.1365-2125.2007.03064.x.

4. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170(16):1433–41. doi:10.1001/archinternmed.2010.271.

5. Hamilton K, Davis C, Falk J, Singer A, Bugden S. Assessing prescribing of NSAIDs, antiplatelets, and anticoagulants in Canadian family medicine using chart review. Int J Clin Pharm. 2016;38(5):1094–1102. doi:10.1007/s11096-016-0335-0.

6. Engel J, van der Wulp I, Poldervaart JM, Reitsma JB, de Bruijne MC, Wagner C. Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction: protocol of a clinical vignette study. *BMJ Open*. 2015;5(4):e006441.

7. Bachmann LM, Mühleisen A, Bock A, Riet ter G, Held U, Kessels AG. Vignette studies of medical choice and judgement to study caregivers' medical decision behaviour: systematic review. *BMC Med Res Methodol*. 2008;8:50.

8. Peabody JW, Luck J, Glassman P, Dresselhaus TR, Lee M. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. *JAMA*. 2000;283(13):1715-1722.

9. Peabody JW, Luck J, Glassman P, et al. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med*. 2004;141(10):771-780.

Appendix 1: Example of a clinical vignette

At your medical consultation, you meet Mr R, 86 years old (weight: 81 kg, body mass index: 24 kg/m^2). Mr R is a widower, a smoker (10 cigarettes a day, 50 pack-years) and is autonomous in all daily activities. He has no personal medical history. His last biological test did not find any abnormalities (serum creatinine value: 77 µM/L, creatinine clearance using the Cockcroft formula: 70 ml/min).

He comes to see you in consultation because for more than 1 week, he has had palpitations with exercise. You perform electrocardiogram (ECG) in your office and you diagnose non-valvular atrial fibrillation. The biological assessment is without particularity (in particular blood ionography and thyroid-stimulating hormone). Cardiac ultrasonography revealed a dilated left atrium with no valve abnormality.

1) How many antithrombotic treatments will you prescribe during this consultation?

- 0
- 1
- 2
- 3

2) If you answered 0 to question 1, go to question 5. If not, which molecule(s) of antithrombotic(s) will you prescribe during this consultation?

- Warfarin
- Rivaroxaban
- Apixaban
- Aspirin
- Clopidogrel

3) Which dosage will you prescribe this(these) molecule(s)? (For each molecule checked on the previous question, it will appear:)

- Warfarin:
  - INR (International Normalized Ratio): 2-3
  - INR (International Normalized Ratio): 2.5-3.5
- Rivaroxaban
  - 15 mg per day
  - 20 mg per day
- Apixaban
  - 2.5 mg twice a day
  - 5 mg twice a day
- Aspirin
  - 75-100 mg per day
  - 300 mg per day
- Clopidogrel
  - 75 mg per day
  - 300 mg per day

4) How long does the antithrombotic treatment prescribed in the previous question need to be continued?

- 1 month
- 6 months
- 12 months
- For life

5) On a scale of 0 to 10, what is your degree of confidence in the adequacy of your prescription in relation to the guidelines?

For the experimental group, after completion of the 3 clinical vignettes:

Regarding the prescription support tool, please note the following items from 0 (strongly disagree) to 10 (strongly agree):

- The prescription support-tool helped me answer to the clinical vignettes:../10
- The prescription support-tool has modified the answers that I spontaneously made to clinical vignettes:../10
- The prescription support-tool is clear:../10
- The prescription support-tool is operational:../10
- The prescription support-tool is useful for practice:../10
- I would be ready to use this prescription support-tool:../10
- I would recommend the use of this prescription support-tool:../10

Notes on the tool: What are the points of the prescription support-tool that could be improved: useless information, missing information, presentation, etc:

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → **line 223, page 10**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → **line 223, page 10**
Funding	4	Sources and types of financial, material, and other support → **line 216, page 10**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → **Title page and lines 212- 215 page 10**
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → **Lines 74 – 94, page 4**
	6b	Explanation for choice of comparators

Objectives	7	Specific objectives or hypotheses → **Lines 96 – 108, page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) → **Lines 109 - 110, page 5**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → **Lines 114 - 115 page 5 and Lines 147 – 148 page 7**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → **Lines 147 – 149 page 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → **Lines 158 – 167, page 7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) → **Lines 167 – 168, page 7**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → **Lines 170 – 177, page 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → **Lines 170 – 177, page 7 + Line 188 page 8 + Line 224 page 10**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **→ Lines 195 – 200, page 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **→ Lines 167 – 168 page 7**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Lines 179 – 183 page 8**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Lines 179 – 183 page 8**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Lines 179 – 183 page 8**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **→ Lines 185 – 188 page 8**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol → **Lines 185 – 188 page 8**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → **Lines 201 – 203, page 9**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → **Lines 206 – 210 page 9**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → **Lines 186 – 187, page 8**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → **Line 213, page 9**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → **Lines 206 – 207, page 9**
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial

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ABSTRACT

Introduction: Improving the appropriateness of prescriptions of oral antithrombotic (AT) drugs, especially AT combinations, is crucial because these drugs are implicated in bleeding events. We developed a prescription support-tool synthesizing guidelines on chronic management of oral AT combinations. Our main objective is to assess the impact of this tool on improving the prescription of oral AT combinations to comply with guidelines.

Methods and analysis: A randomized controlled trial will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians will be invited to participate to an online survey by email via physician associations, social networks or word of mouth. They will be randomized to two arms: the experimental arm (access to the prescription support-tool) or the control arm (no prescription support-tool). Then, all participants will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each vignette (oral AT or not, number of ATs, type, duration and dosage of each AT). A computer-generated randomization scheme implemented in the online survey will be used to allocate physicians to the experimental or control arm, then stratified by medical specialty. The primary outcome will be AT prescriptions that comply with the guidelines. To demonstrate a 5% increase on prescriptions that comply with guidelines, we will need to include a minimum of 230 physicians per arm. A generalized mixed model with a clinical-vignette effect and a physician-effect nested in the arm of the study will be used.

Ethics and dissemination: The *Institutional Review Board* of Inserm (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool improves the prescription of oral AT combinations to comply with guidelines, we will create an interactive web tool and will assess its impact in terms of clinical outcomes in real-life.

(ClinicalTrials.gov ID: NCT03630874)

Article summary: strengths and limitations of this study

- Strengths:
  - This is a national, multicenter, randomized controlled study to evaluate the impact of a new and innovative prescription support-tool for oral antithrombotic combination prescriptions.
  - A scientific committee and an expert committee have developed and validated 30 clinical vignettes that we will use to evaluate the prescription support-tool.
- Limitations:
  - Selected physicians may not be representative of general practitioners or cardiologists because they are volunteers.
  - Non-access to the prescription support-tool in the control arm cannot be completely guaranteed (contamination bias).
  - The study will be undertaken in France, which could limit generalizability.

INTRODUCTION

Antithrombotic (AT) drugs, which include antiplatelet (AP) and anticoagulant (AC) therapies, are used to prevent and treat many cardiovascular disorders.[1] With the increase in prevalence of cardiovascular diseases and medical progress, these treatments are increasingly being prescribed all around the world.[1] Furthermore, ATs are the most frequent drug class implicated in serious and fatal adverse drug events (ADEs), particularly bleeding events,[2,3] among which 70% could be preventable.[4]

AT combinations (dual or triple AT therapy) greatly increase this risk. For example, Hansen et al. reported a 3.1-fold higher risk of fatal and non-fatal bleeding with dual warfarin and clopidogrel therapy and a 3.7-fold higher risk with triple therapy (warfarin, aspirin and clopidogrel) than warfarin monotherapy in patients with non-valvular atrial fibrillation (NV-AF).[5] So far, no study has evaluated the rate of prescriptions of AT combinations not complying with guidelines for adults, taking into account the drugs prescribed but also the dosage and duration of the prescription. Although tools assessing inappropriate prescribing such as the Beers or STOPP/START criteria[6,7] have a section dedicated to ATs, they mention only a few conditions for prescribing AT combinations and are relevant to older people only. Only one Canadian cohort study was specifically designed to assess the appropriateness of AT combinations in adults.[8] It concluded that approximately 15% of patients with AT combinations had inappropriate dual or triple oral AT therapy. However, the appropriateness of the prescribing was limited to the type of drugs combined and did not cover duration and dosage.

To assess the appropriateness of prescribing AT combinations (considering number of drugs, type of drugs, dosage and duration at the same time) in a French cohort of adults, we performed a systematic review of international guidelines (2012-2017) to define which AT combination is recommended, when and for how long. Guidelines dealing with oral AT

combinations were numerous (n=63) and none encompassed all the clinical situations requiring oral AT combinations. This review highlighted the difficulty for a physician to quickly find the most up-to-date recommendation and the one most relevant to the patient's clinical situation. These findings agreed with clinical experience and led us to synthesize all the recommendations into a prescription support-tool (L Zerah et al, A comprehensive prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines) to help physicians prescribe oral AT combinations.

Our hypothesis is that this prescription support-tool would improve the prescription of oral AT prescriptions to comply with guidelines. Our primary objective is to assess the impact of this tool on improving the prescription of oral AT combinations to comply with guidelines (in terms of number of drugs, drug class, duration and dosage at the same time.

METHODS AND ANALYSIS

Study design, study setting and eligibility criteria

A web-based, open randomized controlled trial involving clinical vignettes will be performed in France via an online survey. This study will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive hospital practice will not be eligible.

Physicians will be identified and contacted to participate in the online survey by email via physician associations, social networks or word of mouth. The survey will gather information on physicians' characteristics, including age, sex, medical specialty, place of exercise, years of medical practice, approximate proportion of patients prescribed oral AT combinations in their practice, whether physicians feel comfortable or not with management of oral AT prescriptions, and whether physicians know where to find the most recent guidelines on oral

AT prescriptions. Then, physicians will be randomized to 2 arms: the experimental arm, having access to the prescription support-tool, and the control arm, with no prescription support-tool. For physicians in the experimental arm, the prescription support-tool will be provided with an explanatory guide, both downloaded (or just viewed) online in pdf format. Then, participants from both arms will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each vignette (AT or not, number of ATs, type, duration and dosage of each AT) by answering 5 multiple-choice questions (each question on a separate web page). Physicians in the experimental arm will answer each question with the help of the tool, downloadable (or viewable on each page). Physicians in the control arm will be asked to answer according to their actual clinical practice as closely as possible. Once the answer is given, physicians cannot go back or change their answer. Physicians must answer the questions consecutively; however, they will be allowed to stop and continue at any time (on the same computer). Physicians from the control arm will be able to download the prescription support-tool once they have completed their answers for the 3 clinical vignettes.

The scientific and expert committee have created and validated 30 clinical vignettes. To ensure that each clinical vignette will be read the same number of times in both arms, we created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized, all clinical vignettes will be read once. The randomization unit will be the physician and the unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle ground to ensure the feasibility of the study considering both participants' availability (acceptable time to complete the clinical vignettes) and statistical need (number of vignettes needed). To maximize the participation rate, physicians will be sent reminders every 20 days.

Outcomes

The primary outcome is prescription of AT combinations that comply with guidelines in terms of number of drugs, drug class, duration and dosage at the same time. An expert committee will determine the correct answer, based on the prescription support-tool. Secondary outcomes are (1) prescription of AT combinations that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately; (2) prescription of AT combinations that comply with guidelines by medical specialty of physicians responding; (3) the degree of confidence of physicians have that their prescription of AT combinations complies with guidelines**;** 4) for physicians allocated to receive the prescription support-tool only, the overall usefulness of the tool.

Intervention

We developed, from a systematic review of international guidelines published between 2012 and 2017 (n=63, bibliography of the guidelines is in **Appendix 1 for reviewers only**), a prescription support-tool (L Zerah et al, A comprehensive prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines) to help physicians prescribe oral AT combinations for complying with guidelines. This prescription support-tool synthesizes, on a double-sided page, selected international guidelines on chronic management (at least 1 month) of oral AT combinations (indication, drugs, dosages and duration) in adults, without considering in-hospital management and bridging therapy. We excluded particular clinical situations that require inevitably specialist medical advice: active cancer, autoimmune diseases, haemophilia, HIV, paediatrics and pregnancy. The pathologies non-valvular atrial fibrillation, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery disease and venous thromboembolism are included in this tool because they are the main causes leading to the prescription of ATs (single, dual or triple therapy) in adults.[1] Our tool also specifies the

type of oral ATs that should never be combined (combinations of oral anticoagulants [OACs], combinations of P2Y12 inhibitors or combining one OAC with one potent P2Y12 inhibitor, namely ticagrelor or prasugrel), the clinical situations in which oral AT combinations are never indicated and the contraindications of ATs. This prescription support-tool aims to give physicians quick access to the recommendation that fits most of their patient's clinical situation. The prescription support-tool is accompanied by an explanatory guide (how to read and use the tool, with examples). The tool and guide are under currently under review (L Zerah et al, A comprehensive prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines) and are provided in **Appendixes 2 and 3 for reviewers only.**

Clinical vignettes

The clinical vignettes illustrating plausible clinical situations have been developed to reflect clinical practice.[9,10] Such an approach has been found valid in measuring quality of care.[11,12] Each clinical vignette corresponds to a specific situation for which physicians will have to indicate, by answering a multiple-choice question, whether they would prescribe oral ATs, with the number, type, duration and dosage. Each clinical vignette is accompanied by 5 questions, all on separate web pages. An example of a clinical vignette is presented in **Appendix 4.** Two physicians (1 cardiologist and 1 internist-geriatrician) from the scientific committee have created 30 clinical vignettes covering most outpatient clinical situations for which the long-term use of oral AT combinations (single, dual or triple therapy) is recommended or needs to be stopped according to the guidelines.

Randomization

Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated randomization scheme implemented in the online survey (1:1 ratio), then stratified by their medical specialty**.**

Data collection methods and data management

Data from physicians' answers will be automatically integrated in a database for statistical analysis. The data will be completely anonymous. In particular, neither the physician's name nor email address will be collected (there will be no login for participants). There is no planned follow-up in this trial.

Sample size and statistical considerations

Considering that 85% of AT prescriptions comply with guidelines in the control arm,[8] to demonstrate an increase in this proportion up to 90% in the experimental arm, we need to include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per arm. To obtain a multiple of 10 physicians (because each physician will complete 3 of 30 vignettes and to have all clinical vignettes completed the same number of times in each arm), we plan to include at least 230 physicians per arm. However, if more physicians participate, all collected data will be considered. Because each participant intends to complete 3 vignettes, this intra-physician correlation will be taken into account in the analysis by using a generalized mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. All analyses will involve use of R v3.4.0 (www.cran.r-project.org).

Scientific and expert committees

Our study involves a scientific committee and an expert committee. The scientific committee consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2 epidemiologists. The scientific committee designed the study protocol, created and validated the clinical vignettes and will be responsible for data analysis and writing of the manuscript. The expert committee consists of a cardiologist, a geriatrician, an internist and 2 general practitioners (medical specialties that often deal with patients needing chronic oral AT prescriptions). The expert committee had to review all clinical vignettes with the prescription support-tool (external validation) to confirm the agreement of the vignettes with clinical

practice and their readability. The committee estimated the time needed to complete 3 clinical vignettes at 10 minutes.

Patient and Public Involvement

Patients and/or the public have not been involved in the development of the research or in the study design because only physicians are enrolled and they will not care for patients in the context of this trial; they just complete clinical vignettes. The main objective of this study is to evaluate a tool for physicians to help with prescribing AT combinations.

ETHICS AND DISSEMINATION

The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool is associated with improving the prescription of oral AT combinations to comply with guidelines, it will be disseminated to help improve AT combination prescriptions. Moreover, we will create an interactive web tool to improve the ergonomics of the tool and to facilitate the updates. We will assess the impact of this interactive web tool in terms of clinical outcomes in real life. This will be the second step, but we feel that we must first demonstrate that the use of the tool is associated with better prescription appropriateness before launching a trial involving patients with clinical outcomes. Results of this trial will be disseminated in a paper submitted to a peer-reviewed journal and presentations at relevant conferences.

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Authors' contributions: LZ, DBZ, AD and FT designed the study. YDR designed the statistical analysis. LZ and MHM designed the clinical vignettes. PF, AMM, EP, PC and JPC reviewed the clinical vignettes. LZ, DBZ, MHM, AD and FT validated the vignettes. LZ drafted and prepared the manuscript for publication. All authors re-read and corrected the manuscript. All authors approved the final manuscript.

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Ethics approval: The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) reviewed and approved our research project on 06/12/2018 (no. 18-492). The ethics evaluation committee of Inserm reviewed and approved a revised version of the protocol on 10/03/18 (no. 18-492 bis) to allow us to communicate our trial via social networks or word of mouth.

Trial registration: ClinicalTrials.gov ID: NCT03630874.

The study start date is September 2018.

The systematic review and the prescription support tool are currently under review: Zerah L, Bun RS, Guillo S, Collet JP, Bonnet-Zamponi D, Tubach F. A comprehensive prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines

REFERENCES

1. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet. 2015;386(9990):281–91. doi:10.1016/S0140-6736(15)60243-4.
2. Patel NS, Patel TK, Patel PB, Naik VN, Tripathi CB. Hospitalizations due to preventable adverse reactions—a systematic review. Eur J Clin Pharmacol. 2017;73(4):385–98. doi:10.1007/s00228-016-2170-6.
3. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. Brit J Clin Pharmaco. 2008;65(4):573–9. doi:10.1111/j.1365-2125.2007.03064.x.
4. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-19
5. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170(16):1433–41. doi:10.1001/archinternmed.2010.271.
6. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2014;44(2):213-218. doi:10.1093/ageing/afu145.
7. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-2246. doi:10.1111/jgs.13702.
8. Hamilton K, Davis C, Falk J, Singer A, Bugden S. Assessing prescribing of NSAIDs, antiplatelets, and anticoagulants in Canadian family medicine using chart review. Int J Clin Pharm. 2016;38(5):1094–1102. doi:10.1007/s11096-016-
9. Engel J, van der Wulp I, Poldervaart JM, Reitsma JB, de Bruijne MC, Wagner C. Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction: protocol of a clinical vignette study. BMJ Open. 2015;5(4):e006441. doi: 10.1136/bmjopen-2014-006441.
10. Bachmann LM, Mühleisen A, Bock A, Riet ter G, Held U, Kessels AG. Vignette studies of medical choice and judgement to study caregivers' medical decision behaviour: systematic review. BMC Med Res Methodol. 2008;8:50. doi: 10.1186/1471-2288-8-50.
11. Peabody JW, Luck J, Glassman P, Dresselhaus TR, Lee M. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. JAMA. 2000;283(13):1715-1722.
12. Peabody JW, Luck J, Glassman P, et al. Measuring the quality of physician practice by

using clinical vignettes: a prospective validation study. Ann Intern Med. 2004;141(10):771-780.

Appendix 1: Guideline references from our systematic review (FOR REVIEWERS ONLY) [Article under review elsewhere]

Coronary Artery Disease: N = 14	
1.	Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *J Thorac Cardiovasc Surg* 2016;152:1243-1275. doi:10.1016/j.jtcvs.2016.07.044.
2.	Goblirsch G, Bershow S, Cummings K, et al. Stable coronary artery disease. *Institute for Clinical Systems Improvement (ICSI)*. 2013. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.658.3632&rep=rep1&type=pdf
3.	Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003. doi:10.1093/eurheartj/eht296.
4.	National Institute For Health and Care Excellence (NICE). Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease. *NICE Guideline*. 2013. Available from: https://www.nice.org.uk/guidance/cg172
5.	National Clinical Guideline Centre (UK). MI - secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction: partial update of NICE CG48. *NICE Guideline*. 2013. Available from: https://www.nice.org.uk/guidance/cg172/documents/mi-secondary-prevention-update-full-version2
6.	Mancini G, Gosselin G, Chow B, et al. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol* 2014;30:837-849. doi:10.1016/j.cjca.2014.05.013.
7.	JCS Joint Working Group. Guidelines for secondary prevention of myocardial infarction (JCS 2011). *Circ J* 2013;77:231-248. doi:10.1253/circj.CJ-66-0053.
8.	Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315. doi:10.1093/eurheartj/ehv320.
9.	ST-Elevation Myocardial Infarction Guidelines Group, New Zealand Branch of Cardiac Society of Australia and New Zealand. ST-elevation myocardial infarction: New Zealand Management Guidelines, 2013. *N Z Med J* 2013;126:127-164.
10.	Non ST-Elevation Acute Coronary Syndrome Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand. New Zealand 2012 guidelines for the management of non ST-elevation acute coronary syndromes. *N Z Med J* 2012;125:122-147.
11.	Feitosa-Filho GS, Baracioli LM, Barbosa CJDG, et al. SBC Guidelines on unstable angina and non-ST-elevation myocardial infarction. *Arq Bras Cardiol* 2015;105:214-227. doi:10.5935/abc.20150118.
12.	El-Deeb MH, Riyami Al AM, Riyami Al AA, et al. 2012 Oman Heart Association simplified guidelines for the management of patients with unstable angina/non–St-elevation myocardial infarction. *Crit Pathw Cardiol*. 2012;11:139-146. doi:10.1097/HPC.0b013e31825ac653.
13.	Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2017;39:119-177. doi:10.1093/eurheartj/ehx393.
14.	National Heart Association of Malaysia. Management of acute ST segment elevation myocardial infarction (STEMI) 2014 - (3RD Edition). Clinical Practice Guidelines. 2014. Available from: https://www.malaysianheart.org/?p=cpg&a=942.

Atrial Fibrillation: N = 12	
15.	Macle L, Cairns J, Leblanc K, et al. 2016 Focused update of the Canadian cardiovascular society guidelines for the management of atrial fibrillation. *Can J Cardiol* 2016;32:1170-1185. doi:10.1016/j.cjca.2016.07.591.
16.	You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation : Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e531S–e575S. doi:10.1378/chest.11-2304.
17.	Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-2962. doi:10.1093/eurheartj/ehw210.
18.	Chiang C-E, Wu T-J, Ueng K-C, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016;115:893-952. doi:10.1016/j.jfma.2016.10.005.
19.	Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2016;67:e27-e115. doi:10.1016/j.jacc.2015.08.856.
20.	Ministry of Health British Columbia. Atrial Fibrillation – Diagnosis and Management. *BCGuidelinesca*. 2015. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/afib_2015_full.pdf
21.	National Institute For Health and Care Excellence (NICE). Atrial fibrillation: management. *NICE Guideline*. 2014. Available from: https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-pdf-35109805981381
22.	Canadian agency for Drugs and Technologies in Health. New oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation. *Canadian agency for Drugs and Technologies in Health*. 2012. Available from: https://www.cadth.ca/sites/default/files/pdf/tr0002_New-Oral-Anticoagulants_rec_e.pdf
23.	January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2014;64:e1-e76. doi:10.1016/j.jacc.2014.03.022.
24.	El-Deeb MH, Sulaiman KJ, Riyami Al AA, et al. 2014 Oman Heart Association protocol for the management of acute atrial fibrillation. *Crit Pathw Cardiol* 2014;13(3):117-127. doi:10.1097/HPC.0000000000000015.
25.	JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* 2014;78:1997-2021. doi:10.1253/circj.CJ-66-0092.
26.	Ministry of Health British Columbia. Use of Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) in Non-Valvular Atrial Fibrillation. *BCGuidelinesca*. 2015. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/anticoag_2015november_full.pdf
Peripheral Artery Disease: N = 12	
27.	Baker IDI Heart and Diabetes Institute. National evidence-based guideline on secondary prevention of cardiovascular disease in type 2 diabetes. 2015. Available from: http://t2dgr.bakeridi.edu.au
28.	Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2013;34:3035-3087. doi:10.1093/eurheartj/eht108.
29.	Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians

Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2):e637S–e668S. doi:10.1378/chest.11-2306.

30. American Diabetes Association. Cardiovascular Disease and Risk Management. *Diabetes Care*. 2015;38:S49-S57. doi:10.2337/dc15-S011.

31. Aboyans V, Ricco J-B, Bartelink M-LEL, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2017. doi:10.1093/eurheartj/ehx095.

32. Naylor AR, Ricco JB, de Borst GJ, et al. Management of atherosclerotic carotid and vertebral artery disease: 2017, clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;55:3-81. doi:10.1016/j.ejvs.2017.06.021.

33. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. *Cathet Cardiovasc Intervent*. 2013;81:E75-E123. doi:10.1002/ccd.22983.

34. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e669S–e690S. doi:10.1378/chest.11-2307.

35. JBS Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100:ii1-ii67. doi:10.1136/heartjnl-2014-305693.

36. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J am Coll Cardiol* 2017;69:1465-1508. doi:10.1016/j.jacc.2016.11.007.

37. Lawall H, Huppert P, Espinola-Klein C, Zemmrich CS, Ruemenapf G. German guideline on the diagnosis and treatment of peripheral artery disease – a comprehensive update 2016. *Vasa* 2017;46:79-86. doi:10.1024/0301-1526/a000603.

38. Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015;6:2S–41S.e1. doi:10.1016/j.jvs.2014.12.009.

Stroke: N = 7

39. Fuentes B, Gállego J, Gil-Nuñez A, et al. Guidelines for the preventive treatment of ischaemic stroke and TIA (II). Recommendations according to aetiological sub-type. *Neurologia* 2014;29(3):168-183. doi:10.1016/j.nrl.2011.06.003.

40. Intercollegiate Stroke Working Party. National clinical guideline for stroke. *Royal College of physicians*. 2016. Available from: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx

41. Wang Y, Liu M, Pu C. 2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack. *Int J Stroke* 2017;12:302-320. doi:10.1177/1747493017694391.

42. Ministry of Health British Columbia. Stroke and Transient Ischemic Attack – Acute and Long-Term Management. *BCGuidelinesca*. 2015. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/stroketia_2015_full.pdf

43. National Heart Association of Malaysia. Management of ischaemic stroke. *Clinical Practice Guidelines*. 2012. Available from: http://www.neuro.org.my/MSN_GUIDELINE/MSN_GUIDELINE_061112%20CPG%20Management%20of%20Stroke%20(ISBN%20Code)%202.pdf

44. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic

stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e601S–e636S. doi:10.1378/chest.11-2302.

45. Ferro JM, Bousser MG, Canhão P, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. *Eur J Neurol* 2017;24:1203-1213. doi:10.1111/ene.13381.

Valvular Heart Disease: N = 3

46. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739-2791. doi:10.1093/eurheartj/ehx391.

47. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol* 2017;70:252-289. doi:10.1016/j.jacc.2017.03.011.

48. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease : antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e576S–e600S. doi:10.1378/chest.11-2305.

Venous thromboembolism disease: N = 9

49. Tait C, Baglin T, Watson H, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. *Br J Haematol* 2012;159:28-38. doi:10.1111/j.1365-2141.2012.09249.x.

50. National Heart Association of Malaysia. Prevention and treatment of venous thromboembolism. Clinical Practice Guidelines. 2013. Available from : http://www.moh.gov.my/penerbitan/CPG2017/9005.pdf

51. ICSI. Venous thromboembolism diagnosis and treatment. *Institute for Clinical Systems Improvement*. 2012. http://www.seqc.es/download/gpc/29/3089/654287920/2461931/cms/venous_thromboembolism_2012.pdf/

52. National Institute For Health and Care Excellence (NICE). Pulmonary embolism. *NICE Guideline*. 2015. https://cks.nice.org.uk/pulmonary-embolism#!scenario.

53. Liu D, Peterson E, Dooner J, et al. Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline. *CMAJ* 2015;187:1288-1296. doi:10.1503/cmaj.141614/-/DC1.

54. Jacobson BF, Louw S, Mer M, et al. Venous thromboembolism: prophylactic and therapeutic practice guideline. *S Afr Med J* 2013;103:261-7. doi:10.7196/SAMJ.6706.

55. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033-3069. doi:10.1093/eurheartj/ehu283.

56. Baglin T, Bauer K, Douketis J, Büller H, Srivastava A, Johnson G. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost* 2012;10:698-702. doi:10.1111/j.1538-7836.2012.04662.x.

57. Min S-K, Kim YH, Joh JH, et al. Diagnosis and treatment of lower extremity deep vein thrombosis: Korean Practice Guidelines. *Vasc Specialist Int* 2016;32:77-104. doi:10.5758/vsi.2016.32.3.77.

Antithrombotic: N = 6

58. National Institute For Health and Care Excellence (NICE). Antiplatelet treatment. *NICE Guideline*. 2015. https://cks.nice.org.uk/antiplatelet-treatment#!scenario.

59. Scottish Intercollegiate Guidelines Network (SIGN). Antithrombotics: indications and management. A national clinical guideline. *Scottish Intercollegiate Guidelines Network (SIGN)*. 2013. http://www.sign.ac.uk/assets/sign129.pdf

60. Tanguay J-F, Bell AD, Ackman ML, et al. Focused 2012 update of the Canadian Cardiovascular Society

guidelines for the use of antiplatelet therapy. *Can J Cardiol* 2013;29:1334-1345. doi: 10.1016/j.cjca.2013.07.001

61. National Institute For Health and Care Excellence (NICE). Anticoagulation - oral. *NICE Guideline*. 2016. https://cks.nice.org.uk/anticoagulation-oral#!scenario.

62. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease. *Chest* 2016;149:315-352. doi:10.1016/j.chest.2015.11.026.

63. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2017;39:213-260. doi:10.1093/eurheartj/ehx419.

SINGLE — Single Therapy: Antiplatelet (SAPT) or Anticoagulation (SACT)

DUAL APT — Dual Antiplatelet Therapy (DAPT)

DUAL — Dual Therapy (SAPT + SACT)

TRIPLE — Triple Therapy (DAPT + SACT)

THERAPY 1 or THERAPY 2 — Modulation between two therapies depending on patient condition (according to striped colors)

Minimum therapy duration

Maximum therapy duration

Recommended therapy duration

2018 SYNTHESIS OF RECOMMENDATIONS FOR CHRONIC MANAGEMENT OF ANTITHROMBOTIC COMBINATIONS

INDICATIONS, DURATION AND DOSAGE IN ADULTS

Abbreviations

ACS	Acute Coronary Syndrome
Aspi	Aspirin
BMS	Bare-Metal Stent
CABG	Coronary Artery By Pass Graft
CHA2DS2-VASc	**C** Congestive Heart failure (1)
	H Hypertension (1) — **A2** Age ≥ 75 (2)
	D Diabetes Mellitus (1) — **S2** Prior stroke or TIA thromboembolism (2)
	V Vascular disease (1) — **A** Age 65-74 (1)
	Sc Sex category (i.e.: female sex) (1)
Cilo	Cilostazol
Clopi	Clopidogrel
CTLI	Chronic Limb-Threatening Ischemia
DAPT	Dual Antiplatelet Therapy
DCB	Drug-Coated Balloon
DES	Drug-Eluting Stent
DOA	Direct Oral Anticoagulant
DUAL	Dual Therapy: SAPT + SACT
INR	International Normalized Ratio
LEAD	Lower Extremity Artery Disease
LV	Left Ventricular
NSTE-ACS	Non-ST Elevation Acute Coronary Syndrome
NV-AF	Non-valvular atrial fibrillation
OAC	Oral Anticoagulant : VKA or DOA
PCI	Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu	Prasugrel
SAPT	Single Antiplatelet Therapy
SACT	Single Anticoagulation Therapy
SCAD	Stable coronary artery disease
STEMI	ST-Elevation Myocardial Infarction
TAVR	Transcatheter Aortic Valve Replacement
TIA	Transient Ischemic Attack
Tica	Ticagrelor
Triflu	Triflusal
TRIPLE	Triple Therapy: DAPT + SACT
VKA	Vitamin K Antagonist Transcatheter Aortic Valve
VTE	Venous Thromboembolism

TARGET INR FOR MECHANICAL PROSTHESE

Prosthesis thrombogenicity	Patient-related risk factor [a] None	Patient-related risk factor [a] ≥1
Low [b]	2.5	3.0
Medium [c]	3.0	3.5
High [d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction

[a] Mitral or tricuspid valve replacement, previous thromboembolism; atrial fibrillation, mitral stenosis of any degree, LVEF < 35%

[b] Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St-Jude Medical, On-X, Sorin Bicarbon

[c] Other bileaflet valve with insufficient data

[d] Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

IF BLEEDING DURING DAPT, follow these recommendations *(figure 10)*:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt

SPECIFIC CONDITIONS REQUIRING SYSTEMATICALLY AN IN-HOSPITAL SPECIALIST HAVE BEEN EXCLUDED: cancer, auto-immune disease, hemophilia, human immunodeficiency virus (HIV), pediatrics and pregnancy and In-hospital prescriptions (including bridging therapy, perioperative therapy, and treatment of acute phase of cardiovascular event)

Dosage of antithrombotic drugs

Aspirin : 75-100 mg/day
Aspirin/dipyridamole : 25/200 mg twice a day
Cilostazol : 100 mg twice a day
Clopidogrel : 75 mg/day
Prasugrel : 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor : 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal : 600 mg/day
VKA : target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    § NV-AF: 15 mg/day
    § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  § > 80 yo
  § Patients also treated with Verapamil
  § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = \{(140 - Age) \times Weight) / (72 \times S_{Cr})\} \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

Dual or triple anti-thrombotic therapies are NEVER recommended in :

- NV-AF CHA2DS2-VASc score ≥ 2 for male and ≥ 3 for female and/or VTE* (including cerebral venous thrombosis and post-embolic pulmonary hypertension) and/or mechanical heart valve :
  - isolated
  - associated with :
    - ischemic stroke
    - and/or LEAD without recent revascularisation procedure
    - and/or carotid or vertebral stenosis without stent
    - and/or coronary artery disease without recent invasive procedure or acute syndrome
    - and/or bioprosthesis
- Embolic ischemic stroke
- Recurrent stroke despite SAPT
- Mitral stenosis and previous stroke or left atrial thrombus

} Indications for SACT

- Carotid or vertebral stenosis (except with stent) } Indications for SAPT
- Carotid or vertebral dissection } SAPT or SACT: 3-6 month
- Valvular bioprosthesis } 3-6 months of SACT (SAPT for patients with aortic bioprosthesis at high risk of bleeding)

Combinations of anti-thrombotic drugs NEVER recommended :
- 2 OAC (except in switches)
- 2 P2Y12 inhibitors (= Clopidogrel, Ticagrelor, Prasugrel)
- OAC + Ticagrelor or Prasugrel

DOA are contraindicated in patients with a mechanical valve

Date of the procedure or acute medical event — M1 — M3 — M6 — M12 — M = months

STABLE CORONARY ARTERY DISEASE (SCAD)

with PCI (DES, BMS or DCB)
- DAPT: Aspi + Clopi — DAPT **can be extended** to 30 months if no bleeding risk **or shortened** to 1-3 months if high bleeding risk
- DAPT or SINGLE: Aspi (+ Clopi)
- SINGLE: Aspi

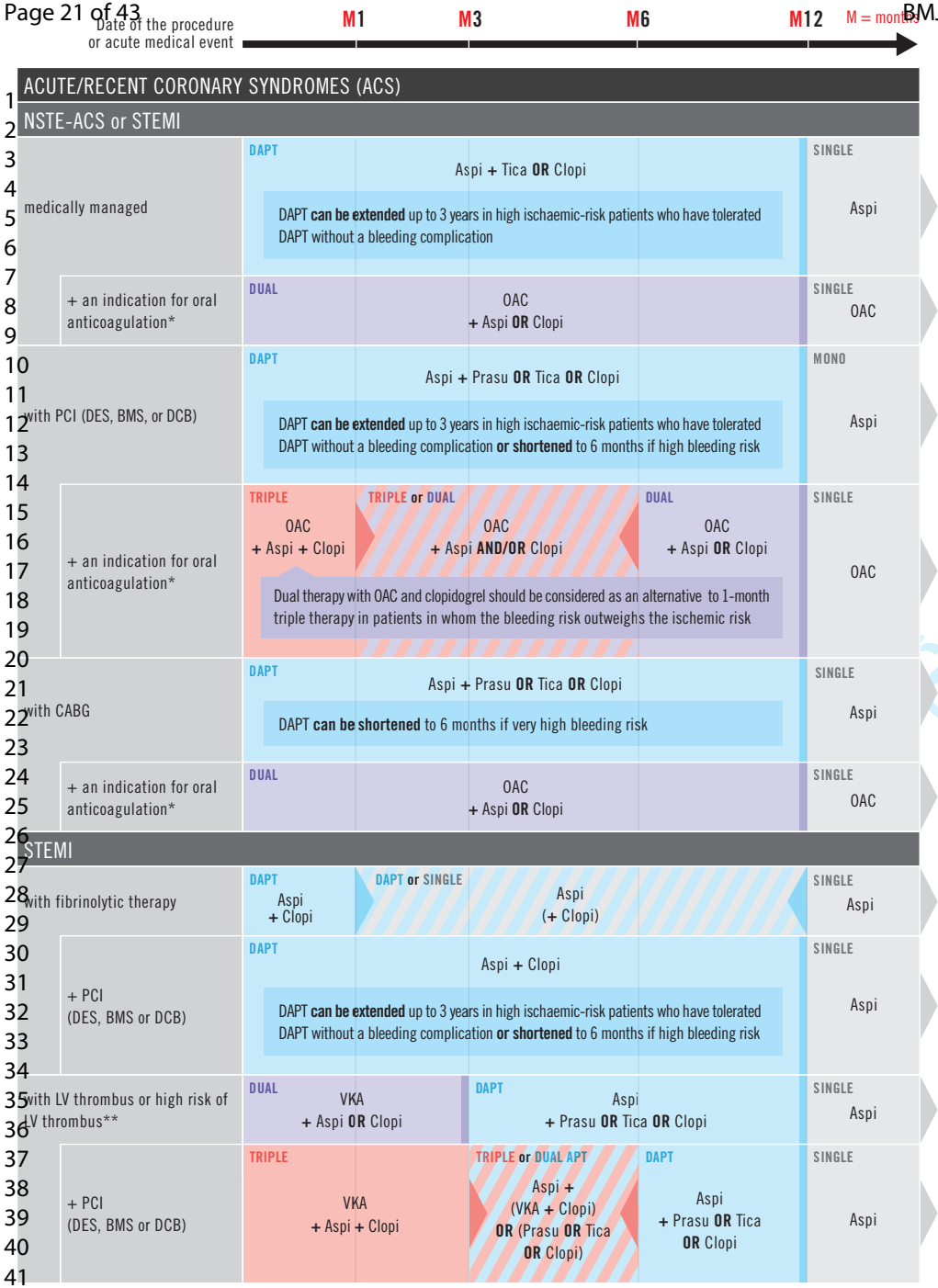
+ an indication for oral anticoagulation**
- TRIPLE: OAC + Aspi + Clopi
- TRIPLE or DUAL: OAC + Aspi **AND/OR** Clopi
- DUAL: OAC + Aspi **OR** Clopi
- SINGLE: OAC

Dual therapy with OAC and clopidogrel should be considered as an alternative to 1-month triple therapy in patients in whom the bleeding risk outweighs the ischemic risk

with CABG
- DAPT: Aspi + Clopi
- SINGLE: Aspi

* Anticoagulant treatment for VTE disease should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk.

** **Indication for OAC :** Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk.



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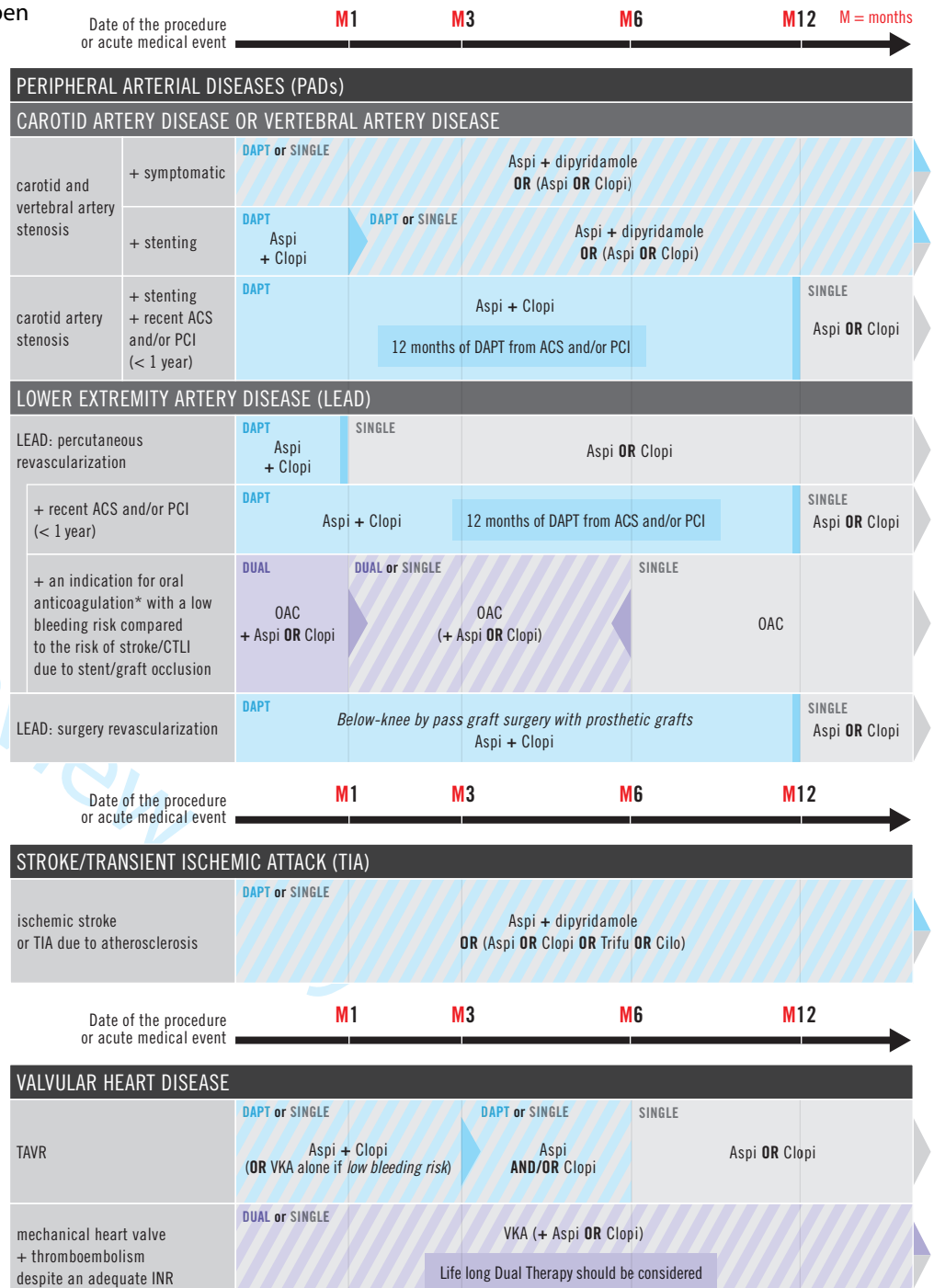
** **High risk for LV thrombus :** Ejection Fraction < 40%, Anteroapical wall motion abnormality.



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How to use the prescription support tool

General presentation of the prescription support tool

Colour codes for single, dual or triple therapy

Codes for duration of treatments

Recommended dosages for each drugs

Abbreviations used in the tool (with CHA2DS2-VASc score reminder)

Target INR for mechanical valves

Link for recommendations if bleeding during DAPT

Specific conditions not included in the tool

Cockcroft and Gault formula

Clinical situations for which a single antithrombotic treatment is recommended (NEVER a combination)

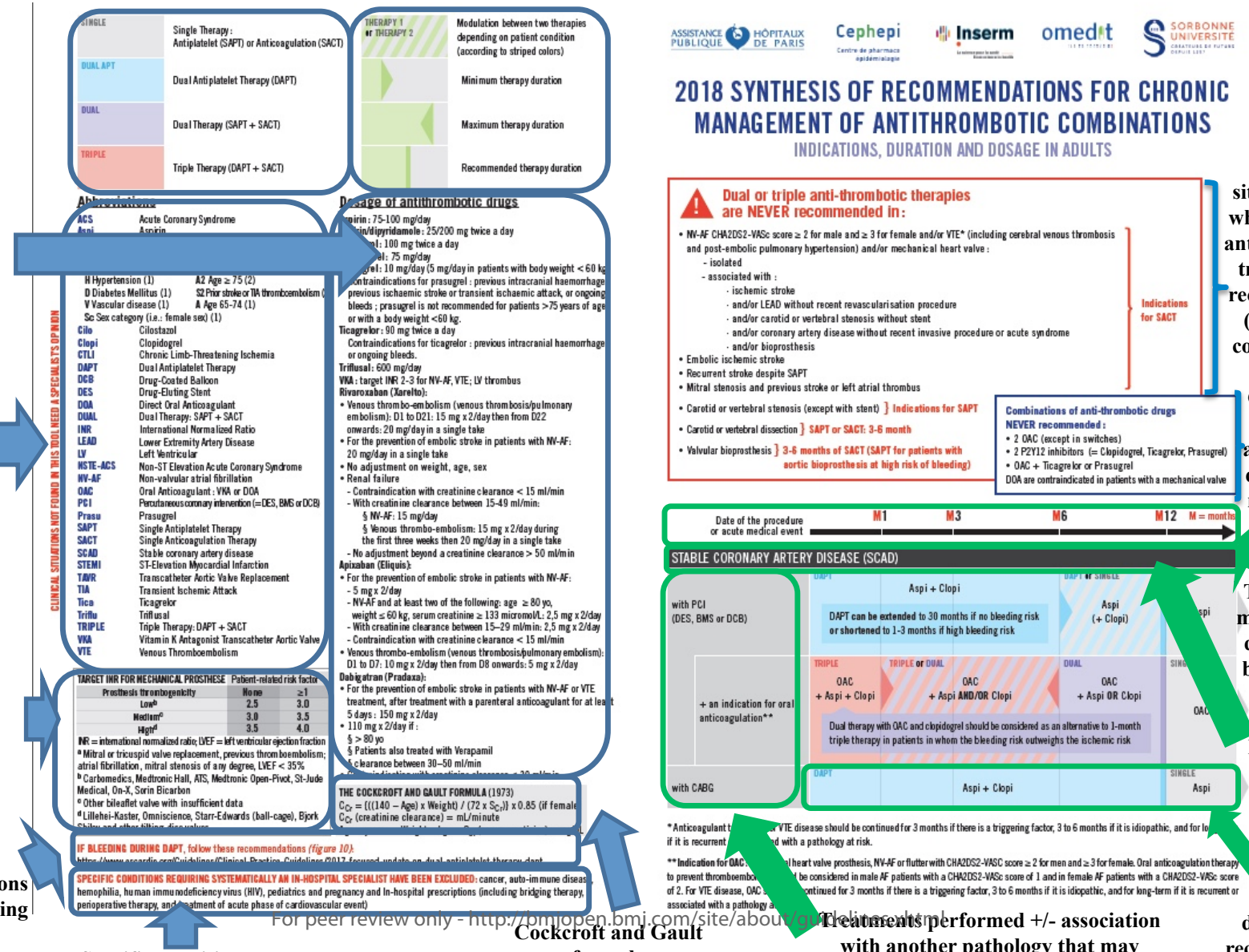
Combinations of antithrombotic drugs NEVER recommended

Timeline (in months) since diagnosis or beginning of treatment

Pathology

Time dependant recommended treatments

Treatments performed +/- association with another pathology that may influence antithrombotic treatment

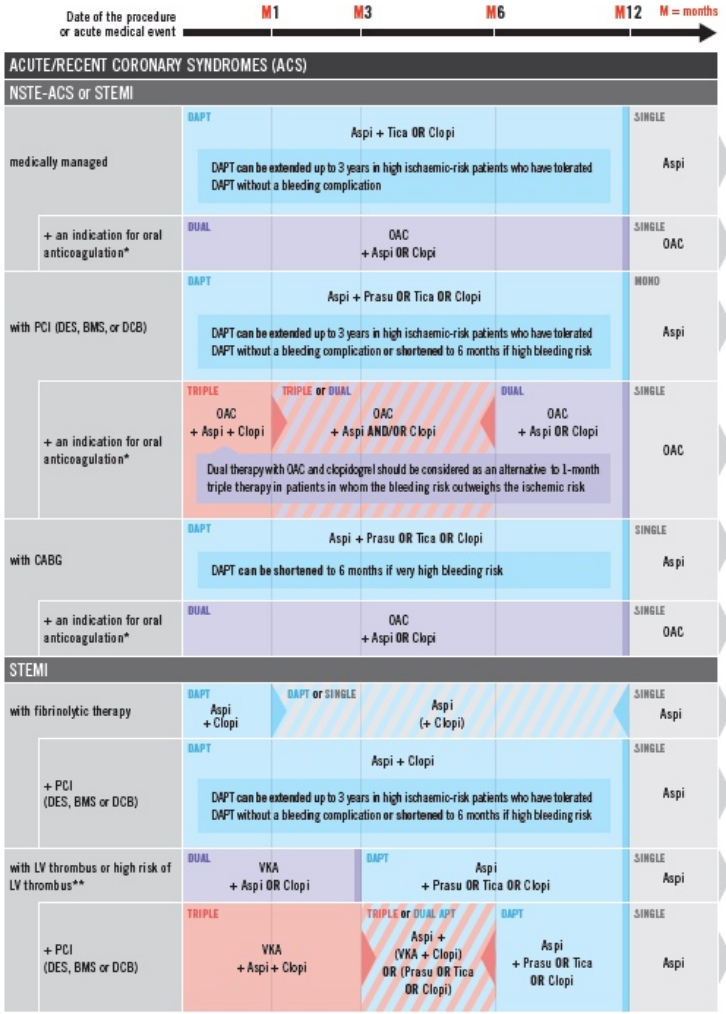


In practice

Example 1: one cardiovascular disease

- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension and Parkinson disease
- He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve replacement (TAVR)
- Which antithrombotic therapy is recommended in this clinical situation?

1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient



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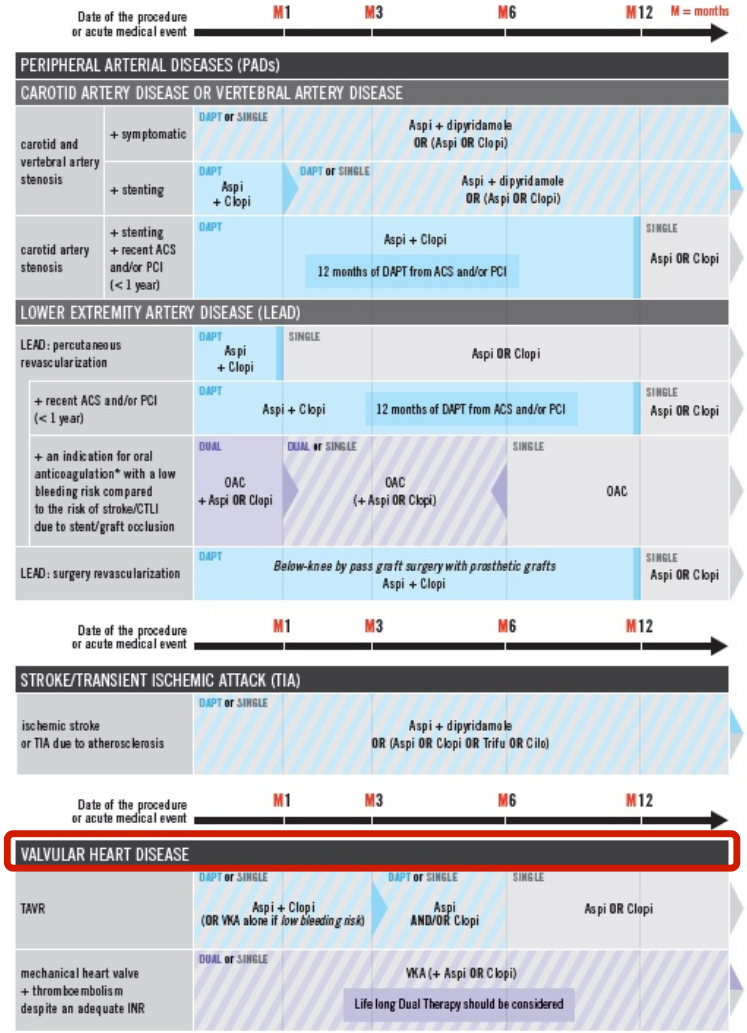
** High risk for LV thrombus : Ejection Fraction < 40%, Anteroapical wall motion abnormality.



