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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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Complete List of Authors:	<p>ZERAH, Lorene; Sorbonne Université, Faculté de médecine Sorbonne Université, INSERM, UMR 1123; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p> <p>Bonnet-Zamponi, Dominique; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi); Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique Ile de France, OMEDIT</p> <p>Frappé, Paul; Institut de recherche en médecine générale; University of Saint-Etienne, Department of General Practice</p> <p>Hauguel-Moreau, Marie; Assistance Publique - Hopitaux de Paris, Département de cardiologie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>De Rycke, Yann; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p> <p>Magnier, Anne-Marie; Assistance Publique - Hopitaux de Paris, Département de médecine générale, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Pautas, Eric; Assistance Publique - Hopitaux de Paris, Département de gériatrie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Charles, Pierre; Institut Mutualiste Montsouris, Médecine Interne</p> <p>Collet, Jean-philippe; Assistance Publique - Hopitaux de Paris, Département de cardiologie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Dechartres, Agnes; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p> <p>Tubach, Florence; Sorbonne Université, Faculté de médecine Sorbonne Université, INSERM, UMR 1123; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p>
Keywords:	prescription support-tool, clinical vignettes, antithrombotic combination

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

4

5 Zerah L¹, Bonnet-Zamponi D^{1,2}, Frappé P^{3,4}, Hauguel-Moreau M⁵, De Rycke Y¹, Magnier
6 AM⁶, Pautas E⁷, Charles P⁸, Collet JP⁵, Dechartres A¹, Tubach F¹

- 7 1. Sorbonne Université, Faculté de médecine Sorbonne Université, AP-HP, Hôpital Pitié-
8 Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre
9 de Pharmacoépidémiologie (Cephepi), INSERM, UMR 1123, CIC-P 1421, F-75013 Paris,
10 France
11 2. Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique
12 Ile de France (OMEDIT), Paris, France.
13 3. Institut de recherche en médecine générale, Paris, France
14 4. Department of General Practice, University of Saint-Etienne, Saint-Etienne, France
15 5. Sorbonne Université, Faculté de médecine Sorbonne Université, AP-HP, Département de
16 cardiologie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix, 75013 Paris, France
17 6. Sorbonne Université, Faculté de médecine Sorbonne Université, AP-HP, Département de
18 médecine générale, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix, 75013 Paris,
19 France
20 7. Sorbonne Université, Faculté de médecine Sorbonne Université, AP-HP, Département de
21 gériatrie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix, 75013 Paris, France
22 8. Département de médecine interne, Institut Mutualiste Montsouris, 75014 Paris, France

23
24 * **Corresponding author: Dr Lorene Zerah**

25 Correspondence to: lorene.zerah@inserm.fr

26 Address: Département Biostatistique Santé Publique et Information Médicale, Centre de
27 Pharmacoépidémiologie (Cephepi), Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l'hôpital,
28 75013, Paris, France

29 Tel: +33 1 42 16 03 47

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3 30 **ABSTRACT**

4 31 **Introduction:** Oral antithrombotic (AT) drugs are widely implicated in serious and
5
6 32 preventable bleeding events, which justifies the implementation of risk minimization actions.
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8 33 Avoiding inappropriate oral AT combinations is a major concern, particularly for patients
9
10 34 with multiple chronic conditions. The first step is to provide fast and easy access to the latest
11
12 35 recommendations. From a systematic review of international guidelines (2012-2017), we
13
14 36 developed a prescription support-tool synthesizing national and international guidelines on
15
16 37 chronic management (≥ 1 month) of oral AT agents without considering in-hospital
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18 38 management and bridging therapy. Our main objective in this study is to evaluate the
19
20 39 accuracy of this tool by measuring the appropriateness of oral AT prescriptions according to
21
22 40 the most recent guidelines.
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28 42 **Methods and analysis:** In this web-based randomized controlled trial, participating French
29
30 43 general practitioners and cardiologists in the outpatient setting will be randomized by use or
31
32 44 not of the prescription support-tool. They will be asked to provide the number of drugs, drug
33
34 45 class, duration and dosage of ATs, within a time window of 10 minutes, for 3 different
35
36 46 clinical situations presented as clinical vignettes (multiple-choice questions). The scientific
37
38 47 committee has created and validated 30 clinical vignettes illustrating outpatient clinical
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40 48 situations for which the use of oral ATs (single, dual or triple therapy) is recommended or not
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42 49 according to the guidelines. All data will be treated anonymously.
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48 51 **Ethics and dissemination:** If the prescription support-tool is associated with more
49
50 52 appropriate prescription of AT combinations, its dissemination to further evaluate outcome
51
52 53 data including haemorrhage, ischemic events, and death will be considered.
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3 54 **Article summary: strengths and limitations of this study**
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5 55 • Strengths:

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7 56 ○ Importance of the study: this study will evaluate a new prescription support-tool
8
9 57 for oral antithrombotic (AT) combination. If the intervention is found to be
10
11 58 effective, it has the potential to avoid a lot of adverse drugs events.

12
13 59 ○ Robust intervention development: first, the prescription support-tool was
14
15 60 developed from a systematic review of international guidelines (2012-2017).
16
17 61 Second, a scientific committee and an expert committee have validated all clinical
18
19 62 vignettes that we will use to evaluate the tool.

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21 63 ○ This is a multicentric, randomized study, with several medical specialties
22
23 64 represented.

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26 65 • Potential study limitations:

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28 66 ○ Bias toward selected physicians who may not be representative of general
29
30 67 practitioners or cardiologists because they volunteered.

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32 68 ○ Access to the prescription support-tool in the control group cannot be avoided.

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34 69 ○ Generalisability: this study will be undertaken in France. Although this may limit
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36 70 generalisability, the prescription support-tool was developed from a systematic
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38 71 review of international guidelines from all over the world.
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72 INTRODUCTION

73 Background

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

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

95 Study objectives and trial design

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2
3 96 Our main hypothesis is that the prescription support-tool increases the rate of “right
4 97 prescription of oral AT combinations” as defined according to the most recent guidelines.

5
6
7 98 The primary objective will be to evaluate the impact of this tool on the global appropriateness
8
9 99 of oral AT prescriptions according to the most recent guidelines (in terms of number of drugs,
10
11 100 drug class, duration and dosage: composite score).

12
13 101 Secondary objectives will be to evaluate the impact of this tool on the appropriateness of oral
14
15 102 AT prescriptions according to the most recent guidelines in terms of the (1) number of drugs,
16
17 103 (2) drug class, (3) dosage, (4) duration, (5) and combinations that should never be prescribed.

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19
20 104 We will also evaluate whether the impact of this tool differs by medical specialty of
21
22 105 physicians responding. Finally, we will evaluate the degree of certainty physicians have about
23
24 106 their AT prescriptions in line with the guidelines. In the experimental group, we will assess
25
26 107 the use of the prescription support-tool to answer questions about clinical vignettes and the
27
28 108 degree of the tool’s perceived usefulness by physicians.