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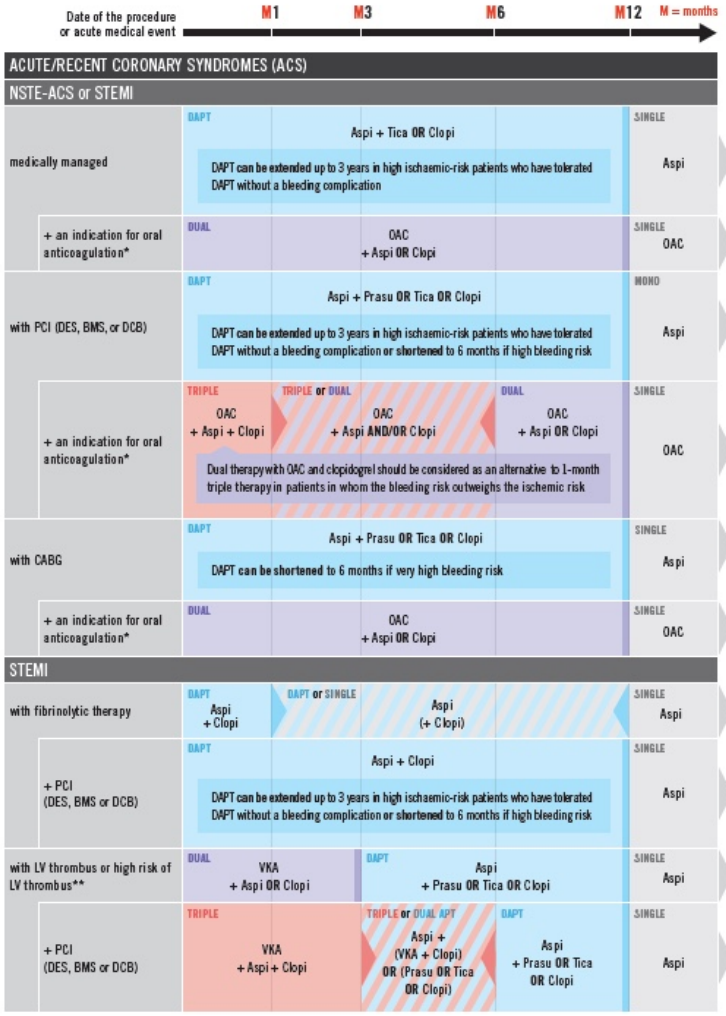
2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



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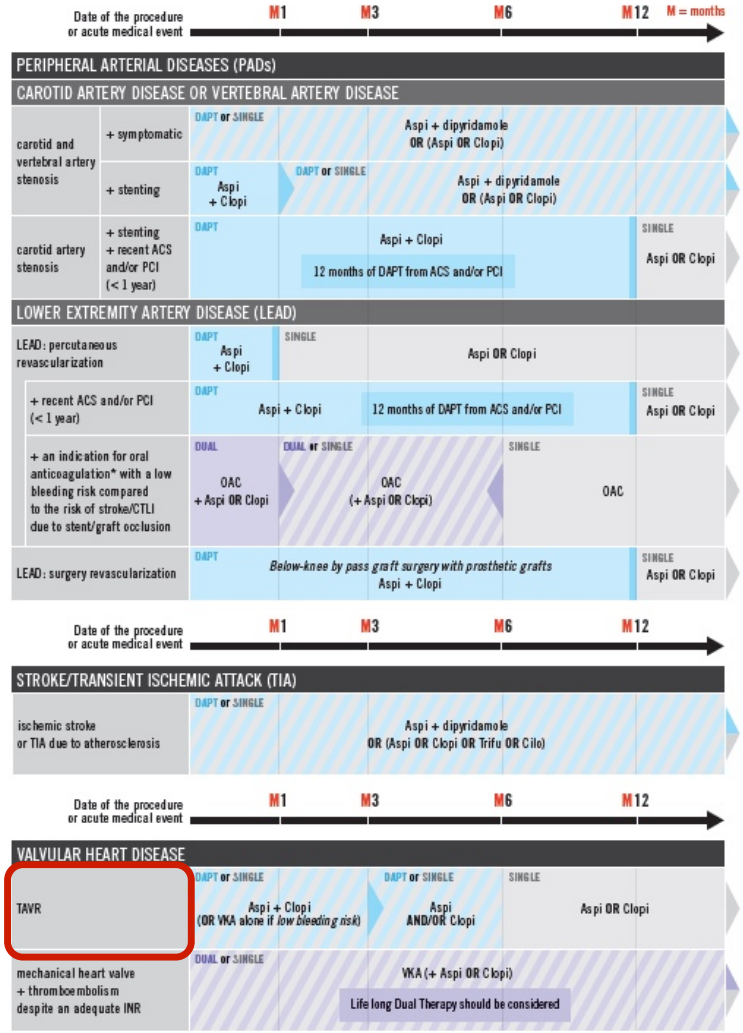

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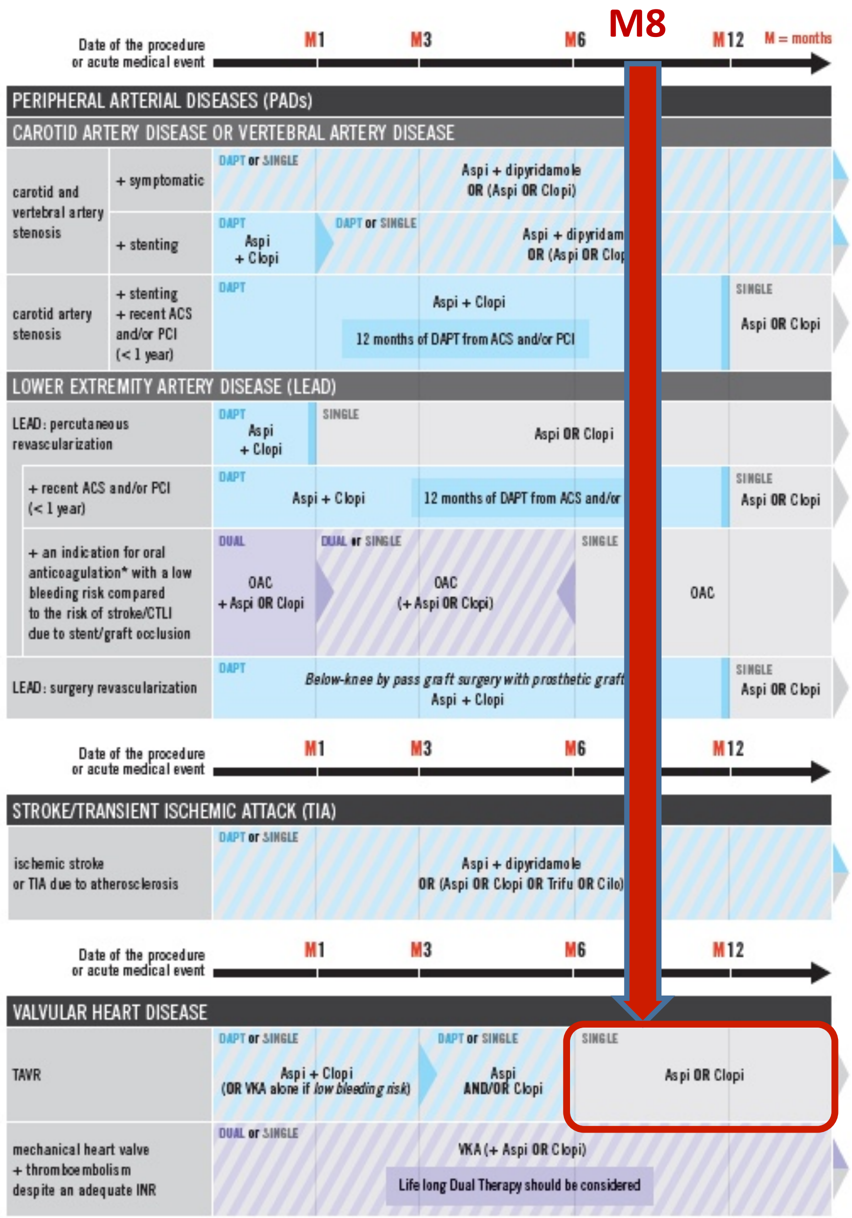

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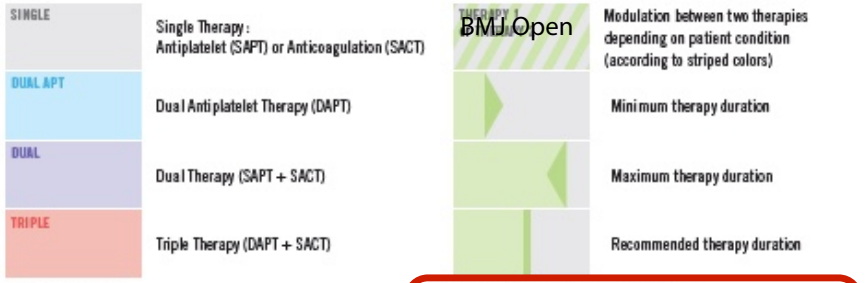
Long-term single antithrombotic therapy is recommended:

1) **Aspirin**
2) **Clopidogrel**

3- In the recommended treatment, find out where your patient is currently (here: 8 months)

4- Check the recommended dosage for the drugs you want to prescribe



Abbreviations

ACS Acute Coronary Syndrome
Aspi Aspirin
BMS Bare-Metal Stent
CABG Coronary Artery By Pass Graft
CHA2DS2-VASc C Congestive Heart failure (1)
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D Diabetes Mellitus (1) S2 Prior stroke or TIA thromboembolism (2)
V Vascular disease (1) A Age 65-74 (1)
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Cilo Cilostazol
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CTLI Chronic Limb-Threatening Ischemia
DAPT Dual Antiplatelet Therapy
DCB Drug-Coated Balloon
DES Drug-Eluting Stent
DOA Direct Oral Anticoagulant
DUAL Dual Therapy: SAPT + SACT
INR International Normalized Ratio
LEAD Lower Extremity Artery Disease
LV Left Ventricular
NSTE-ACS Non-ST Elevation Acute Coronary Syndrome
NV-AF Non-valvular atrial fibrillation
OAC Oral Anticoagulant : VKA or DOA
PCI Percutaneous coronary intervention (=DES, BMS or DCB)
Prasu Prasugrel
SAPT Single Antiplatelet Therapy
SACT Single Anticoagulation Therapy
SCAD Stable coronary artery disease
STEMI ST-Elevation Myocardial Infarction
TAVR Transcatheter Aortic Valve Replacement
TIA Transient Ischemic Attack
Tica Ticagrelor
Triflu Triflusal
TRIPLE Triple Therapy: DAPT + SACT
VKA Vitamin K Antagonist Transcatheter Aortic Valve
VTE Venous Thromboembolism

CLINICAL SITUATIONS NOT FOUND IN THIS TOOL NEED A SPECIALIST'S OPINION

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor [a]	
Prosthesis thrombogenicity	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction
[a] Mitral or tricuspid valve replacement, previous thromboembolism; atrial fibrillation, mitral stenosis of any degree, LVEF < 35%
[b] Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St-Jude Medical, On-X, Sorin Bicarbon
[c] Other bileaflet valve with insufficient data
[d] Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamole: 25/200 mg twice a day
Cilostazol: 100 mg twice a day
Clopidogrel: 75 mg/day
Prasugrel: 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor: 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal: 600 mg/day
VKA: target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    - § NV-AF: 15 mg/day
    - § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  - § > 80 yo
  - § Patients also treated with Verapamil
  - § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = [((140 - Age) \times Weight) / (72 \times S_{Cr})] \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations *(figure 10)*:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-Focused-Update-on-Dual-Antiplatelet-Therapy-dapt

SPECIFIC CONDITIONS REQUIRING SYSTEMATICALLY AN IN-HOSPITAL SPECIALIST HAVE BEEN EXCLUDED: cancer, auto-immune disease, hemophilia, human immunodeficiency virus (HIV), pediatrics and pregnancy and In-hospital prescriptions (including bridging therapy, perioperative therapy, and treatment of acute phase of cardiovascular event)

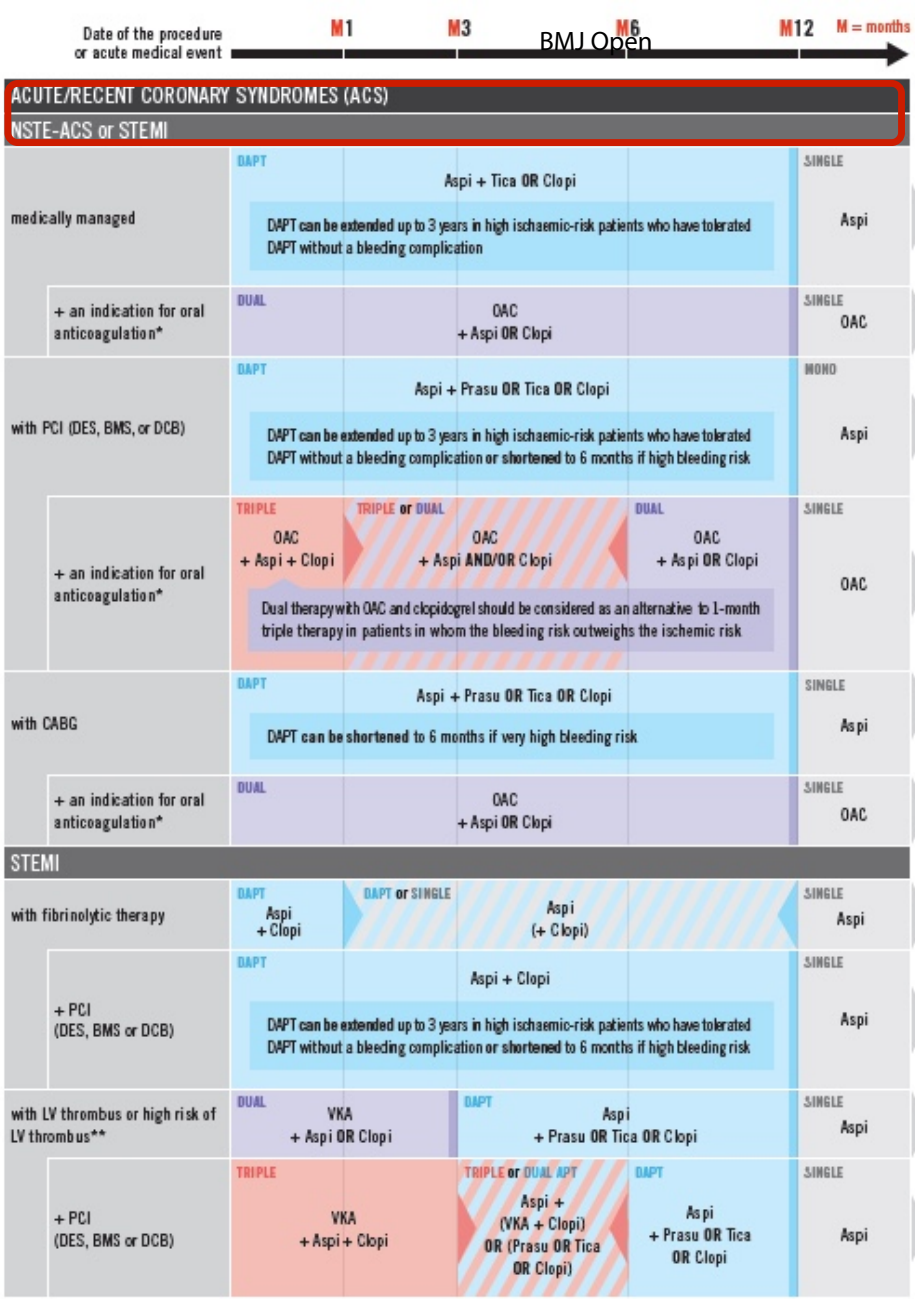
1) Aspirin 75-100 mg/day
2) OR Clopidogrel 75 mg/day

In practice

Example 2: two cardiovascular diseases

- At your medical consultation, you meet Mr V, 55 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension, diabetes, renal failure (creatinine clearance with Cockcroft formula: 30 ml/min) and permanent non-valvular atrial fibrillation
- He had an acute coronary syndrome 5 months ago with a percutaneous coronary intervention (PCI)
- Which antithrombotic therapy is recommended in this clinical situation?

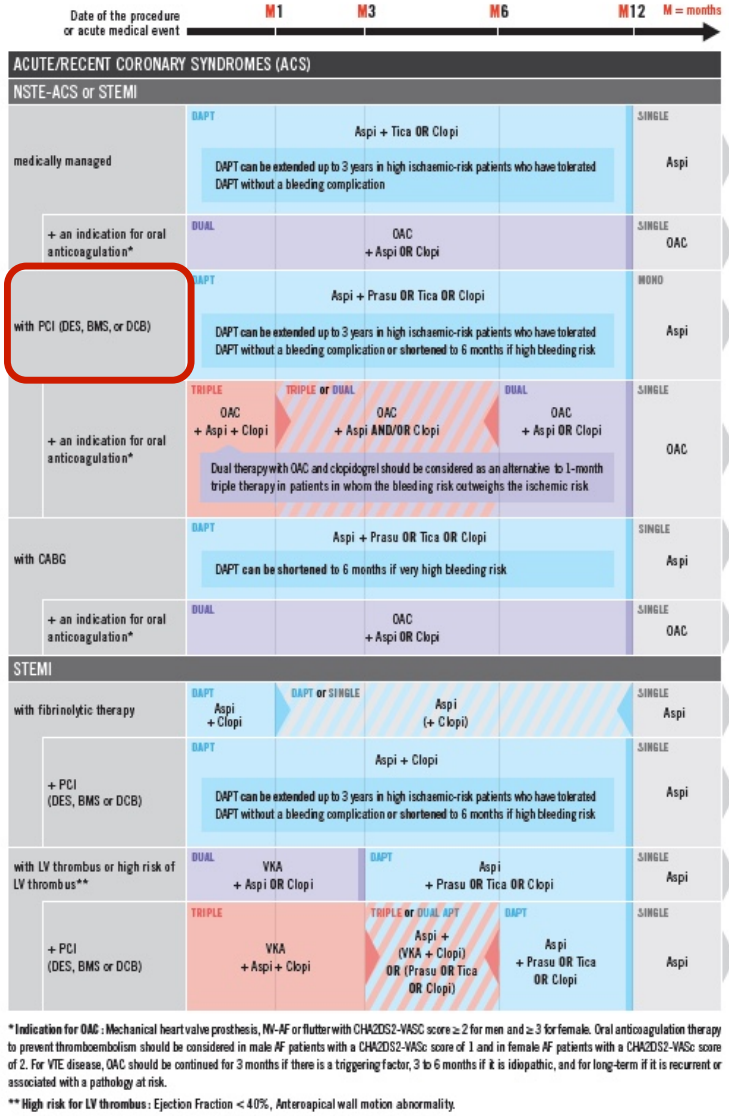
1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient

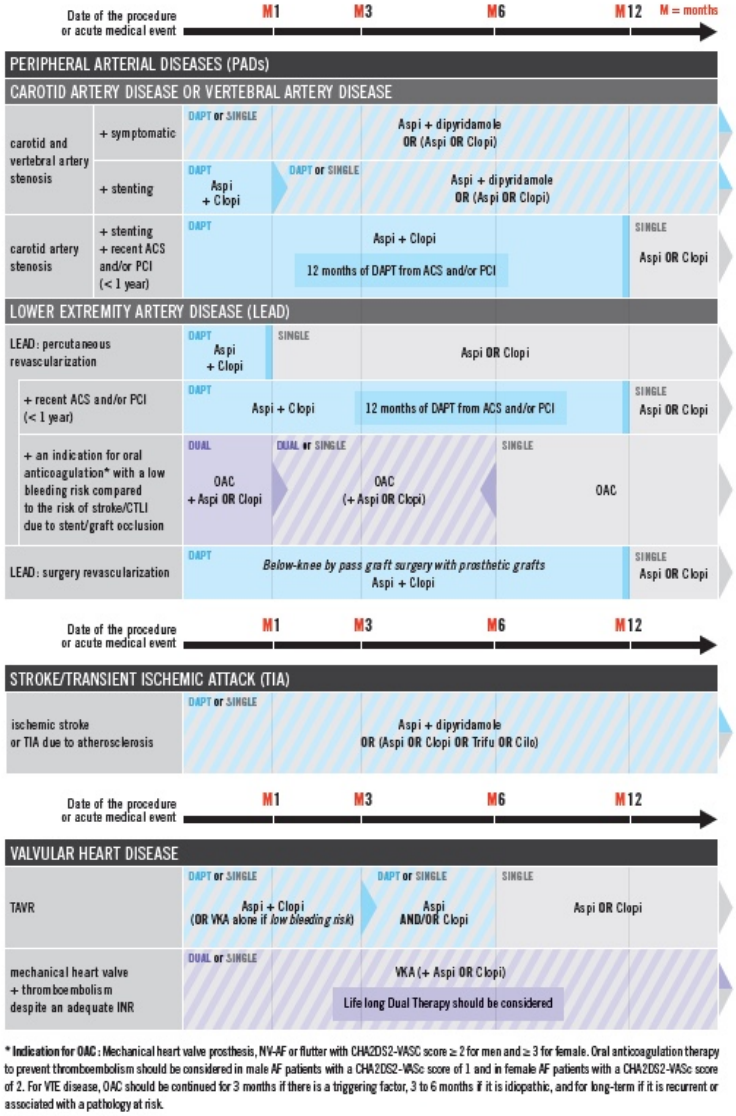


*Indication for OAC : Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASC score of 1, and in female AF patients with a CHA2DS2-VASC score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk.

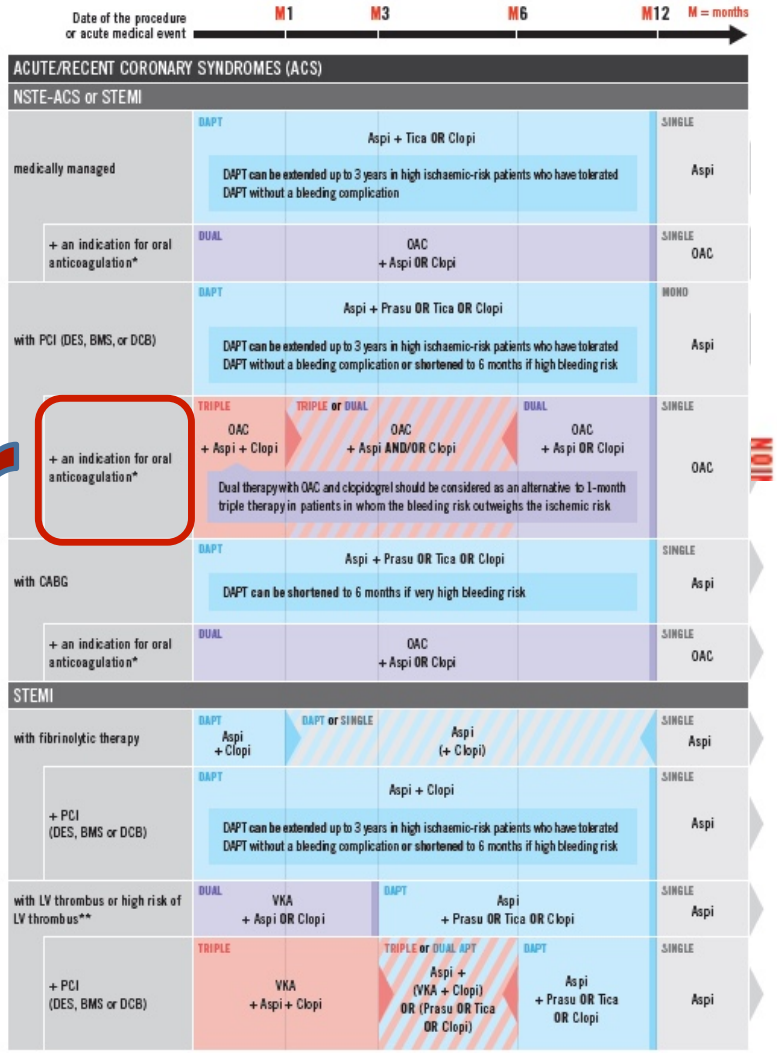
**High risk for LV thrombus : Ejection Fraction < 40%, Anteroapical wall motion abnormality.

2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)





2bis- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



CHA2DS2-VASc score?

Abbreviations

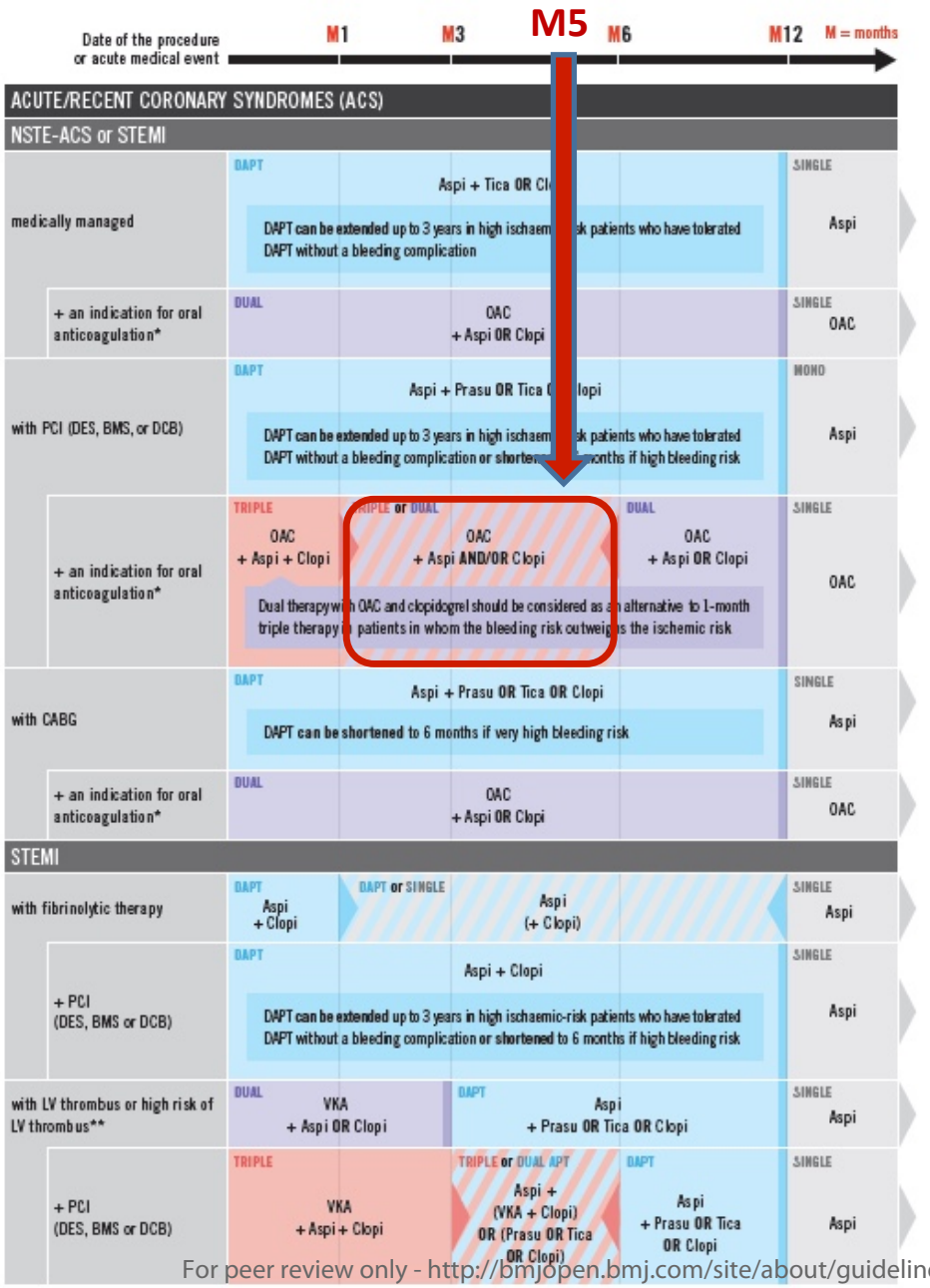
ACS	Acute Coronary Syndrome
Aspi	Aspirin
BMS	Bare-Metal Stent
CABG	Coronary Artery By Pass Graft

CHA2DS2-VASc
C Congestive Heart failure (1)
H Hypertension (1)
A2 Age ≥ 75 (2)
D Diabetes Mellitus (1)
S2 Prior stroke or TIA thromboembolism (2)
V Vascular disease (1)
A Age 65-74 (1)
Sc Sex category (i.e.: female sex) (1)

Hypertension and diabetes = 2 points
→ Indication for oral anticoagulation

*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female.