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31 109 This trial is designed as a web-based, open randomized controlled trial with two parallel
32
33 110 groups.

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35 111

36 37 112 **METHODS AND ANALYSIS**

38 39 113 **Study design**

40
41 114 A web-based, open randomized controlled trial involving clinical vignettes will be performed
42
43 115 in France. Clinical vignettes illustrating plausible situations will be used because they reflect
44
45 116 clinical practice.[6,7] Such an approach has been found valid in measuring quality of
46
47 117 care.[8,9] The randomization unit will be the physician and the unit of analysis the clinical
48
49 118 vignette. Our study will involve a scientific committee and an expert committee. The
50
51 119 scientific committee consists of a cardiologist, 2 internist-geriatricians, a general practitioner
52
53 120 and 2 epidemiologists. The scientific committee designed the study protocol, created and
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3 [121](#) validated the clinical vignettes and will be responsible for data analysis and writing the
4
5 [122](#) manuscript. The expert committee consists of a cardiologist, a geriatrician, an internist and a
6
7 [123](#) general practitioner (medical specialties that often deal with patients needing chronic oral AT
8
9 [124](#) prescriptions). The expert committee had to review all clinical vignettes with the prescription
10
11 [125](#) support-tool (external validation) to confirm their agreement with clinical practice and their
12
13 [126](#) readability and to estimate the time needed to complete 3 clinical vignettes.

[127](#) **Development of clinical vignettes**

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17
18 [128](#) Two physicians (1 cardiologist and 1 internist-geriatrician) created 30 clinical vignettes
19
20 [129](#) covering most outpatient clinical situations for which the long-term use of ATs (single, dual
21
22 [130](#) or triple therapy) is recommended or not. An example of a clinical vignette is presented in

[131](#) **Appendix 1.**

[132](#) **Prescription support tool**

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28 [133](#) This tool is derived from a systematic review of guidelines (N = 63) dealing with the use of
29
30 [134](#) oral ATs for NV-AF, coronary artery disease, ischemic stroke, valvular heart disease,
31
32 [135](#) peripheral artery disease and venous thromboembolism. These pathologies were selected
33
34 [136](#) because most prescriptions of ATs are related to neuro-cardiovascular diseases and because
35
36 [137](#) we would provide a synthesis relevant for clinicians in charge of the follow-up of patients
37
38 [138](#) with oral AT combinations, including patients with more than one indication for AT.
39
40 [139](#) Indication, type of drugs combined, dosage and duration of prescription are synthesized in
41
42 [140](#) this easy-to-use tool, which fits on one double-sided page and can be stored in a physician's
43
44 [141](#) pocket. Our tool also specifies the type of ATs that should never be combined (combinations
45
46 [142](#) of oral anticoagulant (OAC), combinations of P2Y12 inhibitors or the combination of one
47
48 [143](#) OAC with one potent P2Y12 inhibitor, namely ticagrelor or prasugrel), the clinical situations
49
50 [144](#) in which oral AT combinations are never indicated and the contraindications of ATs. The full
51
52 [145](#) description of this tool is under review elsewhere.

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3 **146 Study setting and eligibility criteria**

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5 **147** This study will be conducted among French practicing physicians who are involved in
6
7 **148** outpatient settings, including general practitioners and cardiologists. Physicians with an
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9 **149** exclusive hospital practice will not be considered. Physicians will be identified and contacted
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11 **150** for participation directly by email via physicians' associations. Each physician willing to
12
13 **151** participate will complete, after providing their consent to participate, a questionnaire via a
14
15 **152** web-based survey, including questions on age, sex, medical specialty, and years of medical
16
17 **153** practice. Physicians will be asked about the approximate proportion of patients with oral AT
18
19 **154** combinations in their practice ($\leq 5\%$, 6–10%, 11–20% or $\geq 21\%$), whether they feel
20
21 **155** comfortable or not with management of oral AT prescriptions (totally, partially, rarely, never)
22
23 **156** and whether they know where to find the most recent guidelines on oral AT prescriptions.

24
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26 **157 Intervention**

27
28 **158** Selected physicians will be randomized to 2 groups by use or not of the prescription support-
29
30 **159** tool. In the control group, no tool will be provided. In the experimental group, the tool will be
31
32 **160** provided with an explanatory guide. All selected physicians will receive 3 different clinical
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34 **161** vignettes, each corresponding to a specific situation for which the physician will have to
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36 **162** indicate the “right prescription” of ATs by answering a multiple-choice question, with the
37
38 **163** number, type, duration and dosage of AT provided. They will have to state their degree of
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40 **164** certainty with the prescription. The total completion time will be approximately 10 minutes
41
42 **165** and physicians will be able to stop and continue at any time. Physicians from the control
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44 **166** group will receive the prescription support-tool once they have completed their answers for
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46 **167** the 3 clinical vignettes. To maximize the participation rate, after being selected, physicians
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48 **168** will be sent reminders every 20 days.

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52 **169 Outcomes**

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3 170 The primary outcome measure is the rate of the “right prescription of oral ATs” as defined
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5 171 according to the guidelines in terms of number, class, duration and dosage between the two
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7 172 groups.

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9 173 Secondary outcomes are (1) the primary outcome by physicians’ specialty and (2) the
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11 174 difference between the control and intervention groups in the degree of confidence physicians
12
13 175 have in their AT prescriptions in line with the guidelines. The prescription support-tool,
14
15 176 synthesizing national and international guidelines on chronic management of oral AT
16
17 177 prescriptions, will be the reference.

18 19 20 178 **Randomization**

21
22 179 Concealment and balance between trial arms will be achieved by using a computer-generated
23
24 180 randomization scheme, stratified by whether the physician is a general practitioner or a
25
26 181 cardiologist, in blocks of 4. The clinical vignettes assignment will be randomized in blocks of
27
28 182 30. Physicians allocated to receive the prescription support-tool will be asked to comment on
29
30 183 the overall usefulness of the tool.

31 32 33 184 **Data collection methods and data management**

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35 185 The dedicated website was designed by an engineer. Data from physicians’ answers will be
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37 186 automatically integrated in a database for statistical analysis. The data will be completely
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39 187 anonymous. In particular, neither the physician’s name nor email address will be collected.
40
41 188 There is no planned follow-up in this trial.

42 43 44 189 **Patient and Public Involvement**

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46 190 Patients and / or the public have not been involved in the development of the research or in
47
48 191 the study design because the randomization unit will be the physicians and the unit of analysis
49
50 192 the clinical vignette. The main objective of this study is to evaluate a tool for physicians to
51
52 193 help them with their prescriptions of ATs.