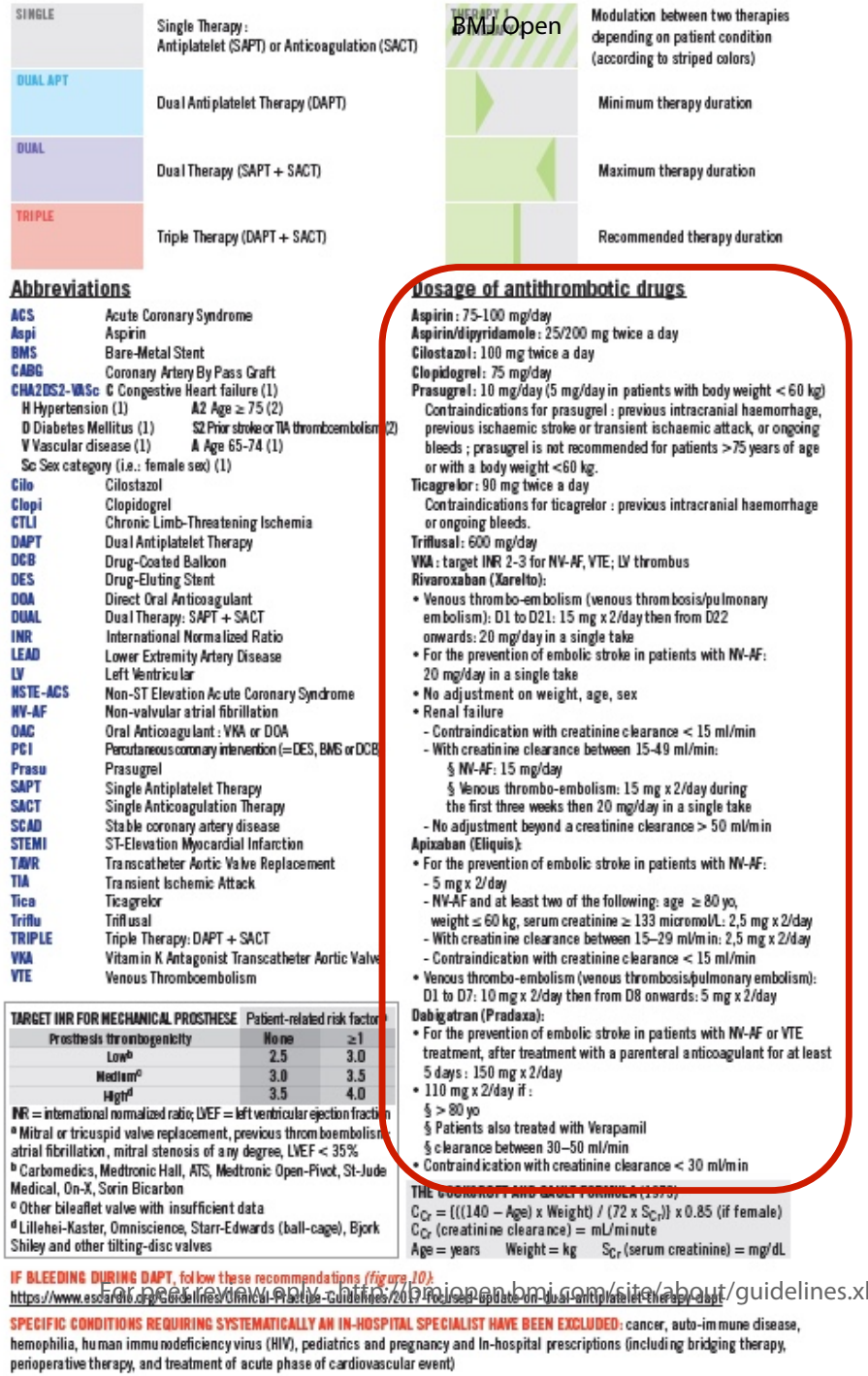
3- In the recommended treatment, find out where your patient is currently (here: 5 months)



Here, two options are possible according to the ischemic and bleeding risk of your patient:

1) Dual therapy: OAC + Aspirin OR Clopidogrel up to 12 months (so for another 7 months)
2) Triple therapy: OAC + Aspirin + Clopidogrel up to 6 months (so for another 1 month) and then a dual therapy with OAC + Aspirin OR Clopidogrel up to 12 months (so for another 6 months)

4- Check the recommended dosage for the drugs you want to prescribe



OAC :

- VKA with a target INR: 2–3
- Rivaroxaban 15 mg/day
- Apixaban 5 mg X 2/day
- Dabigatran is contraindicated

Antiplatelets:

- Aspirin 75-100 mg/day
- Clopidogrel 75 mg/day

Appendix 4: Example of a clinical vignette

At your medical consultation, you meet Mr R, 86 years old (weight: 81 kg, body mass index: 24 kg/m^2). Mr R is a widower, a smoker (10 cigarettes a day, 50 pack-years) and is autonomous in all daily activities. He has no personal medical history and he takes no drug. His last biological test did not find any abnormalities (serum creatinine value: 77 µM/L, creatinine clearance using the Cockcroft-Gault formula: 70 ml/min).
He comes to see you in consultation because for more than 1 week, he has had palpitations with exercise. You perform electrocardiogram (ECG) in your office and you diagnose non-valvular atrial fibrillation. The biological assessment is without particularity (in particular blood ionography and thyroid-stimulating hormone). Cardiac ultrasonography revealed a dilated left atrium with no valve abnormality.

1) How many antithrombotic treatments will you prescribe during this consultation?

- 0
- 1
- 2
- 3

2) If you answered 0 to question 1, go to question 5. If not, which molecule(s) of antithrombotic(s) will you prescribe during this consultation?

- Warfarin
- Rivaroxaban
- Apixaban
- Aspirin
- Clopidogrel

3) Which dosage will you prescribe this(these) molecule(s)? (For each molecule checked on the previous question, it will appear:)

- Warfarin:
  - INR (International Normalized Ratio): 2-3
  - INR (International Normalized Ratio): 2.5-3.5
- Rivaroxaban
  - 15 mg per day
  - 20 mg per day
- Apixaban
  - 2.5 mg twice a day
  - 5 mg twice a day
- Aspirin
  - 75-100 mg per day
  - 300 mg per day
- Clopidogrel
  - 75 mg per day
  - 300 mg per day

4) How long does the antithrombotic treatment prescribed in the previous question need to be continued?

- 1 month
- 6 months
- 12 months
- For life

5) On a scale of 0 to 10, what is your degree of confidence in the adequacy of your prescription in relation to the guidelines?

For the experimental group, after completion of the 3 clinical vignettes:

Regarding the prescription support tool, please note the following items from 0 (strongly disagree) to 10 (strongly agree):

- The prescription support-tool helped me answer to the clinical vignettes:../10
- The prescription support-tool has modified the answers that I spontaneously made to clinical vignettes:../10
- The prescription support-tool is clear:../10
- The prescription support-tool is operational:../10
- The prescription support-tool is useful for practice:../10
- I would be ready to use this prescription support-tool:../10
- I would recommend the use of this prescription support-tool:../10

Notes on the tool: What are the points of the prescription support-tool that could be improved: useless information, missing information, presentation, etc:

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → **Page 2 line 57**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → **line 244 - 248, page 11**
Funding	4	Sources and types of financial, material, and other support → **line 240, page 11**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → **Title page and lines 235 - 239 page 11**
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → **Lines 72 – 101, page 4 - 5**
	6b	Explanation for choice of comparators

Objectives	7	Specific objectives or hypotheses → **Lines 102 - 105, page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → **Lines 109 - 110 page 5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → **Lines 110 - 112 page 5**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → **Lines 113 - 121, page 5 - 6**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) → **Lines 143, page 6**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → **Lines 144 – 153, page 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → **Lines 113 – 143, page 5 - 6**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **→ Lines 196 – 198, page 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **→ Lines 113 - 114 page 5**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Lines 86 - 189 page 8**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Lines 86 - 189 page 8**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Lines 86 - 189 page 8**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **→ Lines 190 – 194 page 8 - 9**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol → **Lines 190 – 194 page 8 - 9**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → **Lines 202 - 205, page 9**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → **Lines 223 - 233 page 10**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → **Lines 192 - 193, page 8 - 9**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → **Line 241, page 11**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → **Lines 232 - 233, page 10**
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial

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Primary Subject Heading:	Pharmacology and therapeutics

Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Public health
Keywords:	prescription support-tool, clinical vignettes, antithrombotic combination

Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial

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ABSTRACT

Introduction: Improving the appropriateness of prescriptions of oral antithrombotic (AT) drugs, especially AT combinations, is crucial because these drugs are implicated in bleeding events. We developed a prescription support-tool synthesizing guidelines on chronic management of oral AT combinations. Our main objective is to assess the impact of this tool on improving the prescription of oral ATs to comply with guidelines.

Methods and analysis: A randomized controlled trial will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians will be invited to participate to an online survey by email via physician associations, social networks or word of mouth. They will be randomized to two arms: the experimental arm (access to the prescription support-tool) or the control arm (no prescription support-tool). Then, all participants will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each vignette (number of ATs, type, duration and dosage of each AT). A computer-generated randomization scheme implemented in the online survey will be used to allocate physicians to the experimental or control arm, then stratified by medical specialty. The primary outcome will be fully appropriate prescription of oral ATs i.e that comply with the guidelines in terms of number of drugs, drug class, duration and dosage. To demonstrate a 5% increase in this proportion, we will need to include a minimum of 230 physicians per arm. A logistic mixed model with a clinical vignette-effect and a physician-effect nested in the arm of the study will be used.

Ethics and dissemination: The *Institutional Review Board* of Inserm (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool improves the prescription of oral ATs, we will create an interactive web tool and will assess its impact in terms of clinical outcomes in real-life.

(ClinicalTrials.gov ID: NCT03630874)

Article summary: strengths and limitations of this study

- Strengths:
  - This is a national, multicenter, randomized controlled study to evaluate the impact of a new and innovative prescription support-tool for chronic management of oral antithrombotic prescriptions (single, dual or triple therapy).
  - A scientific committee and an expert committee have developed and validated 30 clinical vignettes that we will use to evaluate the prescription support-tool.
- Limitations:
  - Selected physicians may not be representative of general practitioners or cardiologists because they are volunteers.
  - Non-access to the prescription support-tool in the control arm cannot be completely guaranteed (contamination bias).
  - The study will be undertaken in France, which could limit generalizability.

INTRODUCTION

Antithrombotic (AT) drugs, which include antiplatelet (AP) and anticoagulant (AC) therapies, are used to prevent and treat many cardiovascular disorders.[1] With the increase in prevalence of cardiovascular diseases and medical progress, these treatments are increasingly being prescribed all around the world.[1] Furthermore, ATs are the most frequent drug class implicated in serious and fatal adverse drug events (ADEs), particularly bleeding events,[2,3] among which 70% could be preventable.[4]

AT combinations (dual or triple AT therapy) greatly increase this risk. For example, Hansen et al. reported a 3.1-fold higher risk of fatal and non-fatal bleeding with dual warfarin and clopidogrel therapy and a 3.7-fold higher risk with triple therapy (warfarin, aspirin and clopidogrel) than warfarin monotherapy in patients with non-valvular atrial fibrillation (NV-AF).[5] So far, no study has evaluated the rate of prescriptions of AT combinations not complying with guidelines for adults, taking into account the drugs prescribed but also the dosage and duration of the prescription. Although tools assessing inappropriate prescribing such as the Beers or STOPP/START criteria[6,7] have a section dedicated to ATs, they mention only a few conditions for prescribing AT combinations and are relevant to older people only. Only one Canadian cohort study was specifically designed to assess the appropriateness of AT combinations in adults.[8] It concluded that approximately 15% of patients with AT combinations had inappropriate dual or triple oral AT therapy. However, the appropriateness of the prescribing was limited to the type of drugs combined and did not cover duration and dosage.

To assess the appropriateness of prescribing AT combinations (considering number of drugs, type of drugs, dosage and duration at the same time) in a French cohort of adults, we performed a systematic review of international guidelines (2012-2018) to define which AT combination is recommended, when and for how long.[9] Guidelines dealing with oral AT

combinations were numerous (n=70) and none encompassed all the clinical situations requiring oral AT combinations. This review highlighted the difficulty for a physician to quickly find the most up-to-date recommendation and the one most relevant to the patient's clinical situation. These findings agreed with clinical experience and led us to synthesize all the recommendations into a prescription support-tool **(Figure 1)**[9] to help physicians prescribe oral AT combinations.

Our hypothesis is that this prescription support-tool would improve the prescription of oral AT prescriptions to comply with guidelines. Our primary objective is to assess the impact of this tool on improving the prescription of oral ATs to comply with guidelines (in terms of number of drugs, drug class, duration and dosage at the same time).

METHODS AND ANALYSIS

Study design, study setting and eligibility criteria

A web-based, open randomized controlled trial involving clinical vignettes will be performed in France via an online survey. This study will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive hospital practice will not be eligible.

Physicians will be identified and contacted to participate in the online survey by email via physician associations, social networks or word of mouth. The survey will gather informations on physicians' characteristics, including age, sex, medical specialty (cardiologist or general practitioner), place of exercise (hospital or ambulatory setting), years of medical practice, approximate proportion of patients prescribed oral AT combinations in their practice (≤ 5%, 6 – 10%, 11-20% or ≥ 21%), whether physicians feel comfortable or not with management of oral AT prescriptions (totally, partially, rarely, never), and whether physicians know where to find the most recent guidelines on oral AT prescriptions. Then, physicians will

be randomized to 2 arms: the experimental arm, having access to the prescription support-tool **(Figure 1),[**9] and the control arm, with no prescription support-tool. For physicians in the experimental arm, the prescription support-tool will be provided with an explanatory guide **(Appendix 1),[**9] both downloaded (or just viewed) online in pdf format. Then, participants from both arms will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each clinical vignette (oral AT or not, number of oral ATs, type, duration and dosage of each oral AT) by answering 4 multiple-choice questions (each question on a separate web page). Question 5 will evaluate the degree of confidence of physicians have that their prescription of ATs complies with guidelines on a scale of 0 to 10. Physicians in the experimental arm will answer each question with the help of the tool, downloadable (or viewable on each page). At the end, we will ask to physicians of the experimental arm to rate, on a scale from 0 and 10, the usefulness of the prescription support-tool, how much they would be willing to use this prescription support-tool in their practice and if they would recommend its use. Physicians in the control arm will be asked to answer according to their actual clinical practice as closely as possible. Once the answer is given, physicians cannot go back or change their answer. Physicians must answer the questions consecutively; however, they will be allowed to stop and continue at any time (on the same computer). Physicians from the control arm will be able to download the prescription support-tool once they have completed their answers for the 3 clinical vignettes.

The scientific and expert committee have created and validated 30 clinical vignettes. To ensure that each clinical vignette will be read the same number of times in both arms, we created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized, all clinical vignettes will be read once. The randomization unit will be the physician and the

unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle ground to ensure the feasibility of the study considering both participants' availability (acceptable time to complete the clinical vignettes) and statistical need (number of clinical vignettes needed). To maximize the participation rate, physicians will be sent reminders every 20 days.

Outcomes

The primary outcome is prescription of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage at the same time, which will be termed fully appropriate prescription. An expert committee will determine the correct answer, based on the prescription support-tool **(Figure 1)**[9]. Secondary outcomes are (1) prescription of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately; (2) prescription of oral ATs that comply with guidelines (fully appropriate prescription, number of drugs, drug class, duration and dosage each assessed separately) by medical specialty of physicians responding (cardiologist or general practitioner); (3) the degree of confidence of physicians have that their prescription of ATs complies with guidelines**;** 4) for physicians allocated to receive the prescription support-tool only, the overall usefulness of the tool.

Intervention

We developed, from a systematic review of international guidelines published between 2012 and 2018 (n=70),[9] a prescription support-tool to help physicians prescribe oral AT combinations for complying with guidelines. This prescription support-tool synthesizes, on a double-sided page, selected international guidelines on chronic management (at least 1 month) of oral AT combinations (indication, drugs, dosages and duration) in adults, without considering in-hospital management, bridging therapy and primary prevention **(Figure 1).**[9]. We excluded particular clinical situations that require inevitably specialist medical advice:

active cancer, autoimmune diseases, haemophilia, HIV, paediatrics and pregnancy. The following pathologies were included in this tool because they are the main causes leading to the prescription of ATs (single, dual or triple therapy) in adults[1]: non-valvular atrial fibrillation, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery disease and venous thromboembolism. Our tool also specifies the type of oral ATs that should never be combined (combinations of oral anticoagulants [OACs], combinations of P2Y12 inhibitors or combining one OAC with one potent P2Y12 inhibitor, namely ticagrelor or prasugrel), the clinical situations in which oral AT combinations are never indicated and the contraindications of ATs. This prescription support-tool aims to give physicians quick access to the recommendation that fits most of their patient's clinical situation. The prescription support-tool is accompanied by an explanatory guide (how to read and use the tool, with examples, **Appendix 1).**[9]

Clinical vignettes

The clinical vignettes illustrating plausible clinical situations have been developed to reflect clinical practice.[10,11] Such an approach has been found valid in measuring quality of care.[12,13] Each clinical vignette corresponds to a specific situation for which physicians will have to indicate, by answering a multiple-choice question, whether they would prescribe oral ATs, with the number, type, duration and dosage. All answers to clinical vignettes' questions can be found in the prescription support-tool. An example of a clinical vignette is presented in **Appendix 2.** Two physicians (1 cardiologist and 1 internist-geriatrician) from the scientific committee have created 30 clinical vignettes covering most outpatient clinical situations (without considering in-hospital management, bridging therapy and primary prevention) for which the long-term use of oral ATs (single, dual or triple therapy) is recommended or needs to be stopped according to the guidelines.

Randomization

Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated randomization scheme implemented in the online survey (1:1 ratio), then stratified by their medical specialty.

Data collection methods and data management

Data from physicians' answers will be automatically integrated in a database for statistical analysis. The data will be completely anonymous. In particular, neither the physician's name nor email address will be collected (there will be no login for participants). There is no planned follow-up in this trial.

Sample size and statistical considerations

Considering that 85% of AT prescriptions fully comply with guidelines in the control arm,[8] to demonstrate an increase in this proportion up to 90% in the experimental arm, we need to include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per arm. To obtain a multiple of 10 physicians (because each physician will complete 3 of 30 clinical vignettes and to have all clinical vignettes completed the same number of times in each arm), we plan to include at least 230 physicians per arm. However, if more physicians participate, all collected data will be considered. For each clinical vignette, we will consider that prescription is fully appropriate (versus inappropriate) if answers to each of the first four questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To compare the percentage of fully appropriate prescriptions between the two randomized arms, taking into account that each participant intends to complete 3 clinical vignettes, we will use a logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. We will use the same method to compare the percentage of prescriptions of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately, between the two randomized arms (secondary analyses). To compare the degree of confidence that physicians have that their prescription of oral AT combinations

complies with guidelines (quantitative variable: scale from 0 and 10), taking into account that each participant intends to complete 3 clinical vignettes, we will use a linear mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. A sub-group analysis for general practitioners and for cardiologist will be done. Finally, to assess the overall usefulness of the tool, we will describe the data of the experimental arm (mean ± SD, median (25–75 interquartile range)). All analyses will involve use of R v3.5.2 (www.cran.r-project.org).

Scientific and expert committees

Our study involves a scientific committee and an expert committee. The scientific committee consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2 epidemiologists. The scientific committee designed the study protocol, created and validated the clinical vignettes and will be responsible for data analysis and writing of the manuscript. The expert committee consists of a cardiologist, a geriatrician, an internist and 2 general practitioners (medical specialties that often deal with patients needing chronic oral AT prescriptions). The expert committee had to review all clinical vignettes with the prescription support-tool (external validation) to confirm the agreement of the clinical vignettes with clinical practice and their readability. The committee estimated the time needed to complete 3 clinical vignettes at 10 minutes.

Patient and Public Involvement

Patients and/or the public have not been involved in the development of the research or in the study design because only physicians are enrolled and they will not care for patients in the context of this trial; they just complete clinical vignettes. The main objective of this study is to evaluate a tool for physicians to help with prescribing AT combinations.

ETHICS AND DISSEMINATION

The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool is associated with improving the prescription of oral ATs to comply with guidelines, it will be disseminated to help improve ATs prescriptions. We will create an interactive web tool to improve the ergonomics of the tool and to facilitate the updates. We will assess the impact of this interactive web tool in terms of clinical outcomes in real life. This will be the second step, but we feel that we must first demonstrate that the use of the prescription support-tool (on paper) is associated with better prescription appropriateness before launching a trial involving patients with clinical outcomes. Results of this trial will be disseminated in a paper submitted to a peer-reviewed journal and presentations at relevant conferences.

Figure 1 legend: 2019 synthesis of recommendations for chronic management of antithrombotic combinations

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Authors' contributions: LZ, DBZ, AD and FT designed the study. YDR designed the statistical analysis. LZ and MHM designed the clinical vignettes. PF, AMM, EP, PC and JPC reviewed the clinical vignettes. LZ, DBZ, MHM, AD and FT validated the clinical vignettes. LZ drafted and prepared the manuscript for publication. All authors re-read and corrected the manuscript. All authors approved the final manuscript.

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Competing interests: None.

Ethics approval: The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) reviewed and approved our research project on 06/12/2018 (no. 18-492). The ethics evaluation committee of Inserm reviewed and approved a revised version of the protocol on 10/03/18 (no. 18-492 bis) to allow us to communicate our trial via social networks or word of mouth.

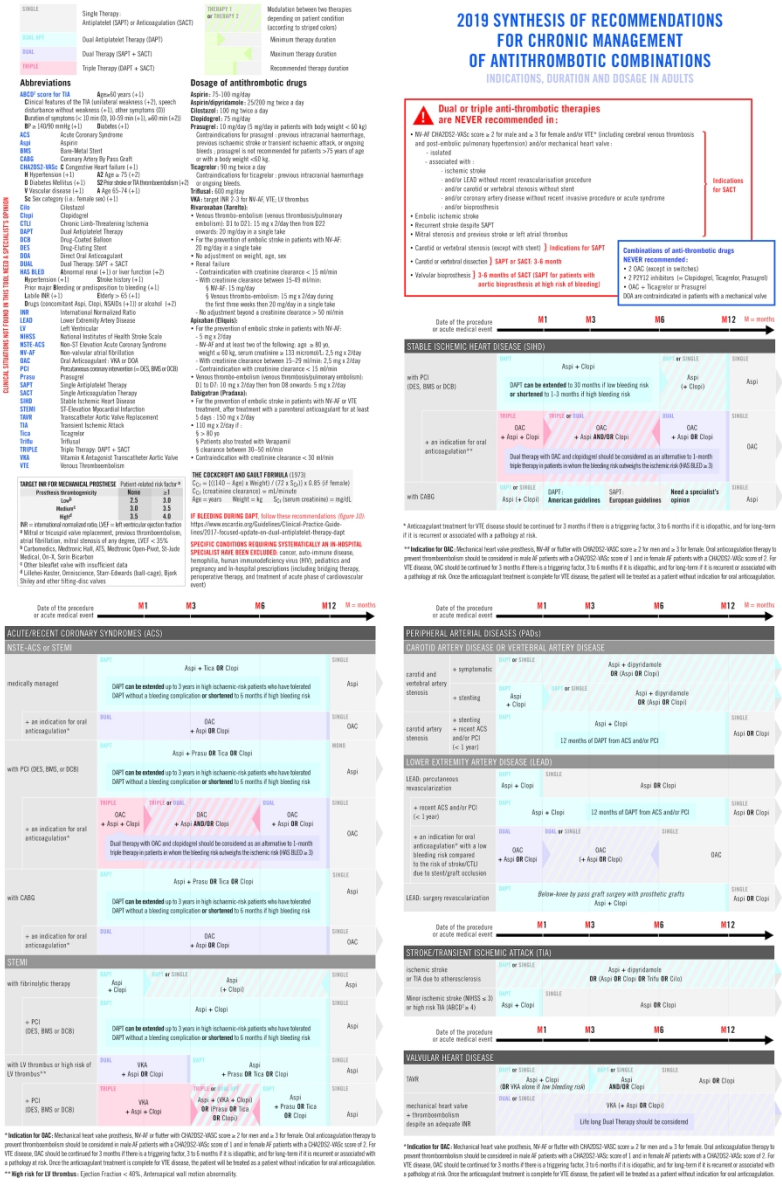
Trial registration: ClinicalTrials.gov ID: NCT03630874.

The study start date is November 2018.

REFERENCES

1. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet* 2015;**386**:281–91. doi:10.1016/S0140-6736(15)60243-4.
2. Patel NS, Patel TK, Patel PB, *et al*. Hospitalizations due to preventable adverse reactions—a systematic review. *Eur J Clin Pharmacol* 2017;**73**:385–98. doi:10.1007/s00228-016-2170-6.
3. Wester K, Jönsson AK, Spigset O, *et al*. Incidence of fatal adverse drug reactions: a population based study. *Brit J Clin Pharmaco* 2008;**65**:573–9. doi:10.1111/j.1365-2125.2007.03064.x.
4. Pirmohamed M, James S, Meakin S, *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;**329**:15-19.
5. Hansen ML, Sørensen R, Clausen MT, *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433–41. doi:10.1001/archinternmed.2010.271.
6. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2014;**44**:213-218. doi:10.1093/ageing/afu145.
7. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;**63**:2227-2246. doi:10.1111/jgs.13702.
8. Hamilton K, Davis C, Falk J, *et al*. Assessing prescribing of NSAIDs, antiplatelets, and anticoagulants in Canadian family medicine using chart review. *Int J Clin Pharm* 2016;**38**:1094–1102. doi: 10.1007/s11096-016-0335-0.
9. Zerah L, Bun RS, Guillo S, *et al*. A prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines. *PLoS One* 2019;**14**:e0211695. doi: 10.1371/journal.pone.0211695.
10. Engel J, van der Wulp I, Poldervaart JM, *et al*. Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction: protocol of a clinical vignette study. *BMJ Open* 2015;**5**:e006441. doi: 10.1136/bmjopen-2014-006441.
11. Bachmann LM, Mühleisen A, Bock A, *et al*. Vignette studies of medical choice and judgement to study caregivers' medical decision behaviour: systematic review. *BMC Med Res Methodol* 2008;8:50. doi: 10.1186/1471-2288-8-50.
12. Peabody JW, Luck J, Glassman P, *et al*. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. *JAMA* 2000;**283**:1715-1722.

13. Peabody JW, Luck J, Glassman P, *et al*. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med* 2004;**141**:771-780.