53 54 55 194 **Sample size and statistical considerations**

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3 195 In considering that 85% of AT prescriptions is appropriate[5] in the control group and hoping
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5 196 to demonstrate an increase in this proportion up to 90% with the support-tool as well as that
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7 197 each physician will complete 3 clinical vignettes, we will need to include (for a power of 80%
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9 198 and an alpha risk of 5%) a minimum of 229 physicians per group. To obtain a multiple of 10
10
11 199 for the randomization (because each physician will complete 3 vignettes), we hope to include
12
13 200 at least 230 physicians per group. If more physicians are willing to participate, all collected
14
15 201 data will be considered. A generalized mixed model with a clinical-vignette effect and a
16
17 202 physician-effect nested in the arm of the study will be used. All analyses will involve use of R
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19 203 v3.4.0 (www.cran.r-project.org).
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205 **ETHICS AND DISSEMINATION**

26 206 Results of this study will be disseminated in a paper submitted to a peer-reviewed journal and
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28 207 presentations at relevant conferences. If the use of the prescription support-tool is associated
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30 208 with an increased rate of appropriate prescribing of oral AT combinations, we will further
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32 209 consider wide dissemination of the support-tool among physicians and evaluate the impact of
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34 210 this diffusion on patients' clinical outcomes (bleeding events, ischemic events, death).
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3 211 **ACKNOWLEDGMENTS**

4 212 **Authors' contributions:** LZ, DBZ, AD and FT designed the study. LZ and MH designed the
5
6
7 213 clinical vignettes and all authors reviewed and validated them. LZ drafted and prepared the
8
9 214 manuscript for publication. All authors re-read and corrected the manuscript. All authors
10
11 215 approved the final manuscript.

12
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14
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16
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18
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20
21 220 **Ethics approval:** The ethics evaluation committee of Inserm, the *Institutional Review Board*
22
23 221 (IRB00003888) has reviewed and approved our research project on 06/12/2018: number 18-
24
25 222 492.

26
27 223 **Trial registration:** submitted to ClinicalTrials.gov (Protocol version 06/21/2018).

28
29 224 **The study start date is summer 2018.**
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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/m²). 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

1
2
3 **4) How long does the antithrombotic treatment prescribed in the previous question need**
4 **to be continued?**

- 5
- 6 • 1 month
 - 7 • 6 months
 - 8 • 12 months
 - 9 • For life
- 10

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

13
14
15
16 **For the experimental group, after completion of the 3 clinical vignettes:**

17
18
19 **Regarding the prescription support tool, please note the following items from 0 (strongly**
20 **disagree) to 10 (strongly agree):**

- 21
- 22 • The prescription support-tool helped me answer to the clinical vignettes:../10
 - 23 • The prescription support-tool has modified the answers that I spontaneously made to
 - 24 clinical vignettes:../10
 - 25 • The prescription support-tool is clear:../10
 - 26 • The prescription support-tool is operational:../10
 - 27 • The prescription support-tool is useful for practice:../10
 - 28 • I would be ready to use this prescription support-tool:../10
 - 29 • I would recommend the use of this prescription support-tool:../10
- 30
31
32

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

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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

1	Objectives	7	Specific objectives or hypotheses → Lines 96 – 108, page 5
2			
3			
4	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
5			
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7			
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9			
10	Methods: Participants, interventions, and outcomes		
11			
12	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
13			
14			
15			
16			
17	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
18			
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21			
22			
23	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
24			
25			
26			
27		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)
28			
29			
30			
31		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
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33			
34			
35			
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
37			
38			
39	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
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48	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
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2	Sample size	14	Estimated number of participants needed to achieve study objectives
3			and how it was determined, including clinical and statistical
4			assumptions supporting any sample size calculations
5			→ Lines 195 – 200, page 9
6			
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
8			target sample size
9			→ Lines 167 – 168 page 7

Methods: Assignment of interventions (for controlled trials)

Allocation:

14			
15	Sequence	16a	Method of generating the allocation sequence (eg, computer-
16	generation		generated random numbers), and list of any factors for stratification.
17			To reduce predictability of a random sequence, details of any planned
18			restriction (eg, blocking) should be provided in a separate document
19			that is unavailable to those who enrol participants or assign
20			interventions
21			Lines 179 – 183 page 8
22			
23			
24	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
25	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
26	mechanism		describing any steps to conceal the sequence until interventions are
27			assigned
28			Lines 179 – 183 page 8
29			
30			
31	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
32			and who will assign participants to interventions
33			Lines 179 – 183 page 8
34			
35	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
36	(masking)		participants, care providers, outcome assessors, data analysts), and
37			how
38			
39		17b	If blinded, circumstances under which unblinding is permissible, and
40			procedure for revealing a participant's allocated intervention during
41			the trial

Methods: Data collection, management, and analysis

44			
45	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
46	methods		trial data, including any related processes to promote data quality (eg,
47			duplicate measurements, training of assessors) and a description of
48			study instruments (eg, questionnaires, laboratory tests) along with
49			their reliability and validity, if known. Reference to where data
50			collection forms can be found, if not in the protocol
51			→ Lines 185 – 188 page 8
52			
53			
54		18b	Plans to promote participant retention and complete follow-up,
55			including list of any outcome data to be collected for participants who
56			discontinue or deviate from intervention protocols
57			
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2	Data	19	Plans for data entry, coding, security, and storage, including any
3	management		related processes to promote data quality (eg, double data entry;
4			range checks for data values). Reference to where details of data
5			management procedures can be found, if not in the protocol
6			→ Lines 185 – 188 page 8
7			
8	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
9	methods		Reference to where other details of the statistical analysis plan can be
10			found, if not in the protocol
11			→ Lines 201 – 203, page 9
12			
13		20b	Methods for any additional analyses (eg, subgroup and adjusted
14			analyses)
15			
16		20c	Definition of analysis population relating to protocol non-adherence
17			(eg, as randomised analysis), and any statistical methods to handle
18			missing data (eg, multiple imputation)
19			

Methods: Monitoring

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21			
22	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
23			and reporting structure; statement of whether it is independent from
24			the sponsor and competing interests; and reference to where further
25			details about its charter can be found, if not in the protocol.
26			Alternatively, an explanation of why a DMC is not needed
27			
28		21b	Description of any interim analyses and stopping guidelines, including
29			who will have access to these interim results and make the final
30			decision to terminate the trial
31			
32			
33	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
34			spontaneously reported adverse events and other unintended effects
35			of trial interventions or trial conduct
36			
37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
38			whether the process will be independent from investigators and the
39			sponsor
40			

Ethics and dissemination

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42			
43	Research ethics	24	Plans for seeking research ethics committee/institutional review board
44	approval		(REC/IRB) approval
45			→ Lines 206 – 210 page 9
46			
47			
48	Protocol	25	Plans for communicating important protocol modifications (eg,
49	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
50			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
51			regulators)
52			
53	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
54			participants or authorised surrogates, and how (see Item 32)
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1		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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3			
4	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
5			→ Lines 186 – 187, page 8
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
11			→ Line 213, page 9
12			
13			
14	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
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18	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
19			
20			
21	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
22			→ Lines 206 – 207, page 9
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28		31b	Authorship eligibility guidelines and any intended use of professional writers
29			
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31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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34	Appendices		
35			
36	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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39	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
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Complete List of Authors:	<p>ZERAH, Lorene; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMR1123; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de Pharmacoepidémiologie (Cephepi), CIC-1421</p> <p>Bonnet-Zamponi, Dominique; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de Pharmacoepidémiologie (Cephepi), CIC-1421; Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique Ile de France, OMEDIT</p> <p>Frappé, Paul; Institut de recherche en médecine générale; University of Saint-Etienne, Department of General Practice</p> <p>Hauguel-Moreau, Marie; Assistance Publique - Hopitaux de Paris, Département de cardiologie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>De Rycke, Yann; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de Pharmacoepidémiologie (Cephepi), CIC-1421</p> <p>Magnier, Anne-Marie; Assistance Publique - Hopitaux de Paris, Département de médecine générale, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Pautas, Eric; Assistance Publique - Hopitaux de Paris, Département de gériatrie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Charles, Pierre; Institut Mutualiste Montsouris, Médecine Interne</p> <p>Collet, Jean-philippe; Assistance Publique - Hopitaux de Paris, Département de cardiologie, Hôpitaux universitaires Pitié-Salpêtrière-Charles Foix</p> <p>Dechartres, Agnes; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de Pharmacoepidémiologie (Cephepi), CIC-1421; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMR1136</p> <p>Tubach, Florence; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMR1123; AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de Pharmacoepidémiologie (Cephepi), CIC-1421</p>

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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

SCHOLARONE™
Manuscripts

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3 **Evaluation of a prescription support-tool for chronic management of oral**
4 **antithrombotic combinations in adults using clinical vignettes: protocol of a randomized**
5 **controlled trial**
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11
12 Zerah L¹, Bonnet-Zamponi D^{1,2}, Frappé P^{3,4}, Hauguel-Moreau M⁵, De Rycke Y¹, Magnier
13 AM⁶, Pautas E⁷, Charles P⁸, Collet JP⁵, Dechartres A⁹, Tubach F¹
14
15

- 16
17 1. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
18 Publique, UMR1123, AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé
19 Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de
20 Pharmacoépidémiologie (Cephepi), CIC-1421, Paris, France
21
22 2. Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique
23 Ile de France (OMEDIT), Paris, France.
24
25 3. Institut de recherche en médecine générale, Paris, France
26
27 4. Department of General Practice, University of Saint-Etienne, Saint-Etienne, France
28
29 5. Sorbonne Université, AP-HP, Département de cardiologie, Hôpitaux universitaires Pitié-
30 Salpêtrière-Charles Foix, 75013 Paris, France
31
32 6. Sorbonne Université, AP-HP, Département de médecine générale, Hôpitaux universitaires
33 Pitié-Salpêtrière-Charles Foix, 75013 Paris, France
34
35 7. Sorbonne Université, AP-HP, Département de gériatrie, Hôpitaux universitaires Pitié-
36 Salpêtrière-Charles Foix, 75013 Paris, France
37
38 8. Département de médecine interne, Institut Mutualiste Montsouris, 75014 Paris, France
39
40 9. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
41 Publique, UMR1136, AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé
42 Publique et Information Médicale, Unité de Recherche Clinique PSL-CFX, Centre de
43 Pharmacoépidémiologie (Cephepi), CIC-1421, Paris, France
44
45
46

47 *** Corresponding author: Dr Lorene Zerah**

48 Correspondence to: lorene.zerah@inserm.fr

49
50
51 Address: Département Biostatistique Santé Publique et Information Médicale, Centre de
52 Pharmacoépidémiologie (Cephepi), Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l'hôpital,
53 75013, Paris, France
54

55
56 Tel: +33 1 42 16 03 47
57
58
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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

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3 combinations were numerous (n=63) and none encompassed all the clinical situations
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5 requiring oral AT combinations. This review highlighted the difficulty for a physician to
6
7 quickly find the most up-to-date recommendation and the one most relevant to the patient's
8
9 clinical situation. These findings agreed with clinical experience and led us to synthesize all
10
11 the recommendations into a prescription support-tool (L Zerah et al, A comprehensive
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13 prescription support-tool for chronic management of oral antithrombotic combinations in
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15 adults based on a systematic review of international guidelines) to help physicians prescribe
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17 oral AT combinations.
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21 Our hypothesis is that this prescription support-tool would improve the prescription of oral
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23 AT prescriptions to comply with guidelines. Our primary objective is to assess the impact of
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25 this tool on improving the prescription of oral AT combinations to comply with guidelines (in
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27 terms of number of drugs, drug class, duration and dosage at the same time.
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32 33 **METHODS AND ANALYSIS**

34 35 **Study design, study setting and eligibility criteria**

36
37 A web-based, open randomized controlled trial involving clinical vignettes will be performed
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39 in France via an online survey. This study will be conducted among French general
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41 practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive
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43 hospital practice will not be eligible.
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47 Physicians will be identified and contacted to participate in the online survey by email via
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49 physician associations, social networks or word of mouth. The survey will gather information
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51 on physicians' characteristics, including age, sex, medical specialty, place of exercise, years
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53 of medical practice, approximate proportion of patients prescribed oral AT combinations in
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55 their practice, whether physicians feel comfortable or not with management of oral AT
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57 prescriptions, and whether physicians know where to find the most recent guidelines on oral
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3 AT prescriptions. Then, physicians will be randomized to 2 arms: the experimental arm,
4 having access to the prescription support-tool, and the control arm, with no prescription
5 support-tool. For physicians in the experimental arm, the prescription support-tool will be
6 provided with an explanatory guide, both downloaded (or just viewed) online in pdf format.
7
8 Then, participants from both arms will be presented 3 different clinical vignettes illustrating
9 outpatient clinical situations and will be asked to propose prescriptions for each vignette (AT
10 or not, number of ATs, type, duration and dosage of each AT) by answering 5 multiple-choice
11 questions (each question on a separate web page). Physicians in the experimental arm will
12 answer each question with the help of the tool, downloadable (or viewable on each page).
13
14 Physicians in the control arm will be asked to answer according to their actual clinical
15 practice as closely as possible. Once the answer is given, physicians cannot go back or change
16 their answer. Physicians must answer the questions consecutively; however, they will be
17 allowed to stop and continue at any time (on the same computer). Physicians from the control
18 arm will be able to download the prescription support-tool once they have completed their
19 answers for the 3 clinical vignettes.
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37 The scientific and expert committee have created and validated 30 clinical vignettes. To
38 ensure that each clinical vignette will be read the same number of times in both arms, we
39 created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical
40 vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm
41 in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized,
42 all clinical vignettes will be read once. The randomization unit will be the physician and the
43 unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle
44 ground to ensure the feasibility of the study considering both participants' availability
45 (acceptable time to complete the clinical vignettes) and statistical need (number of vignettes
46 needed). To maximize the participation rate, physicians will be sent reminders every 20 days.
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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