2019 synthesis of recommendations for chronic management of antithrombotic combinations

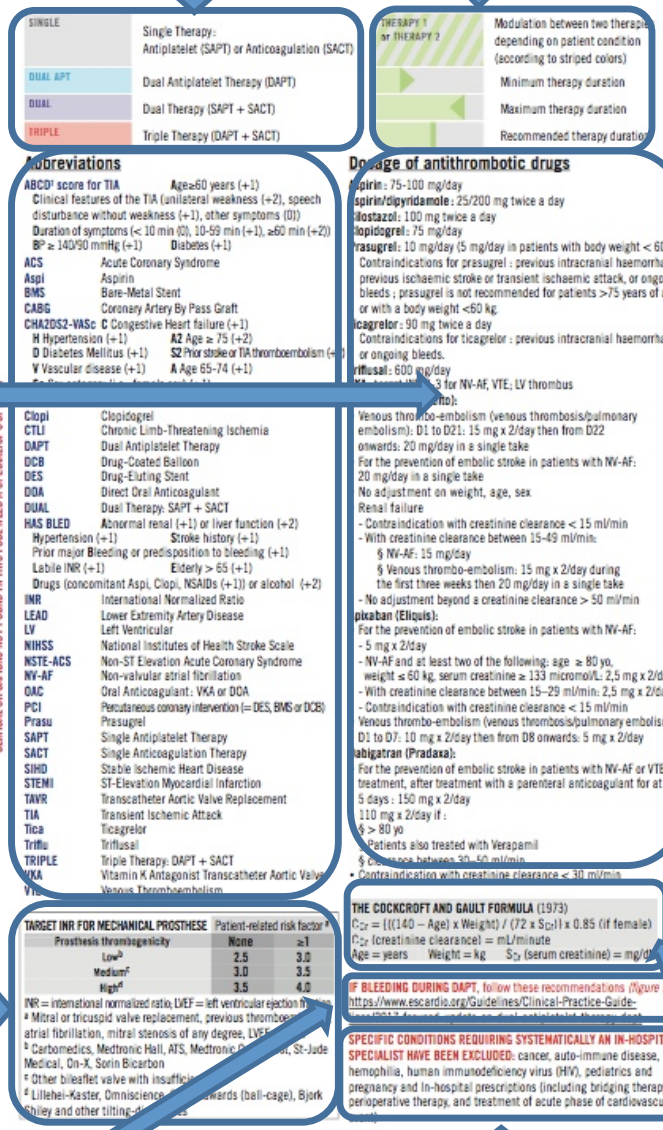
289x420mm (300 x 300 DPI)

How to use the prescription support tool

General presentation of the prescription support tool

Colour codes for single, dual or triple therapy

Codes for duration of treatments



Recommended dosages for each drugs

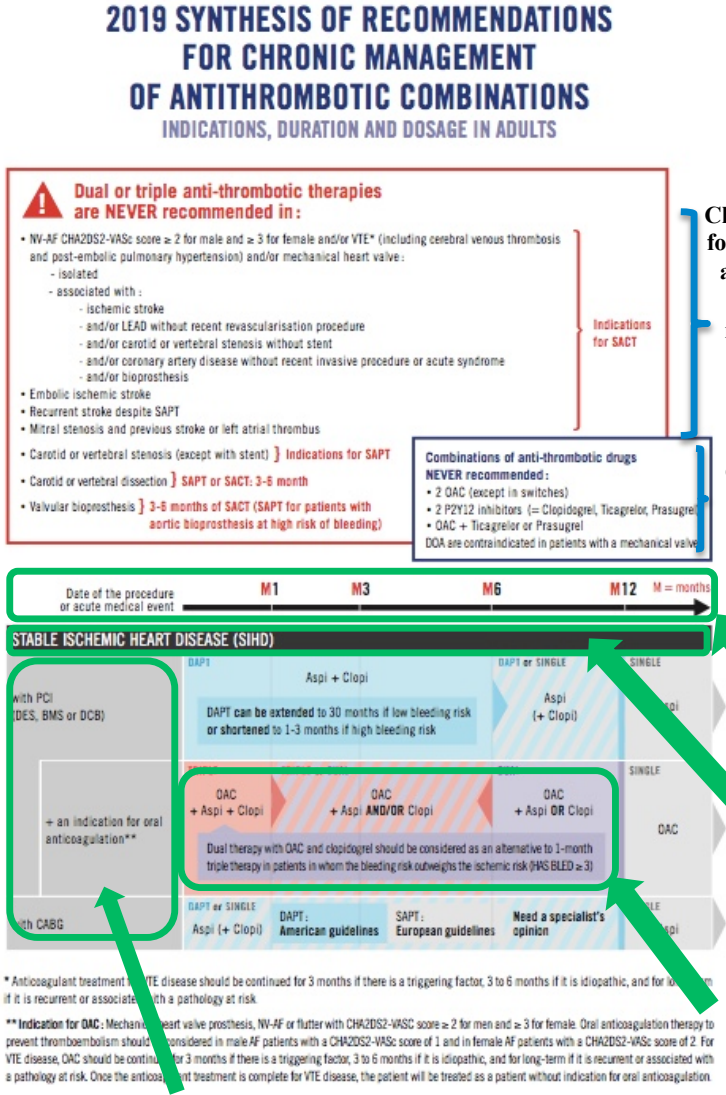
Abbreviations used in the tool

Target INR for mechanical valves

Link for recommendations if bleeding during DAPT

Specific conditions not included in the tool

Cockcroft and Gault formula



Clinical situations for which a single antithrombotic treatment is recommended (NEVER a combination)

Combinations of antithrombotic drugs NEVER recommended

Timeline (in months) since diagnosis or beginning of treatment

Pathology

Time dependant recommended treatments

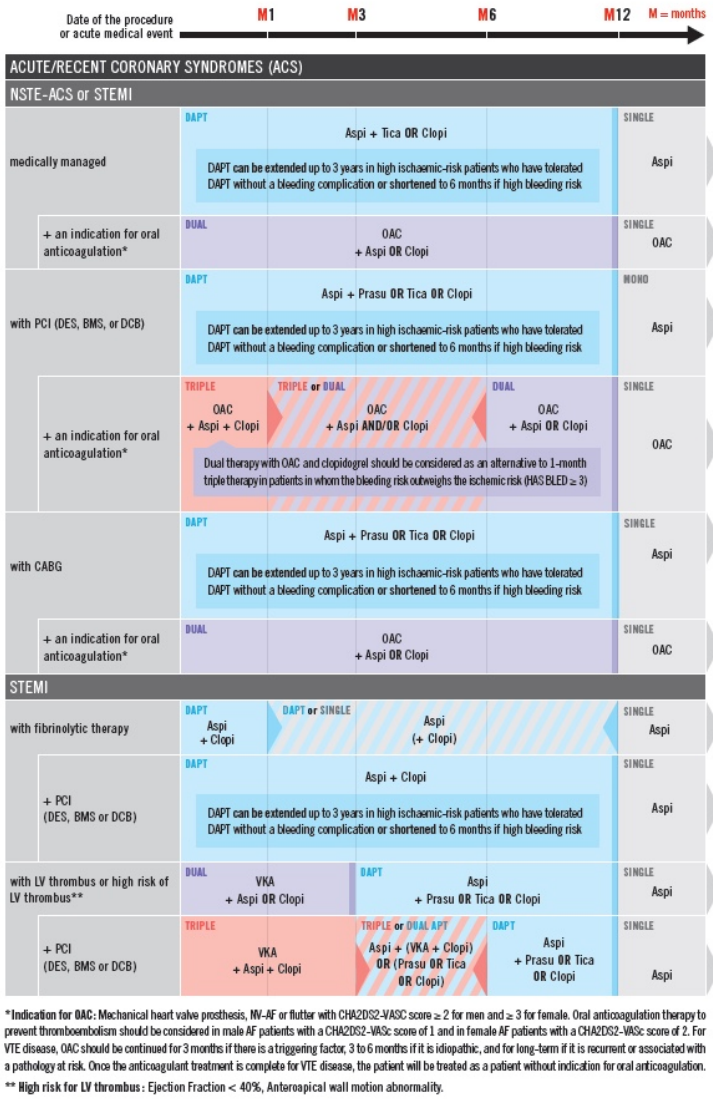
Treatments performed +/- association with another pathology that may influence antithrombotic treatment

In practice

Example 1: one cardiovascular disease

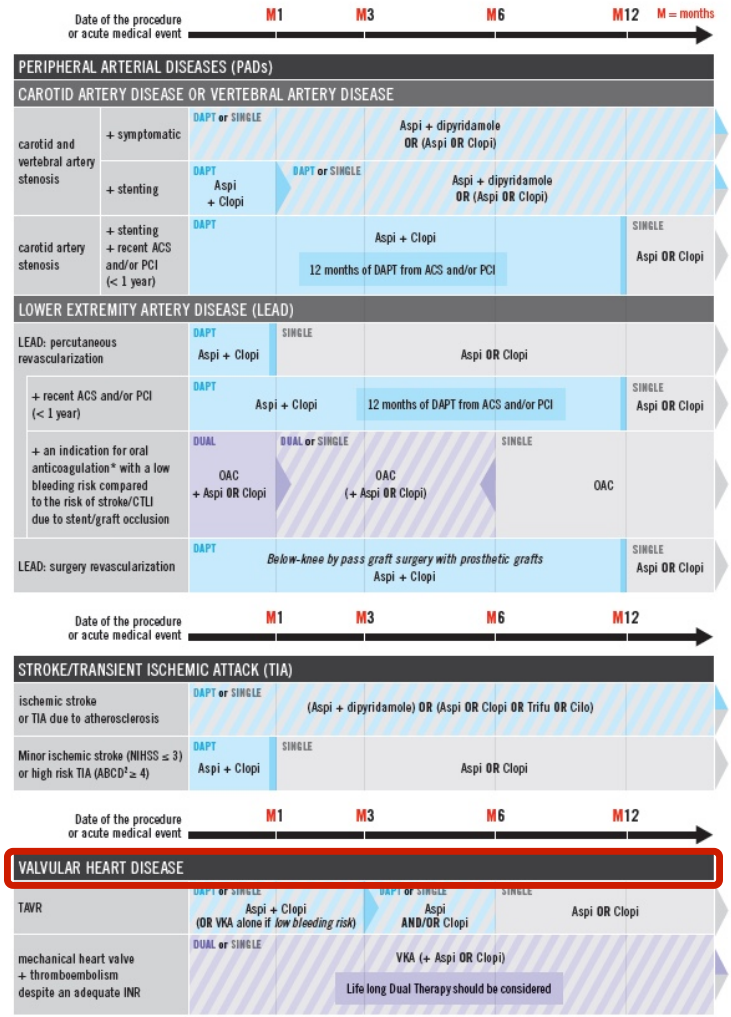
- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension and Parkinson disease
- He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve replacement (TAVR)
- Which antithrombotic therapy is recommended in this clinical situation?

1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient



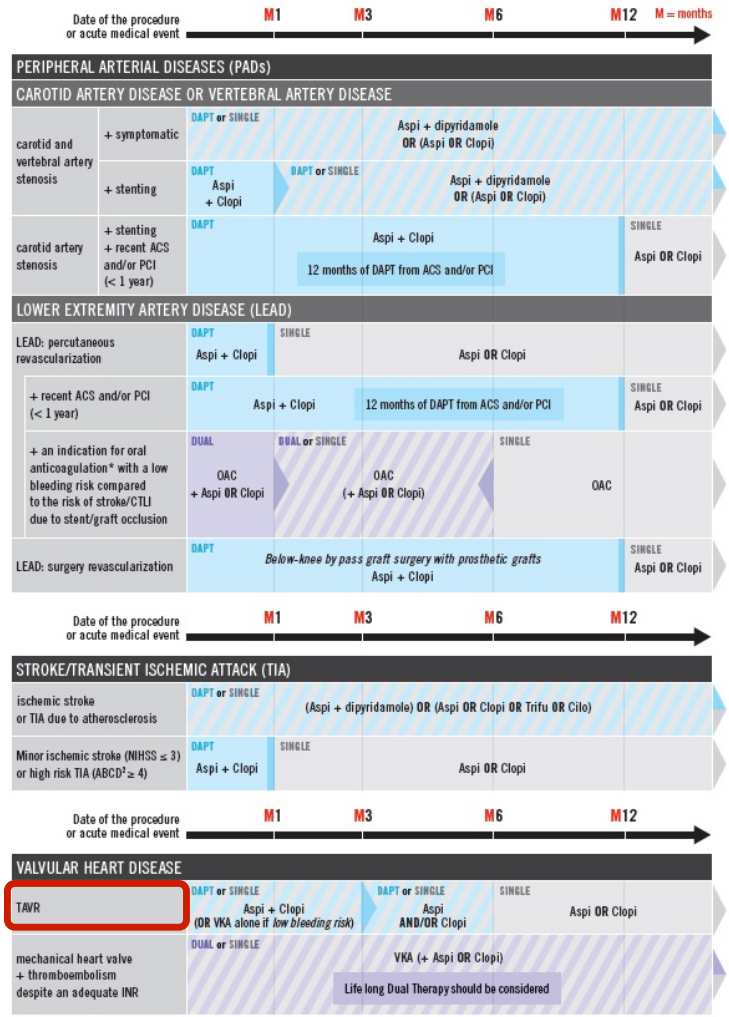
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

** High risk for LV thrombus: Ejection Fraction < 40%, Anteroapical wall motion abnormality.

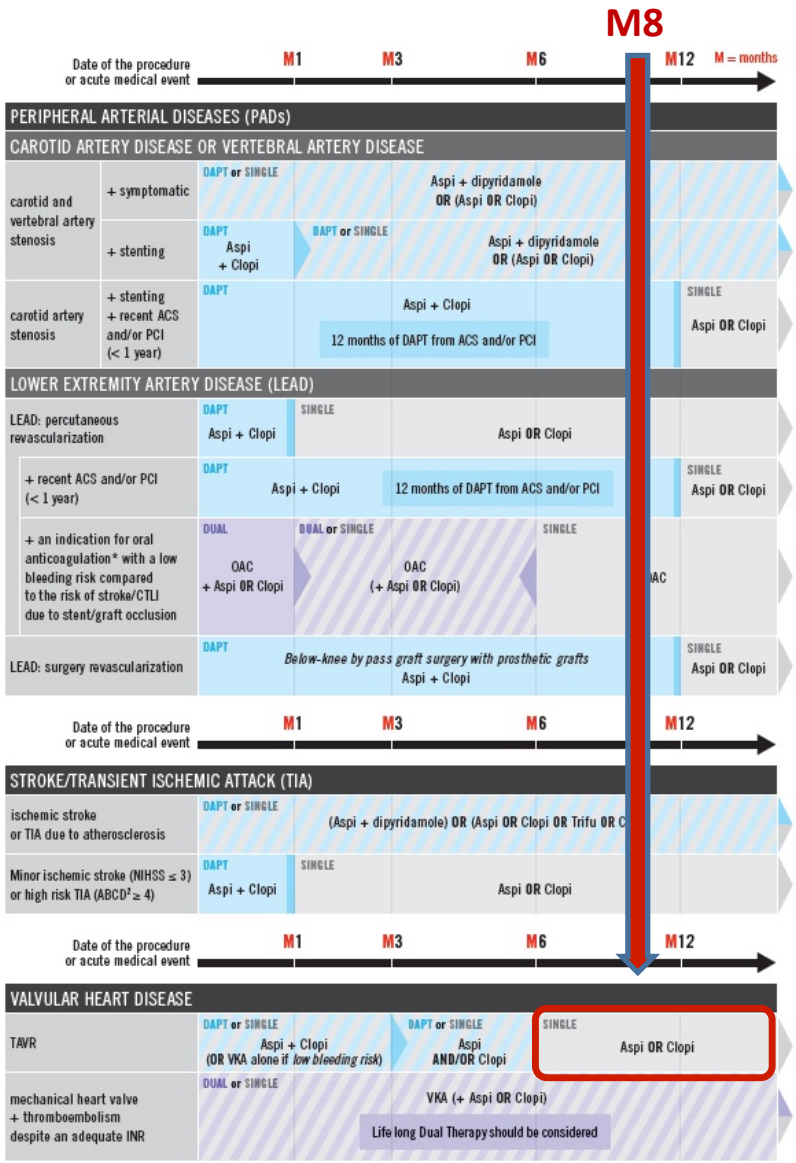


*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



3- In the recommended treatment, find out where your patient is currently (here: 8 months)



Long-term single antithrombotic therapy is recommended:

1) **Aspirin**
2) **Clopidogrel**

4- Check the recommended dosage for the drugs you want to prescribe

SINGLE	Single Therapy: Antiplatelet (SAPT) or Anticoagulation (SACT)
DUAL APT	Dual Antiplatelet Therapy (DAPT)
DUAL	Dual Therapy (SAPT + SACT)
TRIPLE	Triple Therapy (DAPT + SACT)

Modulation between two therapies depending on patient condition (according to striped colors)

Minimum therapy duration

Maximum therapy duration

Recommended therapy duration

Abbreviations

ABCD² score for TIA Age≥60 years (+1)
Clinical features of the TIA (unilateral weakness (+2), speech disturbance without weakness (+1), other symptoms (0))
Duration of symptoms (< 10 min (0), 10-59 min (+1), ≥60 min (+2))
BP ≥ 140/90 mmHg (+1) Diabetes (+1)

ACS Acute Coronary Syndrome
Aspi Aspirin
BMS Bare-Metal Stent
CABG Coronary Artery By Pass Graft
CHA2DS2-VASc C Congestive Heart failure (+1)
H Hypertension (+1) A2 Age ≥ 75 (+2)
D Diabetes Mellitus (+1) S2 Prior stroke or TIAthromboembolism (+2)
V Vascular disease (+1) A Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)
Cilo Cilostazol
Clopi Clopidogrel
CTLI Chronic Limb-Threatening Ischemia
DAPT Dual Antiplatelet Therapy
DCB Drug-Coated Balloon
DES Drug-Eluting Stent
DOA Direct Oral Anticoagulant
DUAL Dual Therapy: SAPT + SACT
HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major Bleeding or predisposition to bleeding (+1)
Labile INR (+1) Elderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)
INR International Normalized Ratio
LEAD Lower Extremity Artery Disease
LV Left Ventricular
NIHSS National Institutes of Health Stroke Scale
NSTE-ACS Non-ST Elevation Acute Coronary Syndrome
NV-AF Non-valvular atrial fibrillation
OAC Oral Anticoagulant : VKA or DOA
PCI Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu Prasugrel
SAPT Single Antiplatelet Therapy
SACT Single Anticoagulation Therapy
SCAD Stable coronary artery disease
STEMI ST-Elevation Myocardial Infarction
TAVR Transcatheter Aortic Valve Replacement
TIA Transient Ischemic Attack
Tica Ticagrelor
Triflu Triflusal
TRIPLE Triple Therapy: DAPT + SACT
VKA Vitamin K Antagonist Transcatheter Aortic Valve
VTE Venous Thromboembolism

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamole: 25/200 mg twice a day
Cilostazol: 100 mg twice a day
Clopidogrel: 75 mg/day
Prasugrel: 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor: 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal: 600 mg/day
VKA: target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    - § NV-AF: 15 mg/day
    - § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  - § > 80 yo
  - § Patients also treated with Verapamil
  - § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = \{(140 - Age) \times Weight) / (72 \times S_{Cr})\} \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations *(figure 10)*:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt

SPECIFIC CONDITIONS REQUIRING SYSTEMATICALLY AN IN-HOSPITAL SPECIALIST HAVE BEEN EXCLUDED: cancer, auto-immune disease, hemophilia, human immunodeficiency virus (HIV), pediatrics and pregnancy and in-hospital prescriptions (including bridging therapy, perioperative therapy, and treatment of acute phase of cardiovascular event)

CLINICAL SITUATIONS NOT FOUND IN THIS TOOL NEED A SPECIALIST'S OPINION

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor [a]	
Prosthesis thrombogenicity	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction
[a] Mitral or tricuspid valve replacement, previous thromboembolism; atrial fibrillation, mitral stenosis of any degree, LVEF < 35%
[b] Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St-Jude Medical, On-X, Sorin Bicarbon
[c] Other bileaflet valve with insufficient data
[d] Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

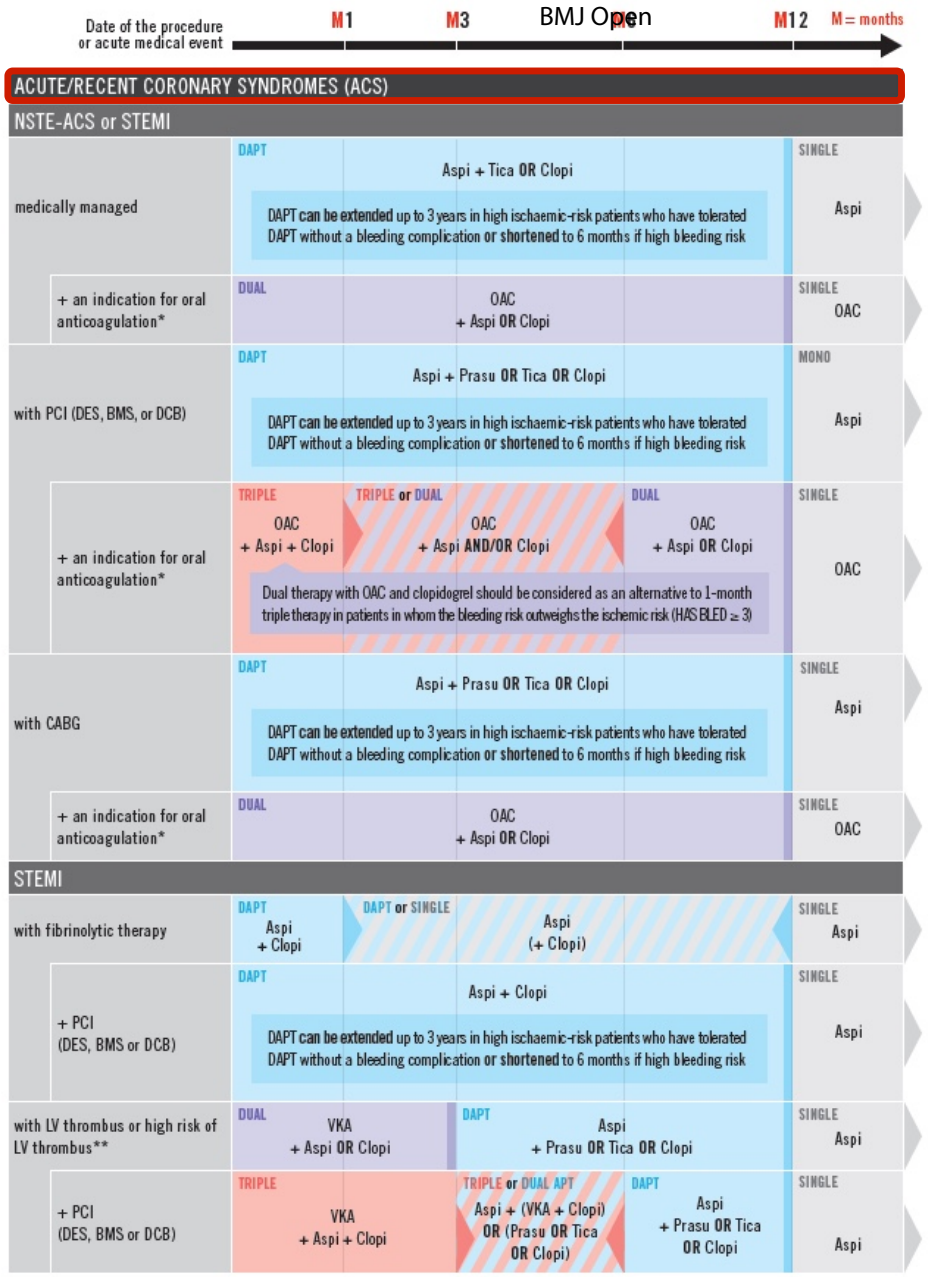
1) Aspirin 75-100 mg/day
2) OR Clopidogrel 75 mg/day

In practice

Example 2: two cardiovascular diseases

- At your medical consultation, you meet Mr V, 55 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension (controlled), diabetes, renal failure (creatinine clearance with Cockcroft formula: 30 ml/min) and permanent non-valvular atrial fibrillation
- He had an acute coronary syndrome 5 months ago with a percutaneous coronary intervention (PCI)
- Which antithrombotic therapy is recommended in this clinical situation?

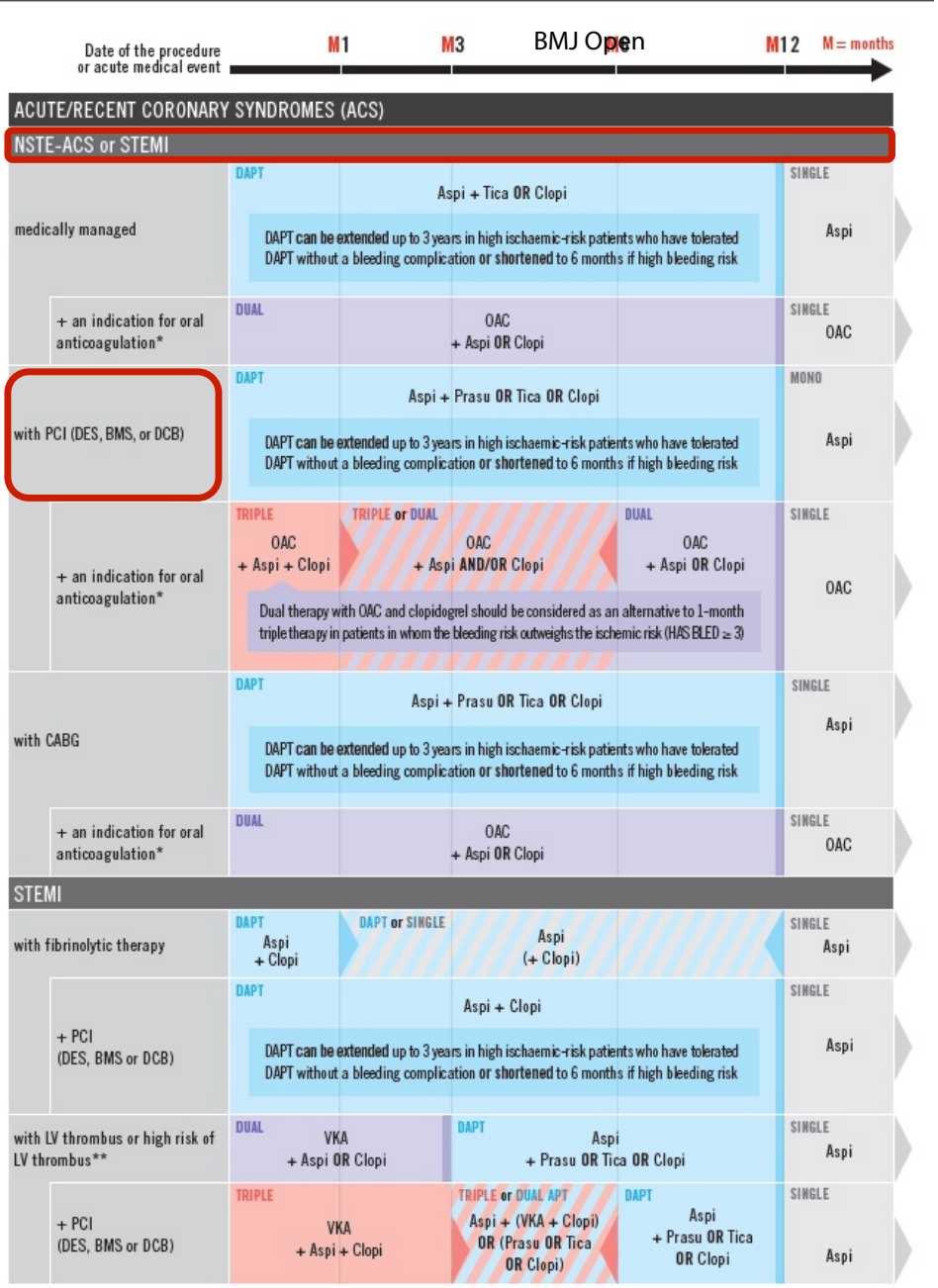
1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient



* **Indication for OAC :** Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

** **High risk for LV thrombus :** Ejection Fraction < 40%, Anteroapical wall motion abnormality.

2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



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** **High risk for LV thrombus :** Ejection Fraction < 40%, Anteroapical wall motion abnormality.

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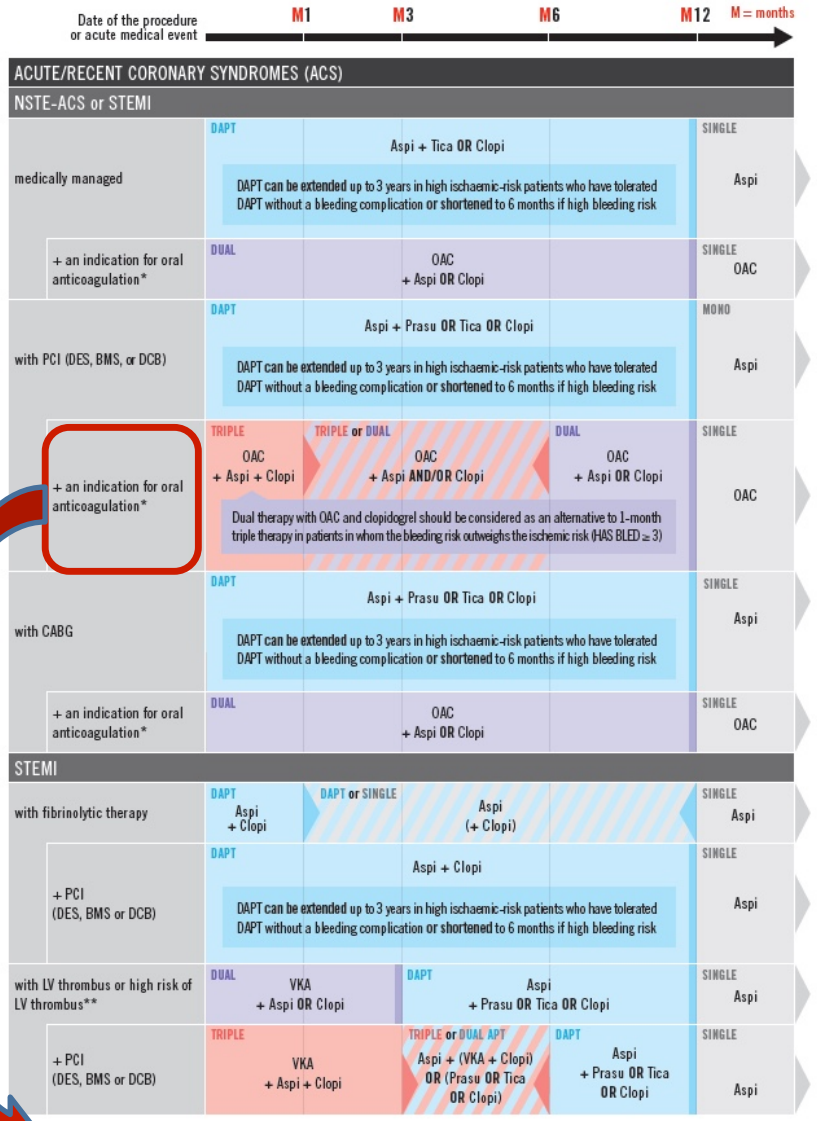


ABBREVIATIONS

CHA2DS2-VASc **C** Congestive Heart failure (+1)
H Hypertension (+1) **A2** Age ≥ 75 (+2)
D Diabetes Mellitus (+1) **S2** Prior stroke or TIA thromboembolism (+2)
V Vascular disease (+1) **A** Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)

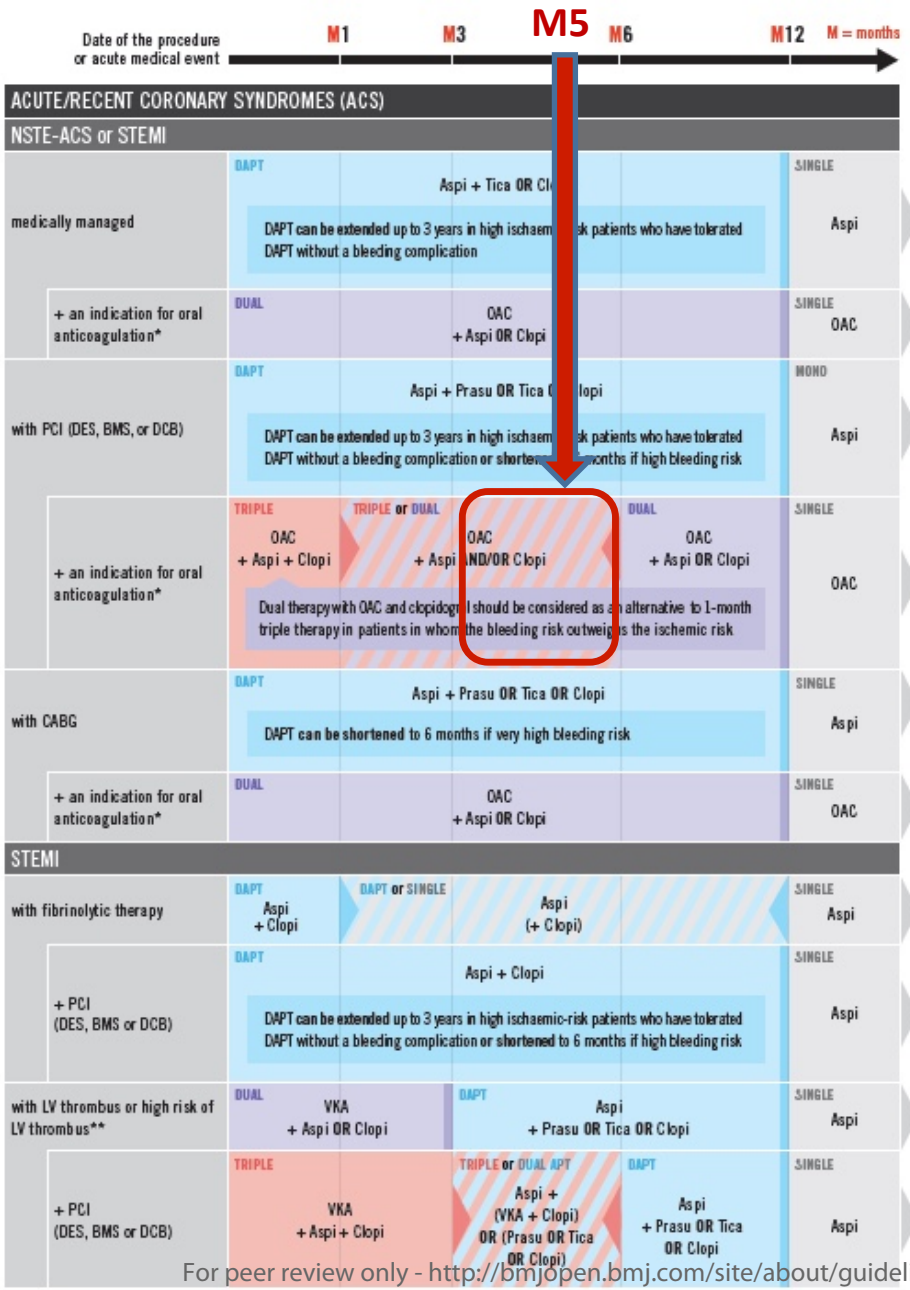
Hypertension and diabetes = 2 points
→ Indication for oral anticoagulation

HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major **B**leeding or predisposition to bleeding (+1)
Labile INR (+1) **E**lderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)

Abnormal renal function = 1 point
Drugs = 1 point
HAS BLED = 2

* **Indication for OAC :** Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For

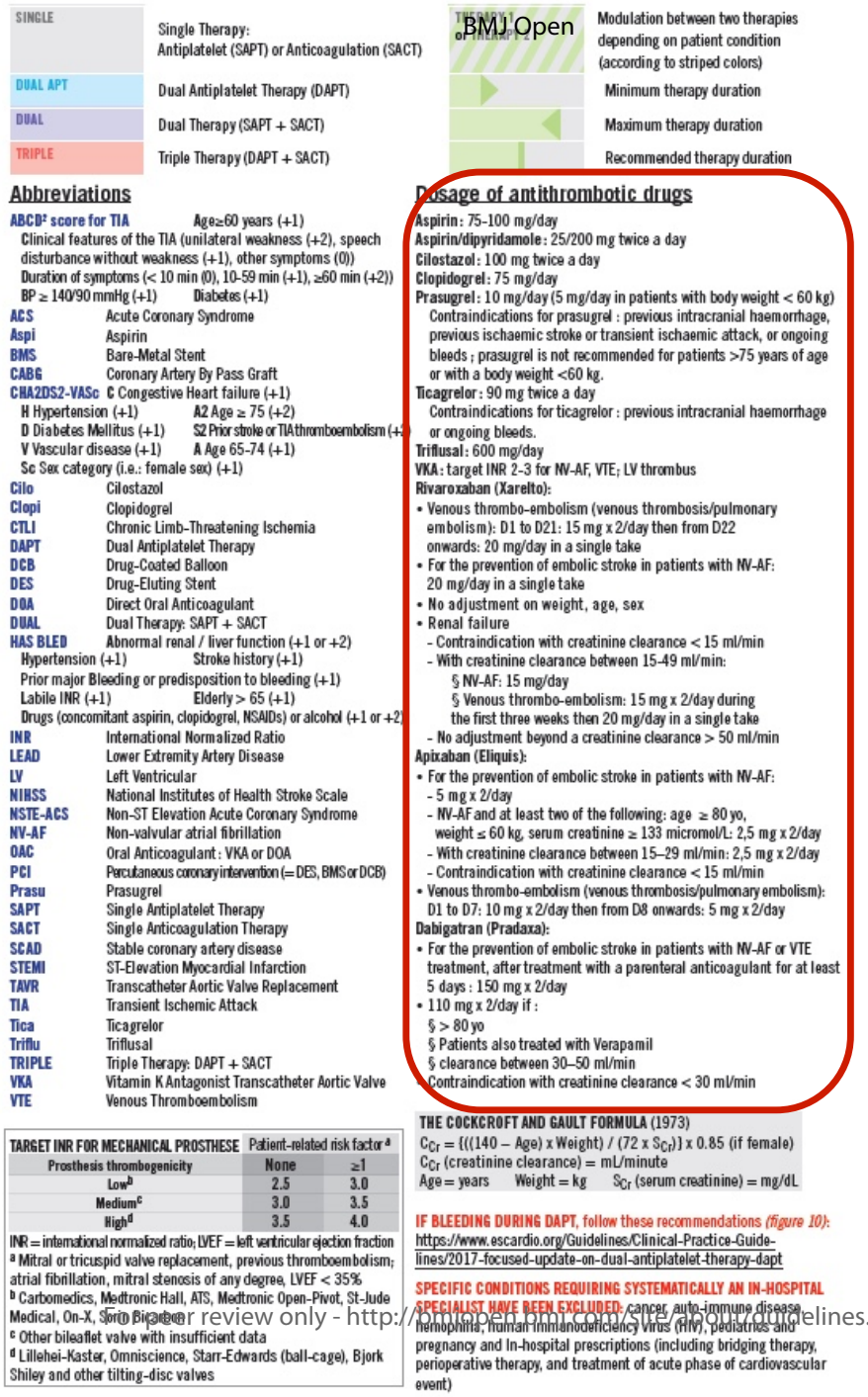
3- In the recommended treatment, find out where your patient is currently (here: 5 months)



Here, two options are possible according to the ischemic and bleeding risk of your patient:

1) Dual therapy: OAC + Aspirin OR Clopidogrel up to 12 months (so for another 7 months)
2) Triple therapy: OAC + Aspirin + Clopidogrel up to 6 months (so for another 1 month) and then a dual therapy with OAC + Aspirin OR Clopidogrel up to 12 months (so for another 6 months)

4- Check the recommended dosage for the drugs you want to prescribe



SINGLE	Single Therapy: Antiplatelet (SAPT) or Anticoagulation (SACT)
DUAL APT	Dual Antiplatelet Therapy (DAPT)
DUAL	Dual Therapy (SAPT + SACT)
TRIPLE	Triple Therapy (DAPT + SACT)

Modulation between two therapies depending on patient condition (according to striped colors)

Minimum therapy duration

Maximum therapy duration

Recommended therapy duration

CLINICAL SITUATIONS NOT FOUND IN THIS TOOL NEED A SPECIALIST'S OPINION

Abbreviations

ABCD² score for TIA Age≥60 years (+1)
Clinical features of the TIA (unilateral weakness (+2), speech disturbance without weakness (+1), other symptoms (0))
Duration of symptoms (< 10 min (0), 10-59 min (+1), ≥60 min (+2))
BP ≥ 140/90 mmHg (+1) Diabetes (+1)

ACS Acute Coronary Syndrome
Aspi Aspirin
BMS Bare-Metal Stent
CABG Coronary Artery By Pass Graft
CHA2DS2-VASc C Congestive Heart failure (+1)
H Hypertension (+1) A2 Age ≥ 75 (+2)
D Diabetes Mellitus (+1) S2 Prior stroke or TIA thromboembolism (+2)
V Vascular disease (+1) A Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)

Cilo Cilostazol
Clopi Clopidogrel
CTLI Chronic Limb-Threatening Ischemia
DAPT Dual Antiplatelet Therapy
DCB Drug-Coated Balloon
DES Drug-Eluting Stent
DOA Direct Oral Anticoagulant
DUAL Dual Therapy: SAPT + SACT
HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major Bleeding or predisposition to bleeding (+1)
Labile INR (+1) Elderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)
INR International Normalized Ratio
LEAD Lower Extremity Artery Disease
LV Left Ventricular
NIHSS National Institutes of Health Stroke Scale
NSTE-ACS Non-ST Elevation Acute Coronary Syndrome
NV-AF Non-valvular atrial fibrillation
OAC Oral Anticoagulant : VKA or DOA
PCI Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu Prasugrel
SAPT Single Antiplatelet Therapy
SACT Single Anticoagulation Therapy
SCAD Stable coronary artery disease
STEMI ST-Elevation Myocardial Infarction
TAVR Transcatheter Aortic Valve Replacement
TIA Transient Ischemic Attack
Tica Ticagrelor
Triflu Triflusal
TRIPLE Triple Therapy: DAPT + SACT
VKA Vitamin K Antagonist Transcatheter Aortic Valve
VTE Venous Thromboembolism

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamole: 25/200 mg twice a day
Cilostazol: 100 mg twice a day
Clopidogrel: 75 mg/day
Prasugrel: 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor: 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal: 600 mg/day
VKA: target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    - § NV-AF: 15 mg/day
    - § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  - § > 80 yo
  - § Patients also treated with Verapamil
  - § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor [a]	
Prosthesis thrombogenicity	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction
[a] Mitral or tricuspid valve replacement, previous thromboembolism; atrial fibrillation, mitral stenosis of any degree, LVEF < 35%
[b] Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St-Jude Medical, On-X, Sorin Bicarbon
[c] Other bileaflet valve with insufficient data
[d] Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = \{((140 - Age) \times Weight) / (72 \times S_{Cr})\} \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations *(figure 10)*:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt

SPECIFIC CONDITIONS REQUIRING SYSTEMATICALLY AN IN-HOSPITAL SPECIALIST HAVE BEEN EXCLUDED: cancer, auto-immune disease, hemophilia, human immunodeficiency virus (HIV), pediatrics and pregnancy and In-hospital prescriptions (including bridging therapy, perioperative therapy, and treatment of acute phase of cardiovascular event)

OAC :

- VKA with a target INR: 2–3
- Rivaroxaban 15 mg/day
- Apixaban 5 mg X 2/day
- Dabigatran is contraindicated

Antiplatelets:

- Aspirin 75-100 mg/day
- Clopidogrel 75 mg/day

Appendix 2: Example of a clinical vignette

At your medical consultation, you meet Mr R, 86 years old (weight: 81 kg, body mass index: 24 kg/m^2). Mr R is a widower, a smoker (10 cigarettes a day, 50 pack-years) and is autonomous in all daily activities. He has no personal medical history and he takes no drug. His last biological test did not find any abnormalities (serum creatinine value: 77 µM/L, creatinine clearance using the Cockcroft-Gault formula: 70 ml/min).
He comes to see you in consultation because for more than 1 week, he has had palpitations with exercise. You perform electrocardiogram (ECG) in your office and you diagnose non-valvular atrial fibrillation. The biological assessment is without particularity (in particular blood ionography and thyroid-stimulating hormone). Cardiac ultrasonography revealed a dilated left atrium with no valve abnormality.

1) How many antithrombotic treatments will you prescribe during this consultation?

- 0
- 1
- 2
- 3

2) If you answered 0 to question 1, go to question 5. If not, which molecule(s) of antithrombotic(s) will you prescribe during this consultation?

- Warfarin
- Rivaroxaban
- Apixaban
- Aspirin
- Clopidogrel

3) Which dosage will you prescribe this(these) molecule(s)? (For each molecule checked on the previous question, it will appear:)

- Warfarin:
  - INR (International Normalized Ratio): 2-3
  - INR (International Normalized Ratio): 2.5-3.5
- Rivaroxaban
  - 15 mg per day
  - 20 mg per day
- Apixaban
  - 2.5 mg twice a day
  - 5 mg twice a day
- Aspirin
  - 75-100 mg per day
  - 300 mg per day
- Clopidogrel
  - 75 mg per day
  - 300 mg per day

4) How long does the antithrombotic treatment prescribed in the previous question need to be continued?

- 1 month
- 6 months
- 12 months
- For life

5) On a scale of 0 to 10, what is your degree of confidence in the adequacy of your prescription in relation to the guidelines?

For the experimental group, after completion of the 3 clinical vignettes:

Regarding the prescription support tool, please note the following items from 0 (strongly disagree) to 10 (strongly agree):

- The prescription support-tool helped me answer to the clinical vignettes:../10
- The prescription support-tool has modified the answers that I spontaneously made to clinical vignettes:../10
- The prescription support-tool is clear:../10
- The prescription support-tool is operational:../10
- The prescription support-tool is useful for practice:../10
- I would be ready to use this prescription support-tool:../10
- I would recommend the use of this prescription support-tool:../10

Notes on the tool: What are the points of the prescription support-tool that could be improved: useless information, missing information, presentation, etc:

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → **Page 2 line 54**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → **line 266 - 270, page 12**
Funding	4	Sources and types of financial, material, and other support → **line 264, page 12**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → **Title page and lines 257 - 261 page 12**
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → **Lines 68 – 98, page 4 - 5**
	6b	Explanation for choice of comparators

Objectives	7	Specific objectives or hypotheses → **Lines 99 - 102, page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → **Lines 106 - 107 page 5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → **Lines 107 - 109 page 5**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → **Lines 110 - 136, page 5 - 6**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → **Lines 148 – 159, page 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → **Lines 110 - 136, page 5 - 6**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **→ Lines 201 – 208, page 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size → **Lines 146-147, page 7**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Lines 137 – 143, page 6-7** **Lines 192 - 195 page 8-9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Lines 192 - 195 page 8-9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Lines 192 - 195 page 8-9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **→ Lines 196 – 200 page 9**

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol → **Lines 196 – 200 page 9**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → **Lines 208 - 223, page 9-10**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) → **Lines 220 - 221, page 10**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → **Lines 243 - 252 page 11**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → **Lines 198 - 199, page 9**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → **Line 265, page 12**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → **Lines 251 - 252, page 11**
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial

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Primary Subject Heading:	Pharmacology and therapeutics

Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Public health
Keywords:	prescription support-tool, clinical vignettes, antithrombotic combination

Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial

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ABSTRACT

Introduction: Improving the appropriateness of prescriptions of oral antithrombotic (AT) drugs, especially AT combinations, is crucial because these drugs are implicated in bleeding events. We developed a prescription support-tool synthesizing guidelines on chronic management of oral AT combinations. Our main objective is to assess the impact of this tool on improving the prescription of oral ATs to comply with guidelines.

Methods and analysis: A randomized controlled trial will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians will be invited to participate to an online survey by email via physician associations, social networks or word of mouth. They will be randomized to two arms: the experimental arm (access to the prescription support-tool) or the control arm (no prescription support-tool). Then, all participants will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each vignette (number of ATs, type, dosage and duration). A computer-generated randomization scheme implemented in the online survey will be used to allocate physicians to the experimental or control arm, then stratified by medical specialty. The primary outcome will be fully appropriate prescription of oral ATs i.e that comply with the guidelines in terms of number of drugs, drug class, dosage and duration. To demonstrate a 5% increase in this proportion, we will need to include a minimum of 230 physicians per arm. A logistic mixed model with a clinical vignette-effect and a physician-effect nested in the arm of the study will be used.

Ethics and dissemination: The *Institutional Review Board* of Inserm (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool improves the prescription of oral ATs, we will create an interactive web tool and will assess its impact in terms of clinical outcomes in real-life.

(ClinicalTrials.gov ID: NCT03630874)

Article summary: strengths and limitations of this study

- Strengths:
  - This is a national, multicenter, randomized controlled study to evaluate the impact of a new and innovative prescription support-tool for chronic management of oral antithrombotic prescriptions (single, dual or triple therapy).
  - A scientific committee and an expert committee have developed and validated 30 clinical vignettes that we will use to evaluate the prescription support-tool.
- Limitations:
  - Selected physicians may not be representative of general practitioners or cardiologists because they are volunteers.
  - Non-access to the prescription support-tool in the control arm cannot be completely guaranteed (contamination bias).
  - The study will be undertaken in France, which could limit generalizability.

INTRODUCTION

Antithrombotic (AT) drugs, which include antiplatelet (AP) and anticoagulant (AC) therapies, are used to prevent and treat many cardiovascular disorders.[1] With the increase in prevalence of cardiovascular diseases and medical progress, these treatments are increasingly being prescribed all around the world.[1] Furthermore, ATs are the most frequent drug class implicated in serious and fatal adverse drug events (ADEs), particularly bleeding events,[2,3] among which 70% could be preventable.[4]

AT combinations (dual or triple AT therapy) greatly increase this risk. For example, Hansen et al. reported a 3.1-fold higher risk of fatal and non-fatal bleeding with dual warfarin and clopidogrel therapy and a 3.7-fold higher risk with triple therapy (warfarin, aspirin and clopidogrel) than warfarin monotherapy in patients with non-valvular atrial fibrillation.[5] So far, no study has evaluated the rate of prescriptions of AT combinations not complying with guidelines for adults, taking into account the drugs prescribed but also the dosage and duration of the prescription. Although tools assessing inappropriate prescribing such as the Beers or STOPP/START criteria[6,7] have a section dedicated to ATs, they mention only a few conditions for prescribing AT combinations and are relevant to older people only. Only one Canadian cohort study was specifically designed to assess the appropriateness of AT combinations in adults.[8] It concluded that approximately 15% of patients with AT combinations had inappropriate dual or triple oral AT therapy. However, the appropriateness of the prescribing was limited to the type of drugs combined and did not cover duration and dosage.

To assess the appropriateness of prescribing oral AT combinations (considering number of drugs, type of drugs, dosage and duration at the same time) in a French cohort of adults, we performed a systematic review of international guidelines (2012-2018) to define which oral AT combination is recommended, when and for how long.[9] Guidelines dealing with oral

AT combinations were numerous (n=70) and none encompassed all the clinical situations requiring oral AT combinations. This review highlighted the difficulty for a physician to quickly find the most up-to-date recommendation and the one most relevant to the patient's clinical situation. These findings, agreed with clinical experience, led us to synthesize all the recommendations into a prescription support-tool **(Figure 1)**[9] to help physicians prescribe oral AT combinations.

Our hypothesis is that this prescription support-tool would improve the prescription of oral ATs to comply with guidelines. Our primary objective is to assess the impact of this tool on improving the prescription of oral ATs to comply with guidelines (in terms of number of drugs, drug class, dosage and duration at the same time).

METHODS AND ANALYSIS

Study design, study setting and eligibility criteria

A web-based, open randomized controlled trial involving clinical vignettes will be performed in France via an online survey. This study will be conducted among French general practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive hospital practice will not be eligible.

Physicians will be identified and contacted to participate in the online survey by email via physician associations, social networks or word of mouth. The survey will gather informations on physicians' characteristics, including age, sex, medical specialty (cardiologist or general practitioner), place of exercise (hospital or ambulatory setting), years of medical practice, approximate proportion of patients prescribed oral AT combinations in their practice (≤ 5%, 6 – 10%, 11-20% or ≥ 21%), whether physicians feel comfortable or not with management of oral AT prescriptions (totally, partially, rarely, never), and whether physicians know where to find the most recent guidelines on oral AT prescriptions. Then, physicians will

be randomized to 2 arms: the experimental arm, having access to the prescription support-tool **(Figure 1),[**9] and the control arm, with no prescription support-tool. For physicians in the experimental arm, the prescription support-tool will be provided with an explanatory guide **(Appendix 1),[**9] both downloaded (or just viewed) online in pdf format. Then, participants from both arms will be presented 3 different clinical vignettes illustrating outpatient clinical situations and will be asked to propose prescriptions for each clinical vignette (oral AT or not, number of oral ATs, type of oral ATs, dosage of each oral AT and duration of the prescription) by answering 4 multiple-choice questions (each question on a separate web page). Question 5 will evaluate the degree of confidence of physicians have that their prescription of ATs complies with guidelines on a scale of 0 to 10. Physicians in the experimental arm will answer each question with the help of the tool, downloadable (or viewable on each page). At the end, we will ask to physicians of the experimental arm to rate, on a scale from 0 and 10, the usefulness of the prescription support-tool, how much they would be willing to use this prescription support-tool in their practice and if they would recommend its use. Physicians in the control arm will be asked to answer according to their actual clinical practice as closely as possible. Once the answer is given, physicians cannot go back or change their answers. Physicians must answer the questions consecutively; however, they will be allowed to stop and continue at any time (on the same computer). Physicians from the control arm will be able to download the prescription support-tool once they have completed their answers for the 3 clinical vignettes.

The scientific and expert committee have created and validated 30 clinical vignettes. To ensure that each clinical vignette will be read the same number of times in both arms, we created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized,

all clinical vignettes will be read once. The randomization unit will be the physician and the unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle ground to ensure the feasibility of the study considering both participants' availability (acceptable time to complete the clinical vignettes) and statistical need (number of clinical vignettes needed). To maximize the participation rate, physicians will be sent reminders every 20 days.

Outcomes

The primary outcome is prescription of oral ATs that comply with guidelines in terms of number of drugs, drug class, dosage and duration at the same time, which will be termed fully appropriate prescription. An expert committee will determine the correct answer, based on the prescription support-tool **(Figure 1)**[9]. Secondary outcomes are (1) prescription of oral ATs that comply with guidelines in terms of number of drugs, drug class, dosage and duration, each assessed separately; (2) prescription of oral ATs that comply with guidelines (fully appropriate prescription, number of drugs, drug class, duration and dosage each assessed separately) by medical specialty of physicians responding (cardiologist or general practitioner); (3) the degree of confidence of physicians have that their prescription of ATs complies with guidelines**;** 4) for physicians allocated to receive the prescription support-tool only, the overall usefulness of the tool.

Intervention

We developed, from a systematic review of international guidelines published between 2012 and 2018,[9] a prescription support-tool to help physicians prescribe oral AT combinations for complying with guidelines. This prescription support-tool synthesizes, on a double-sided page, selected international guidelines on chronic management (at least 1 month) of oral AT combinations (indication, drugs, dosages and duration) in adults, without considering in-hospital management and bridging therapy **(Figure 1).**[9] We excluded particular clinical

situations that require inevitably specialist medical advice: active cancer, autoimmune diseases, haemophilia, HIV, paediatrics and pregnancy. The following pathologies were included in this tool because they are the main causes leading to the prescription of ATs (single, dual or triple therapy) in adults[1]: non-valvular atrial fibrillation, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery disease and venous thromboembolism. Therefore, this tool covers prevention of ischemic and /or embolic events in patients with a history of coronary disease (stable coronary disease or acute coronary syndrome), non-valvular atrial fibrillation, peripheral artery disease, venous thromboembolism disease, ischemic stroke (and transient ischemic attack) and/or valvular heart disease (bioprosthesis, mechanical valve and transcatheter aortic valve replacement). It does not cover primary prevention in other scenarios such as patients without those conditions but at low or high-risk for ischemic events **(Figure 1).**[9] Our tool also specifies the type of oral ATs that should never be combined (combinations of oral anticoagulants [OACs], combinations of P2Y12 inhibitors or combining one OAC with one potent P2Y12 inhibitor, namely ticagrelor or prasugrel), the clinical situations in which oral AT combinations are never indicated and the contraindications of ATs. This prescription support-tool aims to give physicians quick access to the recommendation that fits most of their patient's clinical situation. The prescription support-tool is accompanied by an explanatory guide (how to read and use the tool, with examples, **Appendix 1).**[9]

Clinical vignettes

The clinical vignettes illustrating plausible clinical situations have been developed to reflect clinical practice.[10,11] Such an approach has been found valid in measuring quality of care.[12,13] Each clinical vignette corresponds to a specific situation for which physicians will have to indicate, by answering a multiple-choice question, whether they would prescribe oral ATs, with the number, type, dosage and duration. All answers to clinical vignettes'

questions can be found in the prescription support-tool. An example of a clinical vignette is presented in **Appendix 2.** Two physicians (1 cardiologist and 1 internist-geriatrician) from the scientific committee have created 30 clinical vignettes covering most outpatient clinical situations (without considering in-hospital management and bridging therapy) for which the long-term use of oral ATs (single, dual or triple therapy) is recommended or needs to be stopped according to the guidelines.

Randomization

Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated randomization scheme implemented in the online survey (1:1 ratio), then stratified by their medical specialty**.**

Data collection methods and data management

Data from physicians' answers will be automatically integrated in a database for statistical analysis. The data will be completely anonymous. In particular, neither the physician's name nor email address will be collected (there will be no login for participants). There is no planned follow-up in this trial.