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

25 26 **Clinical vignettes**

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

51 **Randomization**

52
53 Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated
54 randomization scheme implemented in the online survey (1:1 ratio), then stratified by their
55 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

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3 practice and their readability. The committee estimated the time needed to complete 3 clinical
4 vignettes at 10 minutes.
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7 **Patient and Public Involvement**

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

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23 The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888)
24 approved our research project (no. 18-492). If the prescription support-tool is associated with
25 improving the prescription of oral AT combinations to comply with guidelines, it will be
26 disseminated to help improve AT combination prescriptions. Moreover, we will create an
27 interactive web tool to improve the ergonomics of the tool and to facilitate the updates. We
28 will assess the impact of this interactive web tool in terms of clinical outcomes in real life.
29 This will be the second step, but we feel that we must first demonstrate that the use of the tool
30 is associated with better prescription appropriateness before launching a trial involving
31 patients with clinical outcomes. Results of this trial will be disseminated in a paper submitted
32 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

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

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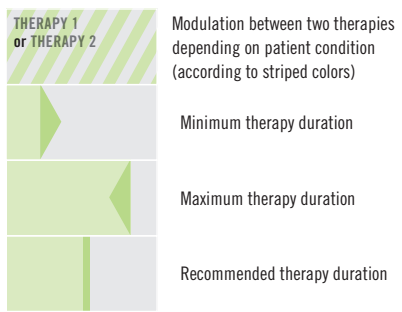
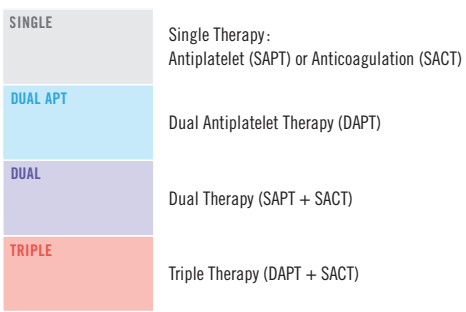
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2018 SYNTHESIS OF RECOMMENDATIONS FOR CHRONIC MANAGEMENT OF ANTITHROMBOTIC COMBINATIONS

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 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

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)
 $C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight})}{(72 \times S_{Cr})} \times 0.85$ (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



Prosthesis thrombogenicity	Patient-related risk factor ^a	
	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

STABLE CORONARY ARTERY DISEASE (SCAD)					
	DAPT	Aspi + Clopi	DAPT or SINGLE	SINGLE	
with PCI (DES, BMS or DCB)			Aspi (+ Clopi)	Aspi	
	DAPT can be extended to 30 months if no bleeding risk or shortened to 1-3 months if high bleeding risk				
+ an indication for oral anticoagulation**	TRIPLE OAC + Aspi + Clopi	TRIPLE or DUAL OAC + Aspi AND/OR Clopi	DUAL OAC + Aspi OR Clopi	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		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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Date of the procedure or acute medical event

M1

M3

M6

M12

M = months

ACUTE/RECENT CORONARY SYNDROMES (ACS)				
1 NSTEMI-ACS or STEMI				
2 medically managed	DAPT	Aspi + Tica OR Clopi		SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication			Aspi
	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
3 + an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
4 with PCI (DES, BMS, or DCB)	DAPT	Aspi + Prasu OR Tica OR Clopi		MONO
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			Aspi
	TRIPLE	TRIPLE or DUAL	DUAL	SINGLE
5 + an indication for oral anticoagulation*	OAC + Aspi + Clopi	OAC + Aspi AND/OR Clopi	OAC + Aspi OR Clopi	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				
6 with CABG	DAPT	Aspi + Prasu OR Tica OR Clopi		SINGLE
	DAPT can be shortened to 6 months if very high bleeding risk			Aspi
	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
7 + an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
8 STEMI				
9 with fibrinolytic therapy	DAPT	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE
	Aspi + Clopi			Aspi
10 + PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi		SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			Aspi
11 with LV thrombus or high risk of LV thrombus**	DUAL	VKA + Aspi OR Clopi	DAPT	SINGLE
	Aspi + Prasu OR Tica OR Clopi		Aspi	Aspi
12 + PCI (DES, BMS or DCB)	TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL	SINGLE
	Aspi + Prasu OR Tica OR Clopi		DAPT	Aspi
Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)			Aspi + Prasu OR Tica OR Clopi	Aspi

42 **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.

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

Date of the procedure or acute medical event

M1

M3

M6

M12

M = months

PERIPHERAL ARTERIAL DISEASES (PADs)				
CAROTID ARTERY DISEASE OR VERTEBRAL ARTERY DISEASE				
carotid and vertebral artery stenosis	+ symptomatic	DAPT or SINGLE	Aspi + dipyridamole OR (Aspi OR Clopi)	
	+ stenting	DAPT	DAPT or SINGLE	Aspi + dipyridamole OR (Aspi OR Clopi)
carotid artery stenosis	+ stenting + recent ACS and/or PCI (< 1 year)	DAPT	Aspi + Clopi	SINGLE
	12 months of DAPT from ACS and/or PCI			Aspi OR Clopi
LOWER EXTREMITY ARTERY DISEASE (LEAD)				
LEAD: percutaneous revascularization	DAPT	SINGLE	Aspi OR Clopi	
Aspi + Clopi				
+ recent ACS and/or PCI (< 1 year)	DAPT	Aspi + Clopi	12 months of DAPT from ACS and/or PCI	SINGLE
Aspi OR Clopi				
+ an indication for oral anticoagulation* with a low bleeding risk compared to the risk of stroke/CTLI due to stent/graft occlusion	DUAL	DUAL or SINGLE	SINGLE	
OAC + Aspi OR Clopi		OAC (+ Aspi OR Clopi)	OAC	
LEAD: surgery revascularization	DAPT	Below-knee by pass graft surgery with prosthetic grafts		SINGLE
Aspi + Clopi			Aspi OR Clopi	

Date of the procedure or acute medical event

M1

M3

M6

M12

STROKE/TRANSIENT ISCHEMIC ATTACK (TIA)

ischemic stroke or TIA due to atherosclerosis	DAPT or SINGLE	Aspi + dipyridamole OR (Aspi OR Clopi OR Trifu OR Cilo)
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Date of the procedure or acute medical event

M1

M3

M6

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VALVULAR HEART DISEASE

TAVR	DAPT or SINGLE	DAPT or SINGLE	SINGLE
Aspi + Clopi (OR VKA alone if low bleeding risk)		Aspi AND/OR Clopi	Aspi OR Clopi
mechanical heart valve + thromboembolism despite an adequate INR	DUAL or SINGLE	VKA (+ Aspi OR Clopi)	
Life long Dual Therapy should be considered			

* **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.

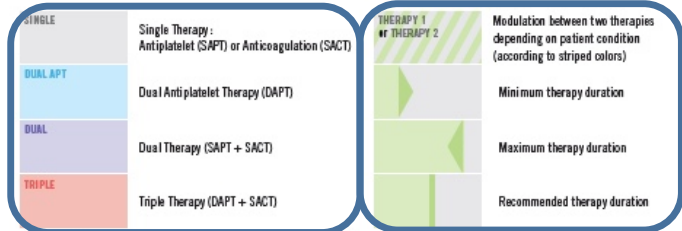
How to use the prescription support tool

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General presentation of the prescription support tool

Colour codes for single, dual or triple therapy

Codes for duration of treatments



Abbreviations

ACS	Acute Coronary Syndrome
Aspi	Aspirin
H	Hypertension (1)
D	Diabetes Mellitus (1)
V	Vascular disease (1)
So	Sex category (i.e.: female sex) (1)
Cilo	Cloistazol
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 Anticoagulation: VNA 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
Trifu	Triflusal
TRIPLE	Triple Therapy: DAPT + SACT
VNA	Vitamin K Antagonist Transcatheter Aortic Valve
VTE	Venous Thromboembolism

Target INR for mechanical valves

Prosthesis thrombogenicity	None	≥1
Low ^a	2.5	3.0
Medium ^b	3.0	3.5
High ^c	3.5	4.0

THE COCKCROFT AND GAULT FORMULA (1973)

$$C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight}) / (72 \times S_{Cr})}{0.85} \text{ (if female)}$$

$$C_{Cr} \text{ (creatinine clearance)} = \text{mL/minute}$$


2018 SYNTHESIS OF RECOMMENDATIONS FOR CHRONIC MANAGEMENT OF ANTITHROMBOTIC COMBINATIONS
INDICATIONS, DURATION AND DOSAGE IN ADULTS

! 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
- Embolism of stroke
- Recurrent stroke despite SAPT
- Mitral stenosis and previous stroke or left atrial thrombus
- Carotid or vertebral stenosis (except with stent)
- Carotid or vertebral dissection } **Indications for SAPT**
- Valvular bioprosthesis } **3-6 months of SACT (SAPT for patients with aortic bioprosthesis at high risk of bleeding)**

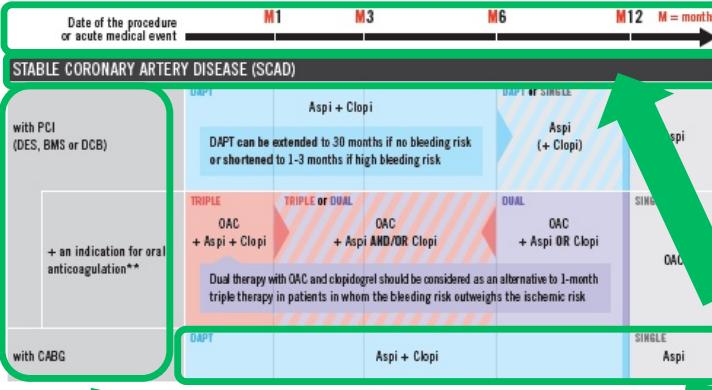
Indications for SACT

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

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 treatments

Recommended dosages for each drugs

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

Link for recommendations of bleeding during DAPT

TARGET INR FOR MECHANICAL PROSTHESES: Patient-related risk factors

Prosthesis thrombogenicity	None	≥1
Low ^a	2.5	3.0
Medium ^b	3.0	3.5
High ^c	3.5	4.0

NR = 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

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

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)

THE COCKCROFT AND GAULT FORMULA (1973)

$$C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight}) / (72 \times S_{Cr})}{0.85} \text{ (if female)}$$

$$C_{Cr} \text{ (creatinine clearance)} = \text{mL/minute}$$

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

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)

Specific conditions not included in the tool

Cockcroft and Gault formula

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

Link for recommendations of bleeding during DAPT

Specific conditions not included in the tool

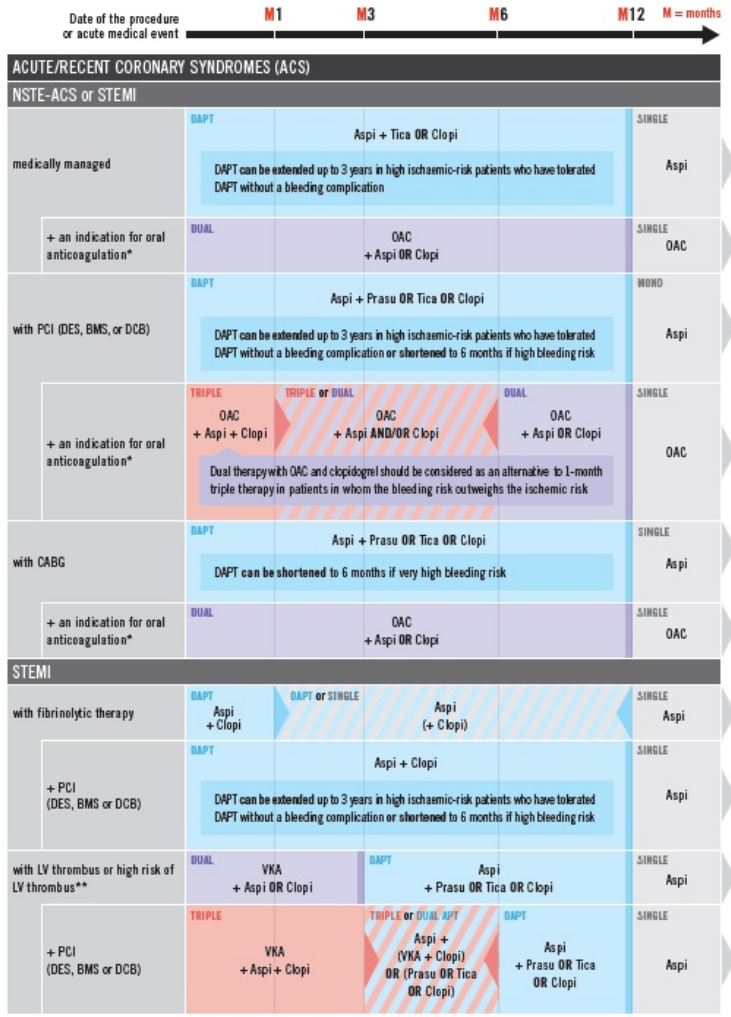
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In practice