Sample size and statistical considerations

Considering that 85% of AT prescriptions fully comply with guidelines in the control arm,[8] to demonstrate an increase in this proportion up to 90% in the experimental arm, we need to include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per arm. To obtain a multiple of 10 physicians (because each physician will complete 3 of 30 clinical vignettes and to have all clinical vignettes completed the same number of times in each arm), we plan to include at least 230 physicians per arm. However, if more physicians participate, all collected data will be considered. For each clinical vignette, we will consider that prescription is fully appropriate (versus inappropriate) if answers to each of the first four questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To

compare the percentage of fully appropriate prescriptions between the two randomized arms, taking into account that each participant intends to complete 3 clinical vignettes, we will use a logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. We will use the same method to compare the percentage of prescriptions of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately, between the two randomized arms (secondary analyses). To compare the degree of confidence that physicians have that their prescription of oral AT combinations complies with guidelines (quantitative variable: scale from 0 and 10), taking into account that each participant intends to complete 3 clinical vignettes, we will use a linear mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. A sub-group analysis for general practitioners and for cardiologist will be done. Finally, to assess the overall usefulness of the tool, we will describe the data of the experimental arm (mean ± SD, median (25–75 interquartile range)). All analyses will involve use of R v3.5.2 (www.cran.r-project.org).

Scientific and expert committees

Our study involves a scientific committee and an expert committee. The scientific committee consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2 epidemiologists. The scientific committee designed the study protocol, created and validated the clinical vignettes and will be responsible for data analysis and writing of the manuscript. The expert committee consists of a cardiologist, a geriatrician, an internist and 2 general practitioners (medical specialties that often deal with patients needing chronic oral AT prescriptions). The expert committee had to review all clinical vignettes with the prescription support-tool (external validation) to confirm the agreement of the clinical vignettes with clinical practice and their readability. The committee estimated the time needed to complete 3 clinical vignettes at 10 minutes.

Patient and Public Involvement

Patients and/or the public have not been involved in the development of the research or in the study design because only physicians will be enrolled and they will not care for patients in the context of this trial; they will just complete clinical vignettes.

ETHICS AND DISSEMINATION

The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) approved our research project (no. 18-492). If the prescription support-tool is associated with improving the prescription of oral ATs to comply with guidelines, it will be disseminated to help improve ATs prescriptions. We will create an interactive web tool to improve the ergonomics of the tool and to facilitate the updates. We will assess the impact of this interactive web tool in terms of clinical outcomes in real life. This will be the second step, but we feel that we must first demonstrate that the use of the prescription support-tool (on paper) is associated with better prescription appropriateness before launching a trial involving patients with clinical outcomes. Results of this trial will be disseminated in a paper submitted to a peer-reviewed journal and presentations at relevant conferences.

Figure 1 legend: 2019 synthesis of recommendations for chronic management of antithrombotic combinations

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Authors' contributions: LZ, DBZ, AD and FT designed the study. YDR designed the statistical analysis. LZ and MHM designed the clinical vignettes. PF, AMM, EP, PC and JPC reviewed the clinical vignettes. LZ, DBZ, MHM, AD and FT validated the clinical vignettes. LZ drafted and prepared the manuscript for publication. All authors re-read and corrected the manuscript. All authors approved the final manuscript.

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Competing interests: None.

Ethics approval: The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888) reviewed and approved our research project on 06/12/2018 (no. 18-492). The ethics evaluation committee of Inserm reviewed and approved a revised version of the protocol on 10/03/18 (no. 18-492 bis) to allow us to communicate our trial via social networks or word of mouth.

Trial registration: ClinicalTrials.gov ID: NCT03630874.

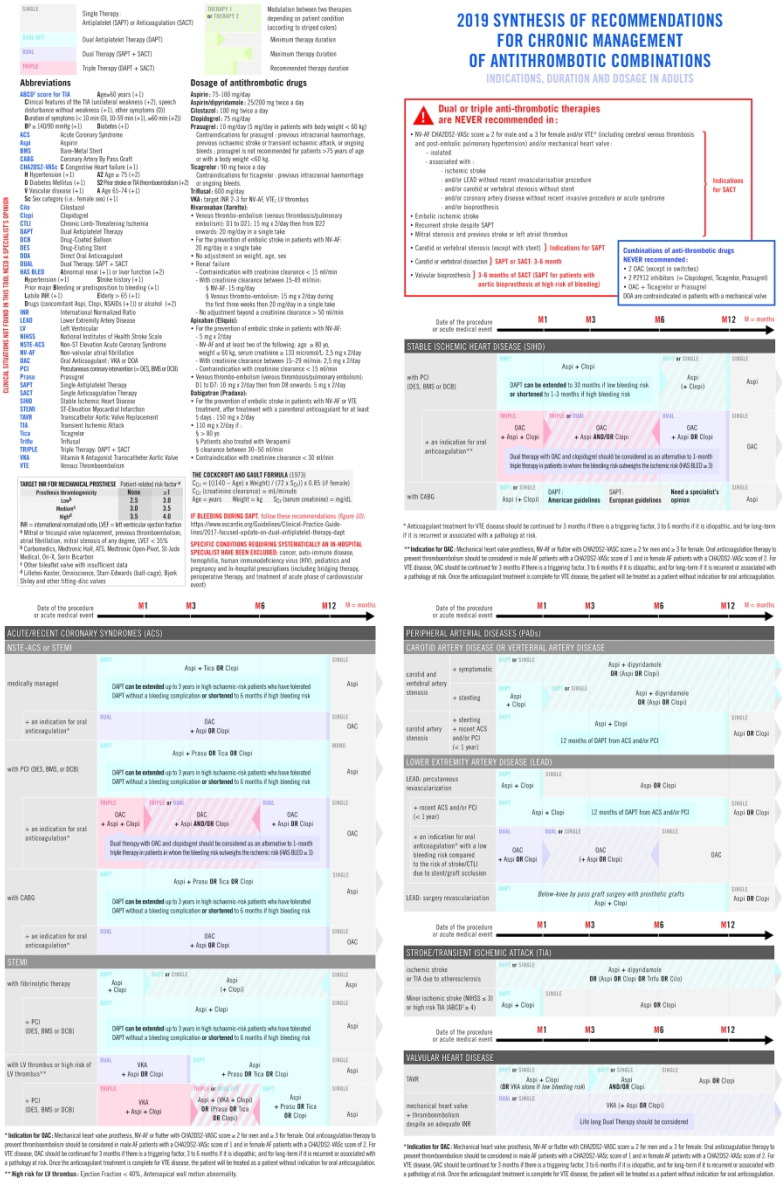
The study start date is November 2018.

Data sharing statement: The manuscript is a protocol for a randomized controlled trial, which does not include data.

REFERENCES

1. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet* 2015;**386**:281–91. doi:10.1016/S0140-6736(15)60243-4.
2. Patel NS, Patel TK, Patel PB, *et al*. Hospitalizations due to preventable adverse reactions—a systematic review. *Eur J Clin Pharmacol* 2017;**73**:385–98. doi:10.1007/s00228-016-2170-6.
3. Wester K, Jönsson AK, Spigset O, *et al*. Incidence of fatal adverse drug reactions: a population based study. *Brit J Clin Pharmaco* 2008;**65**:573–9. doi:10.1111/j.1365-2125.2007.03064.x.
4. Pirmohamed M, James S, Meakin S, *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;**329**:15-19.
5. Hansen ML, Sørensen R, Clausen MT, *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433–41. doi:10.1001/archinternmed.2010.271.
6. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2014;**44**:213-218. doi:10.1093/ageing/afu145.
7. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;**63**:2227-2246. doi:10.1111/jgs.13702.
8. Hamilton K, Davis C, Falk J, *et al*. Assessing prescribing of NSAIDs, antiplatelets, and anticoagulants in Canadian family medicine using chart review. *Int J Clin Pharm* 2016;**38**:1094–1102. doi: 10.1007/s11096-016-0335-0.
9. Zerah L, Bun RS, Guillo S, *et al*. A prescription support-tool for chronic management of oral antithrombotic combinations in adults based on a systematic review of international guidelines. *PLoS One* 2019;**14**:e0211695. doi: 10.1371/journal.pone.0211695.
10. Engel J, van der Wulp I, Poldervaart JM, *et al*. Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction: protocol of a clinical vignette study. *BMJ Open* 2015;**5**:e006441. doi: 10.1136/bmjopen-2014-006441.
11. Bachmann LM, Mühleisen A, Bock A, *et al*. Vignette studies of medical choice and judgement to study caregivers' medical decision behaviour: systematic review. *BMC Med Res Methodol* 2008;8:50. doi: 10.1186/1471-2288-8-50.
12. Peabody JW, Luck J, Glassman P, *et al*. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. *JAMA* 2000;**283**:1715-1722.

13. Peabody JW, Luck J, Glassman P, *et al*. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med* 2004;**141**:771-780.

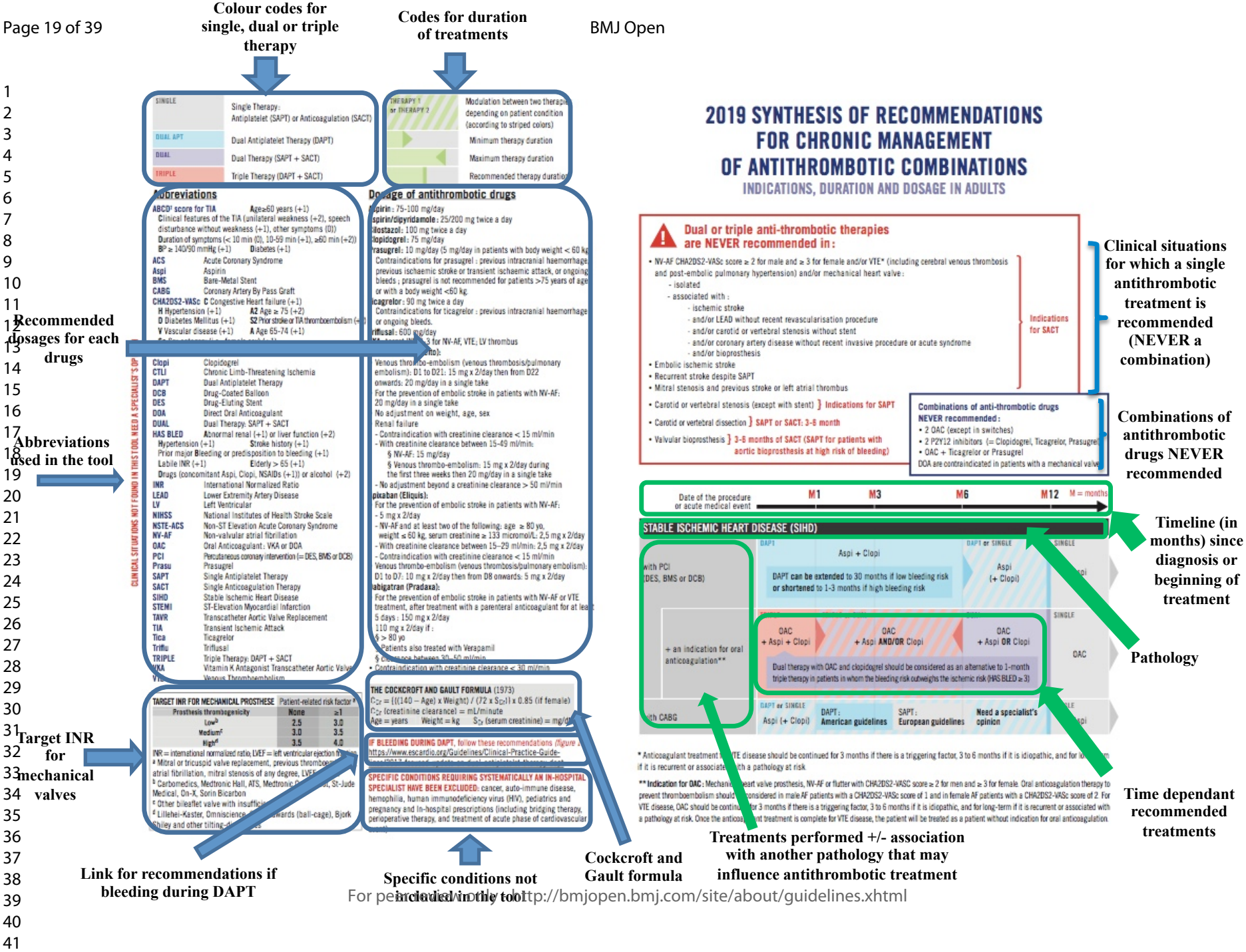


2019 synthesis of recommendations for chronic management of antithrombotic combinations

289x420mm (300 x 300 DPI)

How to use the prescription support tool

General presentation of the prescription support tool

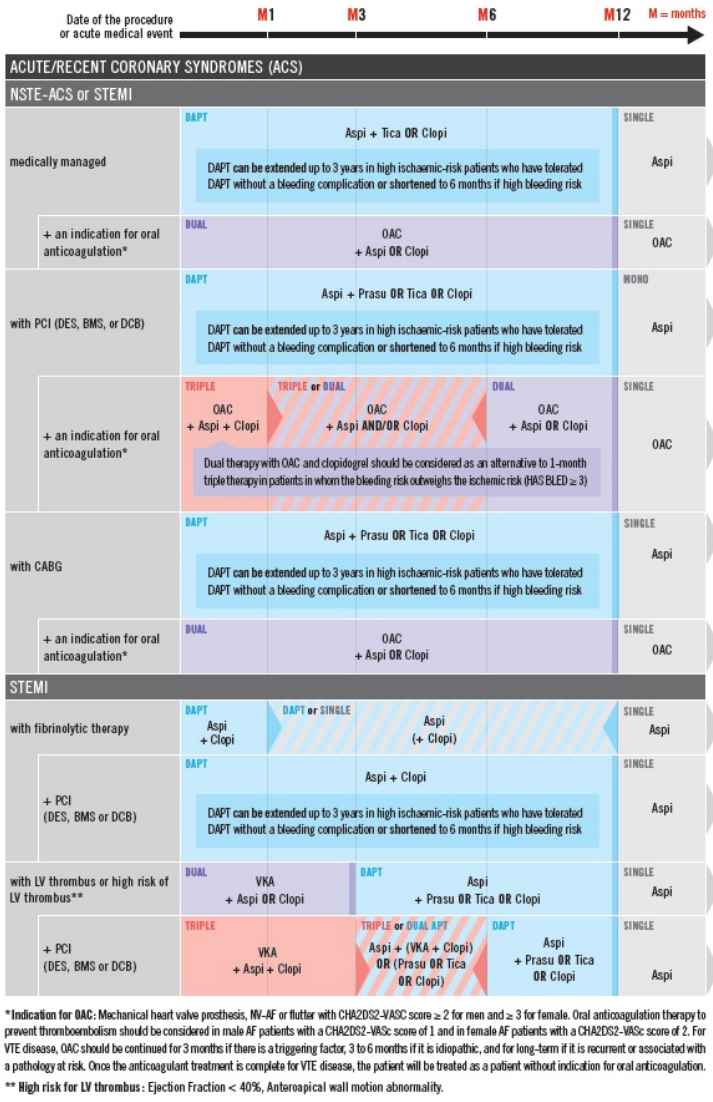


In practice

Example 1: one cardiovascular disease

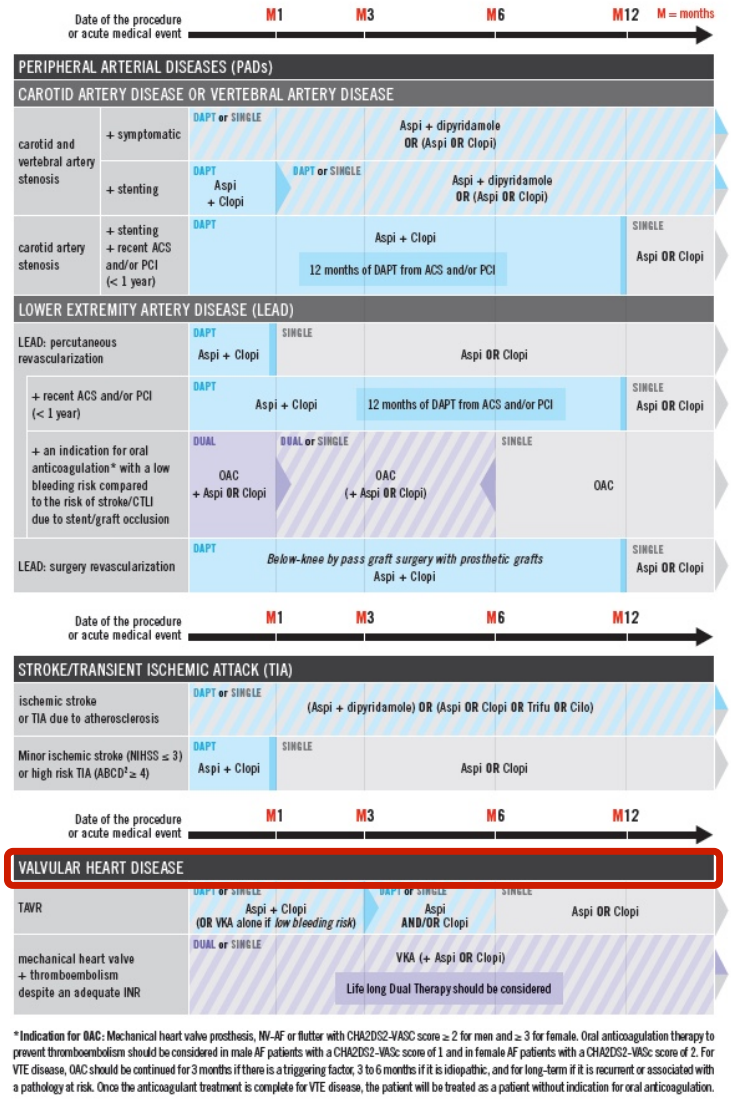
- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension and Parkinson disease
- He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve replacement (TAVR)
- Which antithrombotic therapy is recommended in this clinical situation?

1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient



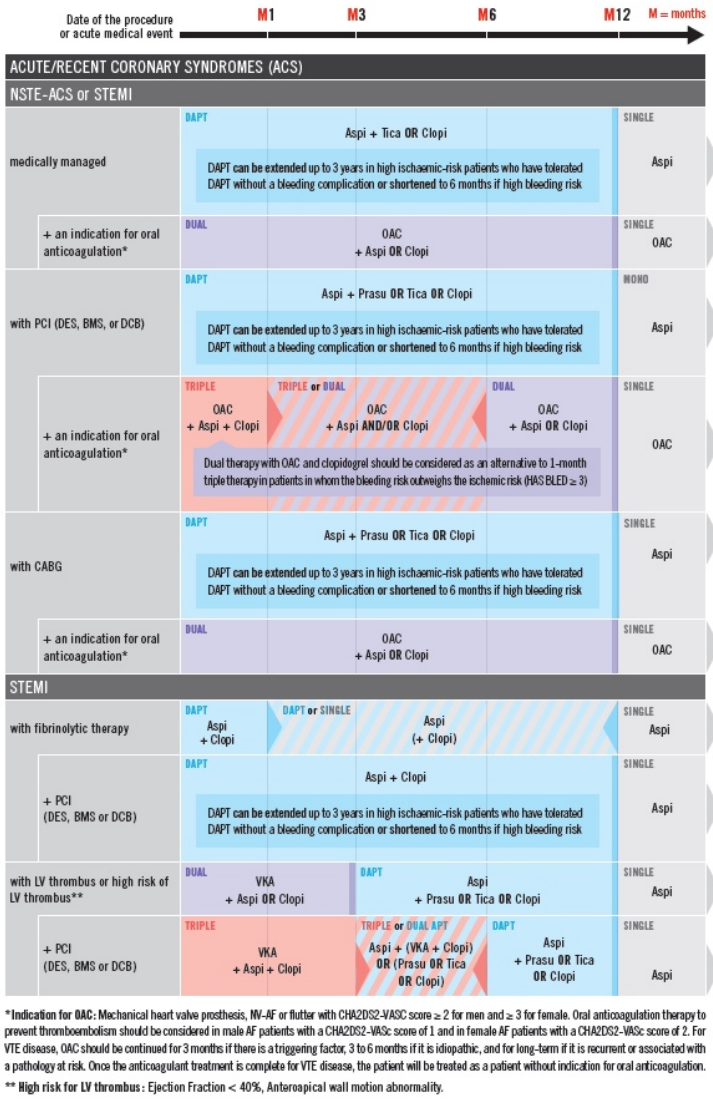
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

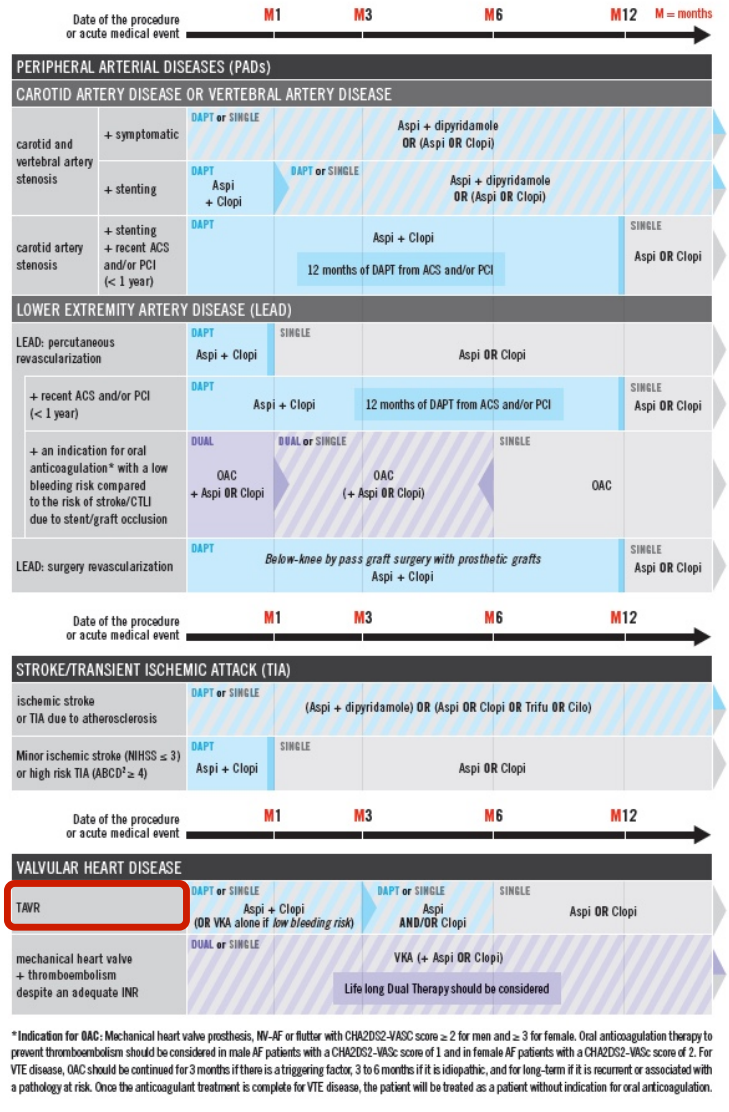
** High risk for LV thrombus: Ejection Fraction < 40%, Anteroapical wall motion abnormality.



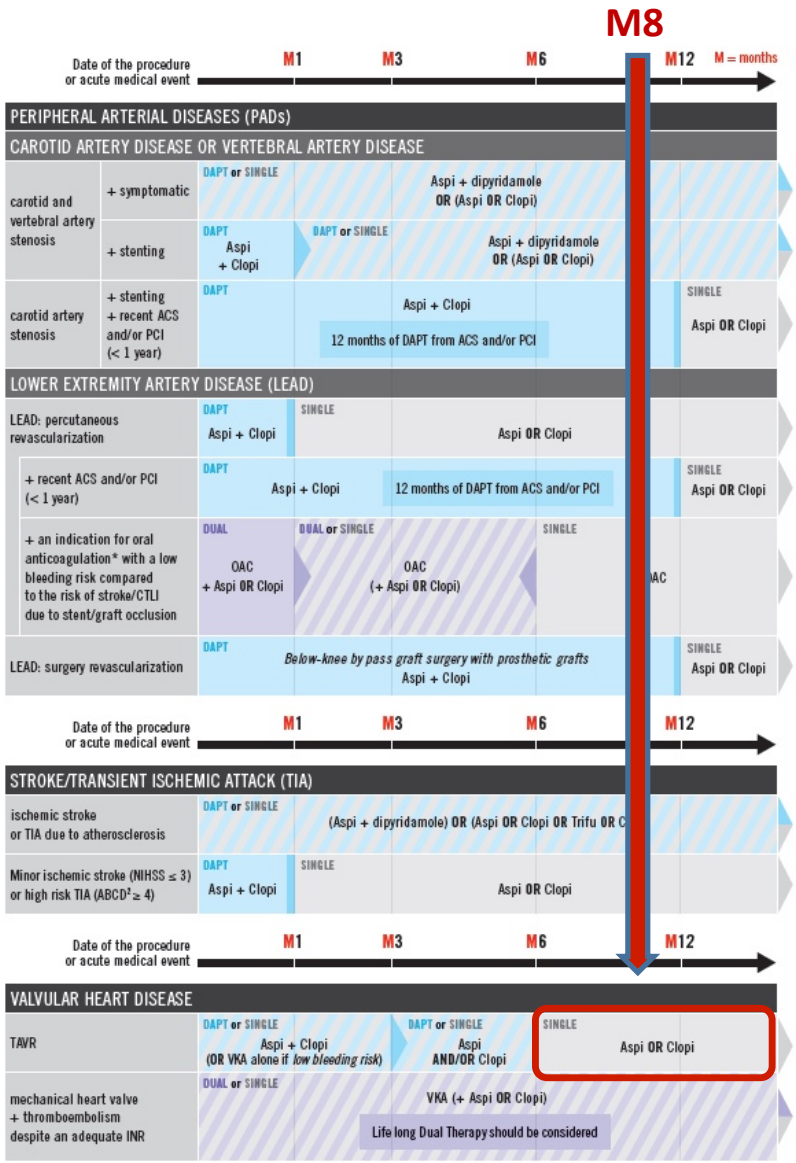
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)





3- In the recommended treatment, find out where your patient is currently (here: 8 months)



Long-term single antithrombotic therapy is recommended:

1) **Aspirin**
2) **Clopidogrel**

4- Check the recommended dosage for the drugs you want to prescribe

SINGLE	Single Therapy: Antiplatelet (SAPT) or Anticoagulation (SACT)
DUAL APT	Dual Antiplatelet Therapy (DAPT)
DUAL	Dual Therapy (SAPT + SACT)
TRIPLE	Triple Therapy (DAPT + SACT)

Modulation between two therapies depending on patient condition (according to striped colors)

Minimum therapy duration

Maximum therapy duration

Recommended therapy duration

Abbreviations

ABCD² score for TIA Age≥60 years (+1)
Clinical features of the TIA (unilateral weakness (+2), speech disturbance without weakness (+1), other symptoms (0))
Duration of symptoms (< 10 min (0), 10-59 min (+1), ≥60 min (+2))
BP ≥ 140/90 mmHg (+1) Diabetes (+1)

ACS Acute Coronary Syndrome
Aspi Aspirin
BMS Bare-Metal Stent
CABG Coronary Artery By Pass Graft
CHA2DS2-VASc C Congestive Heart failure (+1)
H Hypertension (+1) A2 Age ≥ 75 (+2)
D Diabetes Mellitus (+1) S2 Prior stroke or TIAthromboembolism (+2)
V Vascular disease (+1) A Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)
Cilo Cilostazol
Clopi Clopidogrel
CTLI Chronic Limb-Threatening Ischemia
DAPT Dual Antiplatelet Therapy
DCB Drug-Coated Balloon
DES Drug-Eluting Stent
DOA Direct Oral Anticoagulant
DUAL Dual Therapy: SAPT + SACT
HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major Bleeding or predisposition to bleeding (+1)
Labile INR (+1) Elderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)
INR International Normalized Ratio
LEAD Lower Extremity Artery Disease
LV Left Ventricular
NIHSS National Institutes of Health Stroke Scale
NSTE-ACS Non-ST Elevation Acute Coronary Syndrome
NV-AF Non-valvular atrial fibrillation
OAC Oral Anticoagulant : VKA or DOA
PCI Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu Prasugrel
SAPT Single Antiplatelet Therapy
SACT Single Anticoagulation Therapy
SCAD Stable coronary artery disease
STEMI ST-Elevation Myocardial Infarction
TAVR Transcatheter Aortic Valve Replacement
TIA Transient Ischemic Attack
Tica Ticagrelor
Triflu Triflusal
TRIPLE Triple Therapy: DAPT + SACT
VKA Vitamin K Antagonist Transcatheter Aortic Valve
VTE Venous Thromboembolism