Example 1: one cardiovascular disease

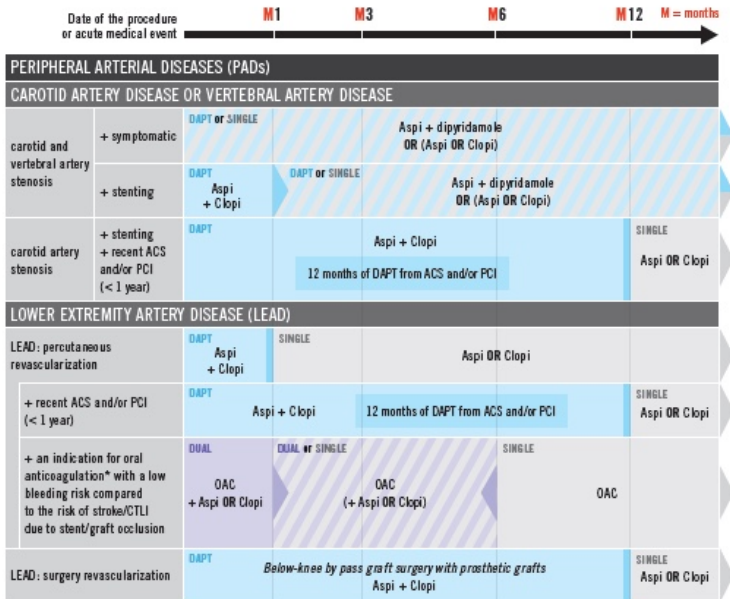
- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m²).
- Medical history: arterial hypertension and Parkinson disease
- He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve replacement (TAVR)
- Which antithrombotic therapy is 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.

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



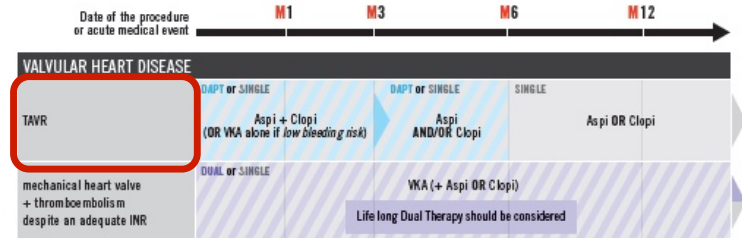
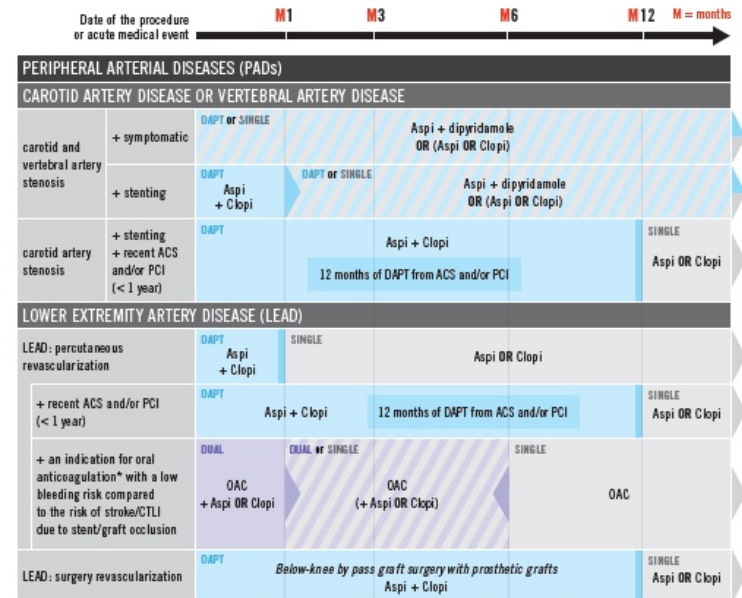
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASc score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc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

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10 **2- Locate**
11 **the precise**
12 **clinical**
13 **situation of**
14 **your patient**
15 **(treatment**
16 **already**
17 **performed,**
18 **associated**
19 **pathologies**
20 **etc.)**

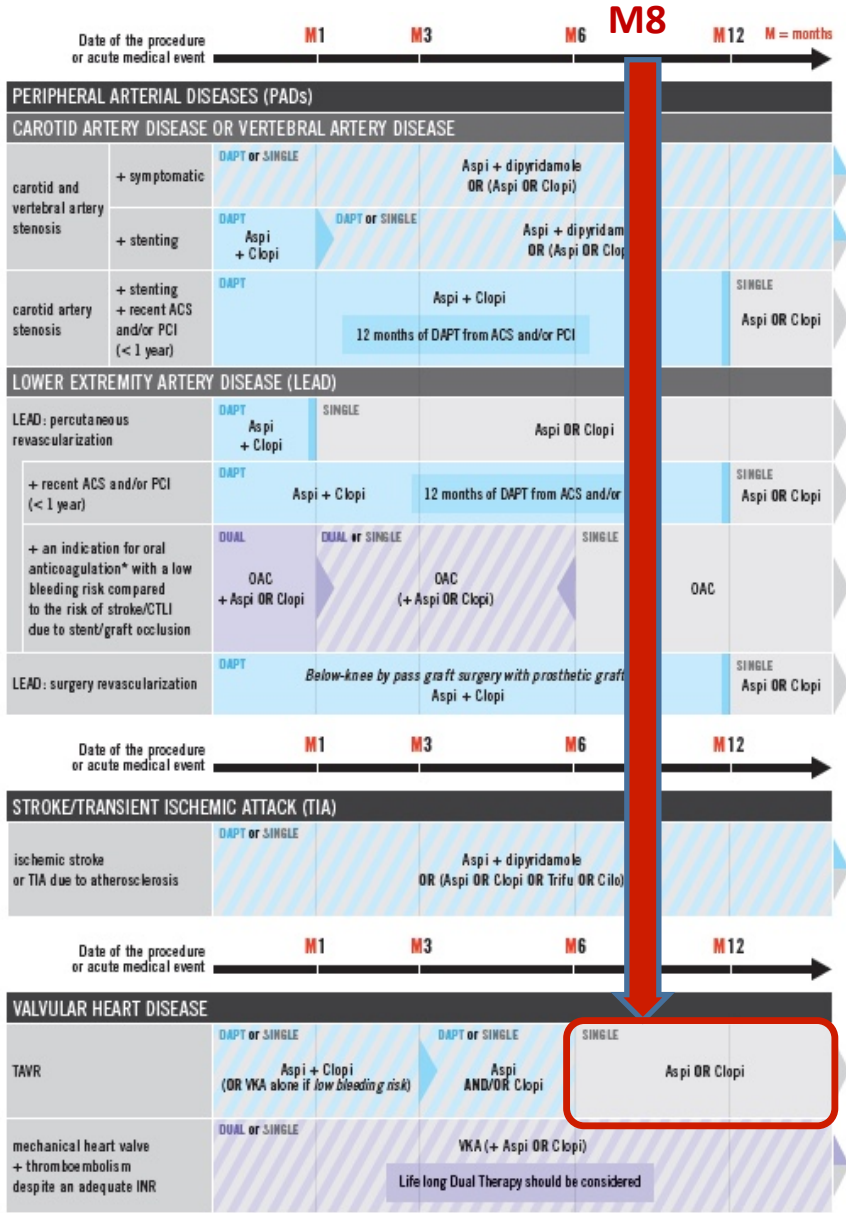


*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASc score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc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



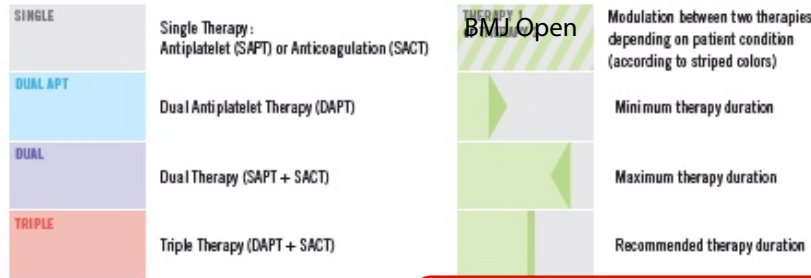
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASc score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc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



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)

* 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 after the last event, but in certain situations, it may be extended to 6 months associated with a pathology at risk.



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 to 5 mg/day in patients with body weight < 60 kg
 Ticagrelor: 90 mg twice a day
 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

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

Abbreviations

ACS	Acute Coronary Syndrome
Aspi	Aspirin
BMS	Bare-Metal Stent
CABG	Coronary Artery Bypass 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
NSTEMI-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	Patient-related risk factor*	
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
 * 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.esdri.nl/onderzoek/onderzoek/Praktische-Guidelines/2019/updates/updates-on-dual-antiplatelet-therapy/about/guidelines.xhtml>

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)

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

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

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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/m²).
- 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

ACUTE/RECENT CORONARY SYNDROMES (ACS)					
NSTE-ACS or STEMI					
medically managed	DAPT	Aspi + Tica OR Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication				Aspi
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
with PCI (DES, BMS, or DCB)	DAPT	Aspi + Prasu OR Tica OR Clopi			MONO Aspi
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				
+ an indication for oral anticoagulation*	TRIPLE	TRIPLE or DUAL	DUAL	SINGLE	
	OAC + Aspi + Clopi	OAC + Aspi AND/OR Clopi	OAC + Aspi OR Clopi	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 + Prasu OR Tica OR Clopi			SINGLE Aspi
	DAPT can be shortened to 6 months if very high bleeding risk				
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
STEMI					
with fibrinolytic therapy	DAPT	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE	
	Aspi + Clopi			Aspi	
+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi			SINGLE Aspi
DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk					
with LV thrombus or high risk of LV thrombus**	DUAL	VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi	SINGLE Aspi
	TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL DAPT	DAPT	SINGLE Aspi
+ PCI (DES, BMS or DCB)			Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	

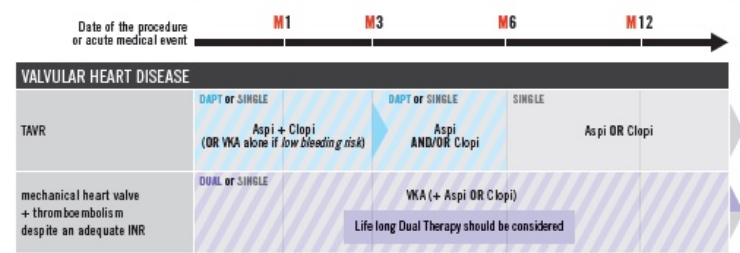
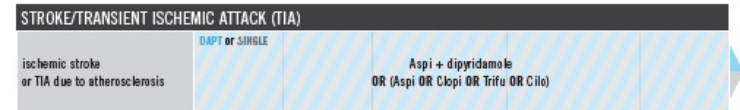
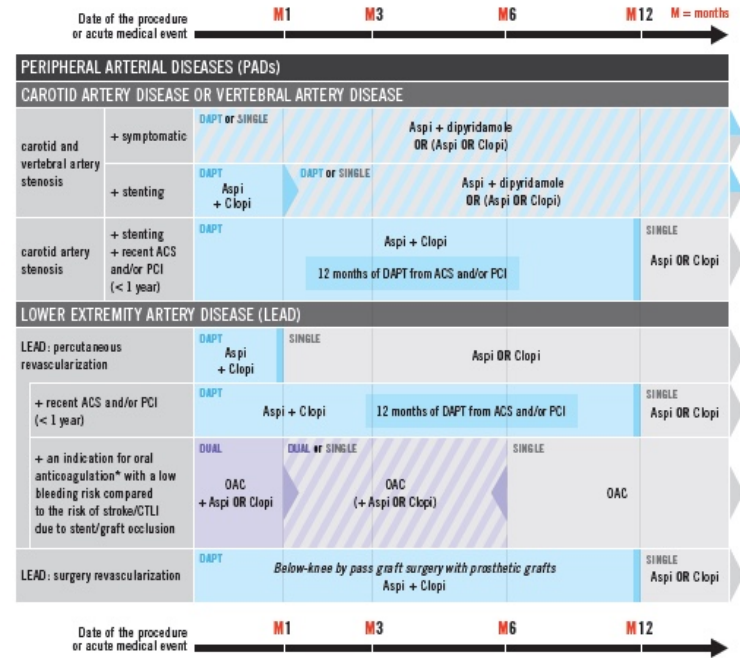
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASc score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc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



* 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.



* 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.

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

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

		Date of the procedure or acute medical event →				
		M1	M3	M6	M12	M = months
ACUTE/RECENT CORONARY SYNDROMES (ACS)						
NSTE-ACS or STEMI						
medically managed		DAPT	Aspi + Tica OR Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication				Aspi
+ an indication for oral anticoagulation*		DUAL	OAC + Aspi OR Clopi			SINGLE
						OAC
with PCI (DES, BMS, or DCB)		DAPT	Aspi + Prasu OR Tica OR Clopi			MONO
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*		TRIPLE	TRIPLE or DUAL	DUAL		SINGLE
		OAC + Aspi + Clopi	OAC + Aspi AND/OR Clopi	OAC + Aspi OR Clopi	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 + Prasu OR Tica OR Clopi			SINGLE
		DAPT can be shortened to 6 months if very high bleeding risk				Aspi
+ an indication for oral anticoagulation*		DUAL	OAC + Aspi OR Clopi			SINGLE
						OAC
STEMI						
with fibrinolytic therapy		DAPT	DAPT or SINGLE	Aspi (+ Clopi)		SINGLE
		Aspi + Clopi			Aspi	
+ PCI (DES, BMS or DCB)		DAPT	Aspi + Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
with LV thrombus or high risk of LV thrombus**		DUAL	VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi	SINGLE
					Aspi	
+ PCI (DES, BMS or DCB)		TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL DAPT	DAPT	SINGLE
				Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	