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamole: 25/200 mg twice a day
Cilostazol: 100 mg twice a day
Clopidogrel: 75 mg/day
Prasugrel: 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor: 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal: 600 mg/day
VKA: target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    - § NV-AF: 15 mg/day
    - § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  - § > 80 yo
  - § Patients also treated with Verapamil
  - § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = \{(140 - Age) \times Weight) / (72 \times S_{Cr})\} \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations *(figure 10)*:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt

SPECIFIC CONDITIONS REQUIRING SYSTEMATICALLY AN IN-HOSPITAL SPECIALIST HAVE BEEN EXCLUDED: cancer, auto-immune disease, hemophilia, human immunodeficiency virus (HIV), pediatrics and pregnancy and in-hospital prescriptions (including bridging therapy, perioperative therapy, and treatment of acute phase of cardiovascular event)

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor[a]	
Prosthesis thrombogenicity	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction
[a] Mitral or tricuspid valve replacement, previous thromboembolism; atrial fibrillation, mitral stenosis of any degree, LVEF < 35%
[b] Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St-Jude Medical, On-X, Sorin Bicarbon
[c] Other bileaflet valve with insufficient data
[d] Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

CLINICAL SITUATIONS NOT FOUND IN THIS TOOL NEED A SPECIALIST'S OPINION

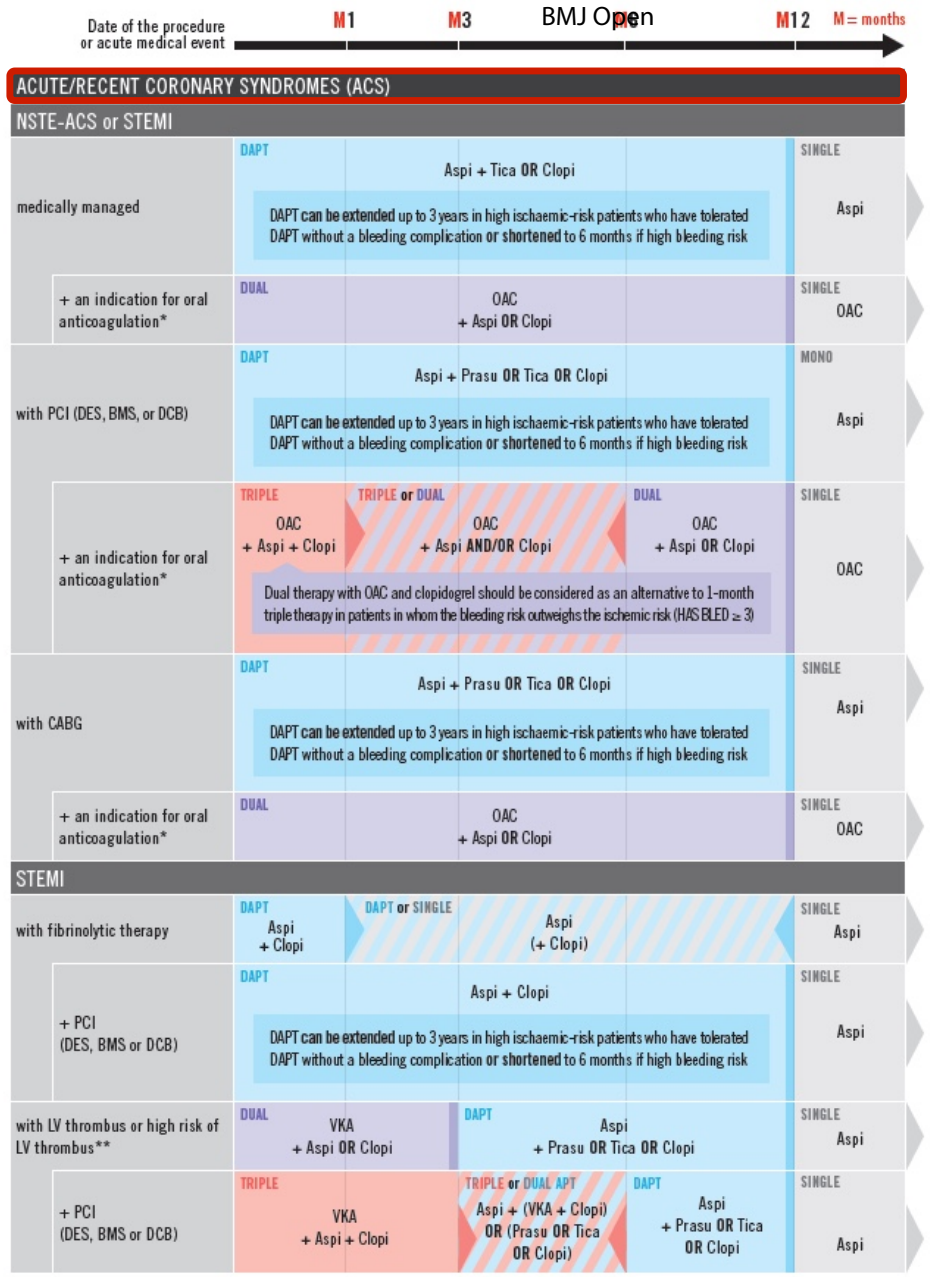
1) Aspirin 75-100 mg/day
2) OR Clopidogrel 75 mg/day

In practice

Example 2: two cardiovascular diseases

- At your medical consultation, you meet Mr V, 55 years old (weight: 81 kg, body mass index: 24 kg/m^2).
- Medical history: arterial hypertension (controlled), diabetes, renal failure (creatinine clearance with Cockcroft formula: 30 ml/min) and permanent non-valvular atrial fibrillation
- He had an acute coronary syndrome 5 months ago with a percutaneous coronary intervention (PCI)
- Which antithrombotic therapy is recommended in this clinical situation?

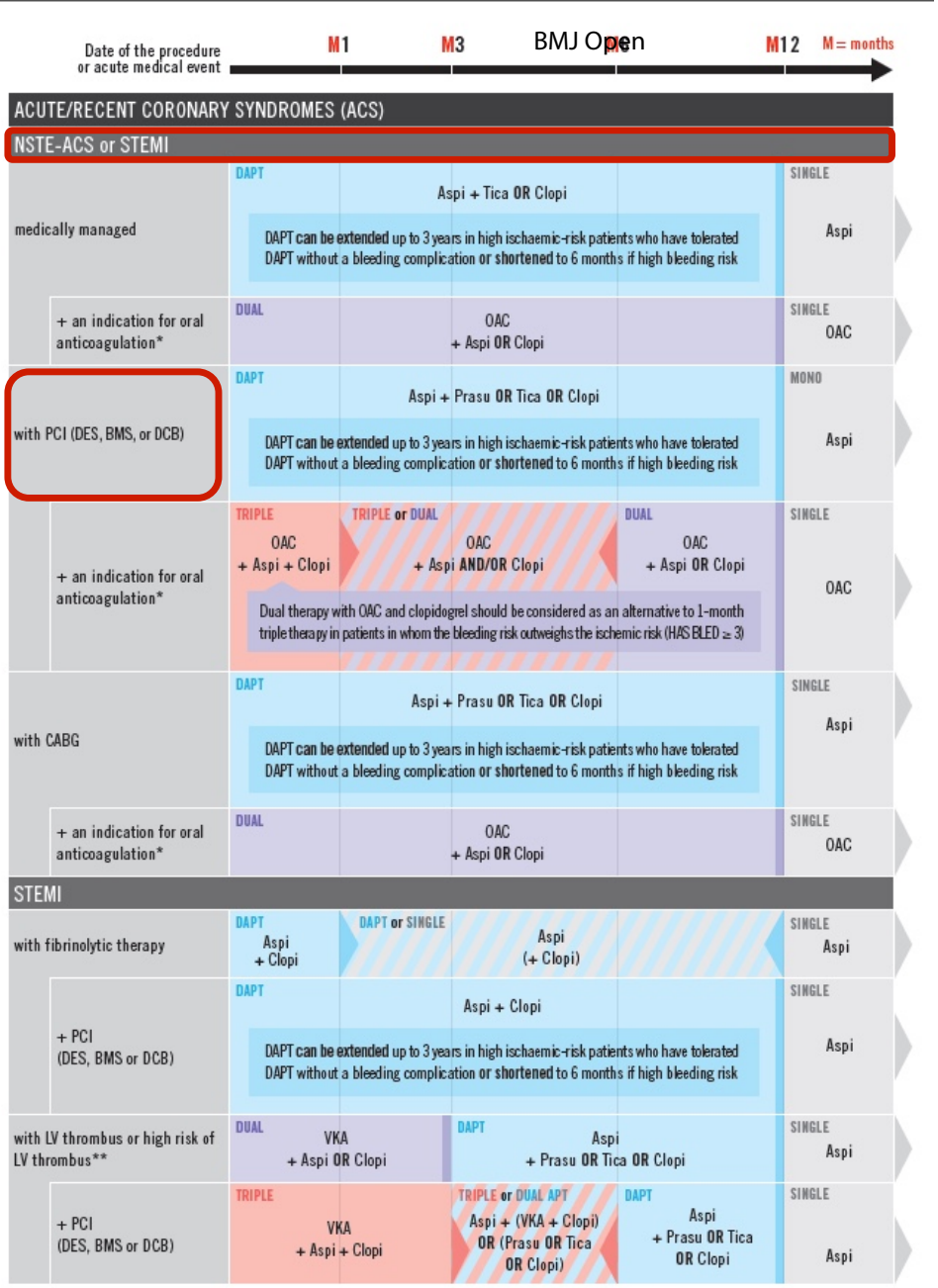
1- Locate in the chapter headings of the tool, the cardiovascular disease of your patient



* **Indication for OAC :** Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For VTE disease, OAC should be continued for 3 months if there is a triggering factor, 3 to 6 months if it is idiopathic, and for long-term if it is recurrent or associated with a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

** **High risk for LV thrombus :** Ejection Fraction < 40%, Anteroapical wall motion abnormality.

2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



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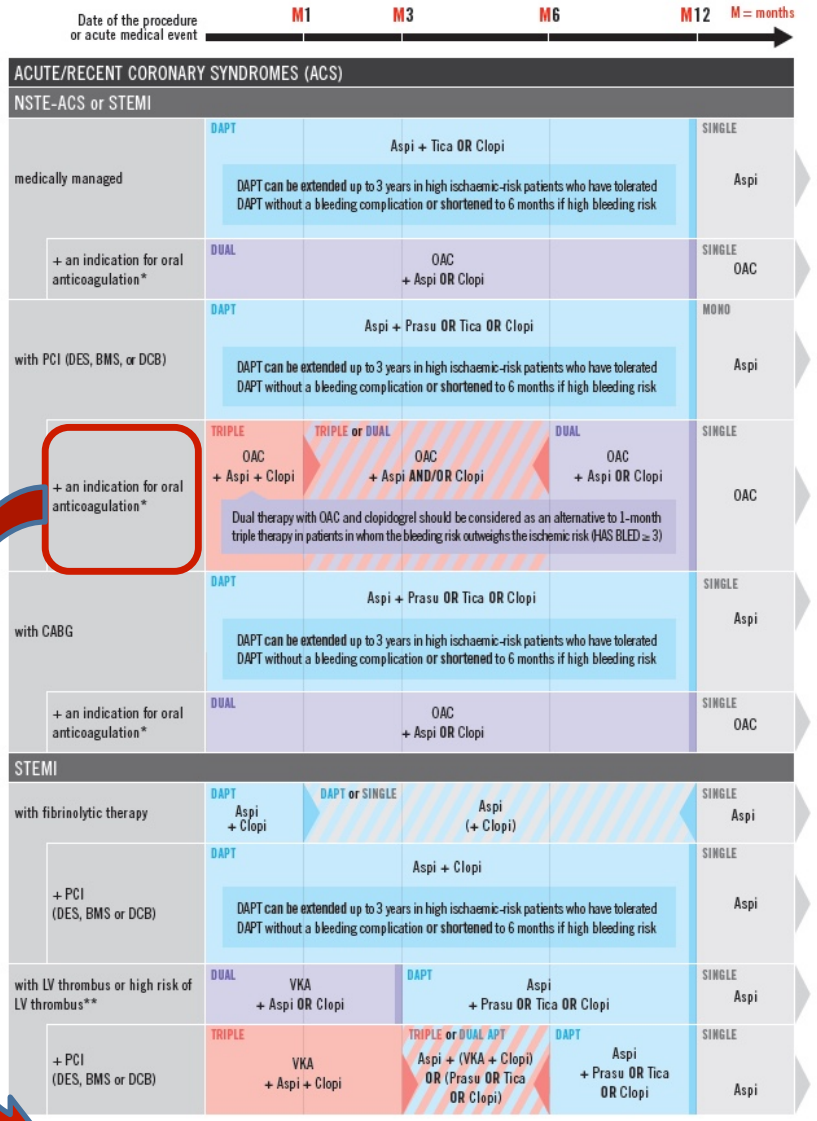
** **High risk for LV thrombus :** Ejection Fraction < 40%, Anteroapical wall motion abnormality.

2bis- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



ABBREVIATIONS

CHA2DS2-VASc **C** Congestive Heart failure (+1)
H Hypertension (+1) **A2** Age ≥ 75 (+2)
D Diabetes Mellitus (+1) **S2** Prior stroke or TIA thromboembolism (+2)
V Vascular disease (+1) **A** Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)

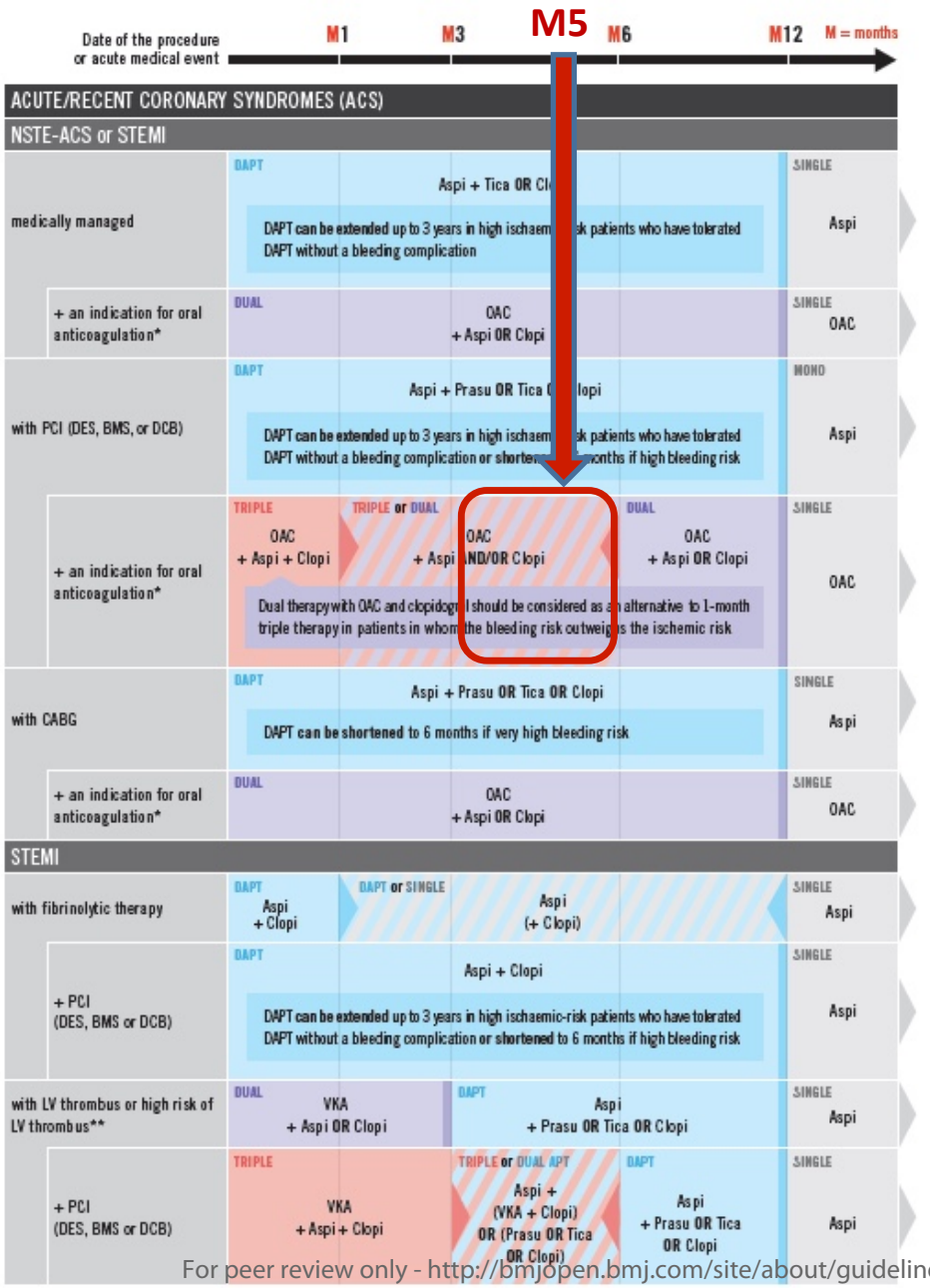
Hypertension and diabetes = 2 points
→ Indication for oral anticoagulation

HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major **B**leeding or predisposition to bleeding (+1)
Labile INR (+1) **E**lderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)

Abnormal renal function = 1 point
Drugs = 1 point
HAS BLED = 2

* **Indication for OAC:** Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of 2. For

3- In the recommended treatment, find out where your patient is currently (here: 5 months)



a pathology at risk. Once the anticoagulant treatment is complete for VTE disease, the patient will be treated as a patient without indication for oral anticoagulation.

** **High risk for LV thrombus** : Ejection Fraction < 40%, Anteroapical wall motion abnormality.

Here, two options are possible according to the ischemic and bleeding risk of your patient:

1) Dual therapy: OAC + Aspirin OR Clopidogrel up to 12 months (so for another 7 months)
2) Triple therapy: OAC + Aspirin + Clopidogrel up to 6 months (so for another 1 month) and then a dual therapy with OAC + Aspirin OR Clopidogrel up to 12 months (so for another 6 months)

4- Check the recommended dosage for the drugs you want to prescribe

SINGLE	Single Therapy: Antiplatelet (SAPT) or Anticoagulation (SACT)
DUAL APT	Dual Antiplatelet Therapy (DAPT)
DUAL	Dual Therapy (SAPT + SACT)
TRIPLE	Triple Therapy (DAPT + SACT)

Modulation between two therapies depending on patient condition (according to striped colors)

Minimum therapy duration

Maximum therapy duration

Recommended therapy duration

Abbreviations

ABCD² score for TIA Age≥60 years (+1)
Clinical features of the TIA (unilateral weakness (+2), speech disturbance without weakness (+1), other symptoms (0))
Duration of symptoms (< 10 min (0), 10-59 min (+1), ≥60 min (+2))
BP ≥ 140/90 mmHg (+1) Diabetes (+1)

ACS Acute Coronary Syndrome
Aspi Aspirin
BMS Bare-Metal Stent
CABG Coronary Artery By Pass Graft
CHA2DS2-VASc C Congestive Heart failure (+1)
H Hypertension (+1) A2 Age ≥ 75 (+2)
D Diabetes Mellitus (+1) S2 Prior stroke or TIA thromboembolism (+2)
V Vascular disease (+1) A Age 65-74 (+1)
Sc Sex category (i.e.: female sex) (+1)

Cilo Cilostazol
Clopi Clopidogrel
CTLI Chronic Limb-Threatening Ischemia
DAPT Dual Antiplatelet Therapy
DCB Drug-Coated Balloon
DES Drug-Eluting Stent
DOA Direct Oral Anticoagulant
DUAL Dual Therapy: SAPT + SACT
HAS BLED Abnormal renal / liver function (+1 or +2)
Hypertension (+1) Stroke history (+1)
Prior major Bleeding or predisposition to bleeding (+1)
Labile INR (+1) Elderly > 65 (+1)
Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)

INR International Normalized Ratio
LEAD Lower Extremity Artery Disease
LV Left Ventricular
NIHSS National Institutes of Health Stroke Scale
NSTE-ACS Non-ST Elevation Acute Coronary Syndrome
NV-AF Non-valvular atrial fibrillation
OAC Oral Anticoagulant : VKA or DOA
PCI Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu Prasugrel
SAPT Single Antiplatelet Therapy
SACT Single Anticoagulation Therapy
SCAD Stable coronary artery disease
STEMI ST-Elevation Myocardial Infarction
TAVR Transcatheter Aortic Valve Replacement
TIA Transient Ischemic Attack
Tica Ticagrelor
Triflu Triflusal
TRIPLE Triple Therapy: DAPT + SACT
VKA Vitamin K Antagonist Transcatheter Aortic Valve
VTE Venous Thromboembolism

CLINICAL SITUATIONS NOT FOUND IN THIS TOOL NEED A SPECIALIST'S OPINION

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamole: 25/200 mg twice a day
Cilostazol: 100 mg twice a day
Clopidogrel: 75 mg/day
Prasugrel: 10 mg/day (5 mg/day in patients with body weight < 60 kg)
Contraindications for prasugrel : previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds ; prasugrel is not recommended for patients >75 years of age or with a body weight <60 kg.
Ticagrelor: 90 mg twice a day
Contraindications for ticagrelor : previous intracranial haemorrhage or ongoing bleeds.
Triflusal: 600 mg/day
VKA: target INR 2-3 for NV-AF, VTE; LV thrombus
Rivaroxaban (Xarelto):
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D21: 15 mg x 2/day then from D22 onwards: 20 mg/day in a single take
- For the prevention of embolic stroke in patients with NV-AF: 20 mg/day in a single take
- No adjustment on weight, age, sex
- Renal failure
  - Contraindication with creatinine clearance < 15 ml/min
  - With creatinine clearance between 15-49 ml/min:
    - § NV-AF: 15 mg/day
    - § Venous thrombo-embolism: 15 mg x 2/day during the first three weeks then 20 mg/day in a single take
  - No adjustment beyond a creatinine clearance > 50 ml/min

Apixaban (Eliquis):
- For the prevention of embolic stroke in patients with NV-AF:
  - 5 mg x 2/day
  - NV-AF and at least two of the following: age ≥ 80 yo, weight ≤ 60 kg, serum creatinine ≥ 133 micromol/L: 2,5 mg x 2/day
  - With creatinine clearance between 15–29 ml/min: 2,5 mg x 2/day
  - Contraindication with creatinine clearance < 15 ml/min
- Venous thrombo-embolism (venous thrombosis/pulmonary embolism): D1 to D7: 10 mg x 2/day then from D8 onwards: 5 mg x 2/day

Dabigatran (Pradaxa):
- For the prevention of embolic stroke in patients with NV-AF or VTE treatment, after treatment with a parenteral anticoagulant for at least 5 days : 150 mg x 2/day
- 110 mg x 2/day if :
  - § > 80 yo
  - § Patients also treated with Verapamil
  - § clearance between 30–50 ml/min
- Contraindication with creatinine clearance < 30 ml/min

THE COCKCROFT AND GAULT FORMULA (1973)
$C_{Cr} = \{((140 - Age) \times Weight) / (72 \times S_{Cr})\} \times 0.85$ (if female)
C_{Cr} (creatinine clearance) = mL/minute
Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor [a]	
Prosthesis thrombogenicity	None	≥1
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
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INR = international normalized ratio; LVEF = left ventricular ejection fraction
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OAC :
- VKA with a target INR: 2–3
- Rivaroxaban 15 mg/day
- Apixaban 5 mg X 2/day
- Dabigatran is contraindicated

Antiplatelets:
- Aspirin 75-100 mg/day
- Clopidogrel 75 mg/day

Appendix 2: Example of a clinical vignette

At your medical consultation, you meet Mr R, 86 years old (weight: 81 kg, body mass index: 24 kg/m^2). Mr R is a widower, a smoker (10 cigarettes a day, 50 pack-years) and is autonomous in all daily activities. He has no personal medical history and he takes no drug. His last biological test did not find any abnormalities (serum creatinine value: 77 µM/L, creatinine clearance using the Cockcroft-Gault formula: 70 ml/min).
He comes to see you in consultation because for more than 1 week, he has had palpitations with exercise. You perform electrocardiogram (ECG) in your office and you diagnose non-valvular atrial fibrillation. The biological assessment is without particularity (in particular blood ionography and thyroid-stimulating hormone). Cardiac ultrasonography revealed a dilated left atrium with no valve abnormality.

1) How many antithrombotic treatments will you prescribe during this consultation?

- 0
- 1
- 2
- 3

2) If you answered 0 to question 1, go to question 5. If not, which molecule(s) of antithrombotic(s) will you prescribe during this consultation?

- Warfarin
- Rivaroxaban
- Apixaban
- Aspirin
- Clopidogrel

3) Which dosage will you prescribe this(these) molecule(s)? (For each molecule checked on the previous question, it will appear:)

- Warfarin:
  - INR (International Normalized Ratio): 2-3
  - INR (International Normalized Ratio): 2.5-3.5
- Rivaroxaban
  - 15 mg per day
  - 20 mg per day
- Apixaban
  - 2.5 mg twice a day
  - 5 mg twice a day
- Aspirin
  - 75-100 mg per day
  - 300 mg per day
- Clopidogrel
  - 75 mg per day
  - 300 mg per day

4) How long does the antithrombotic treatment prescribed in the previous question need to be continued?

- 1 month
- 6 months
- 12 months
- For life

5) On a scale of 0 to 10, what is your degree of confidence in the adequacy of your prescription in relation to the guidelines?

For the experimental group, after completion of the 3 clinical vignettes:

Regarding the prescription support tool, please note the following items from 0 (strongly disagree) to 10 (strongly agree):

- The prescription support-tool helped me answer to the clinical vignettes:../10
- The prescription support-tool has modified the answers that I spontaneously made to clinical vignettes:../10
- The prescription support-tool is clear:../10
- The prescription support-tool is operational:../10
- The prescription support-tool is useful for practice:../10
- I would be ready to use this prescription support-tool:../10
- I would recommend the use of this prescription support-tool:../10

Notes on the tool: What are the points of the prescription support-tool that could be improved: useless information, missing information, presentation, etc:

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → **Page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → **Page 2 line 53, Page 12 line 275**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → **line 270 - 274, page 12**
Funding	4	Sources and types of financial, material, and other support → **line 268, page 12**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → **Title page and lines 263 - 267 page 12**
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → **Lines 67 – 97, page 4 - 5**
	6b	Explanation for choice of comparators

Objectives	7	Specific objectives or hypotheses → **Lines 98 - 101, page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → **Lines 106 - 108 page 5**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → **Lines 106 - 108 page 5**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → **Lines 109 - 136, page 5 - 6**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → **Lines 148 – 159, page 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → **Lines 109 - 136, page 5 - 6**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **→ Lines 208 – 213, page 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size → **Lines 146-147, page 7**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Lines 137 – 143, page 6-7** **Lines 198 - 201 page 9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Lines 198 - 201 page 9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Lines 198 - 201 page 9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **→ Lines 202 – 206 page 9**

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol → **Lines 202 – 206 page 9**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → **Lines 214 - 230, page 9-10**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) → **Lines 226 - 227, page 10**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → **Lines 248 – 249 page 11 and Lines 270 - 274 page 12**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → **Lines 204 - 205, page 9**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → **Line 269, page 12**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators → **Lines 277 – 278, page 12**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → **Lines 256 - 257, page 11**
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT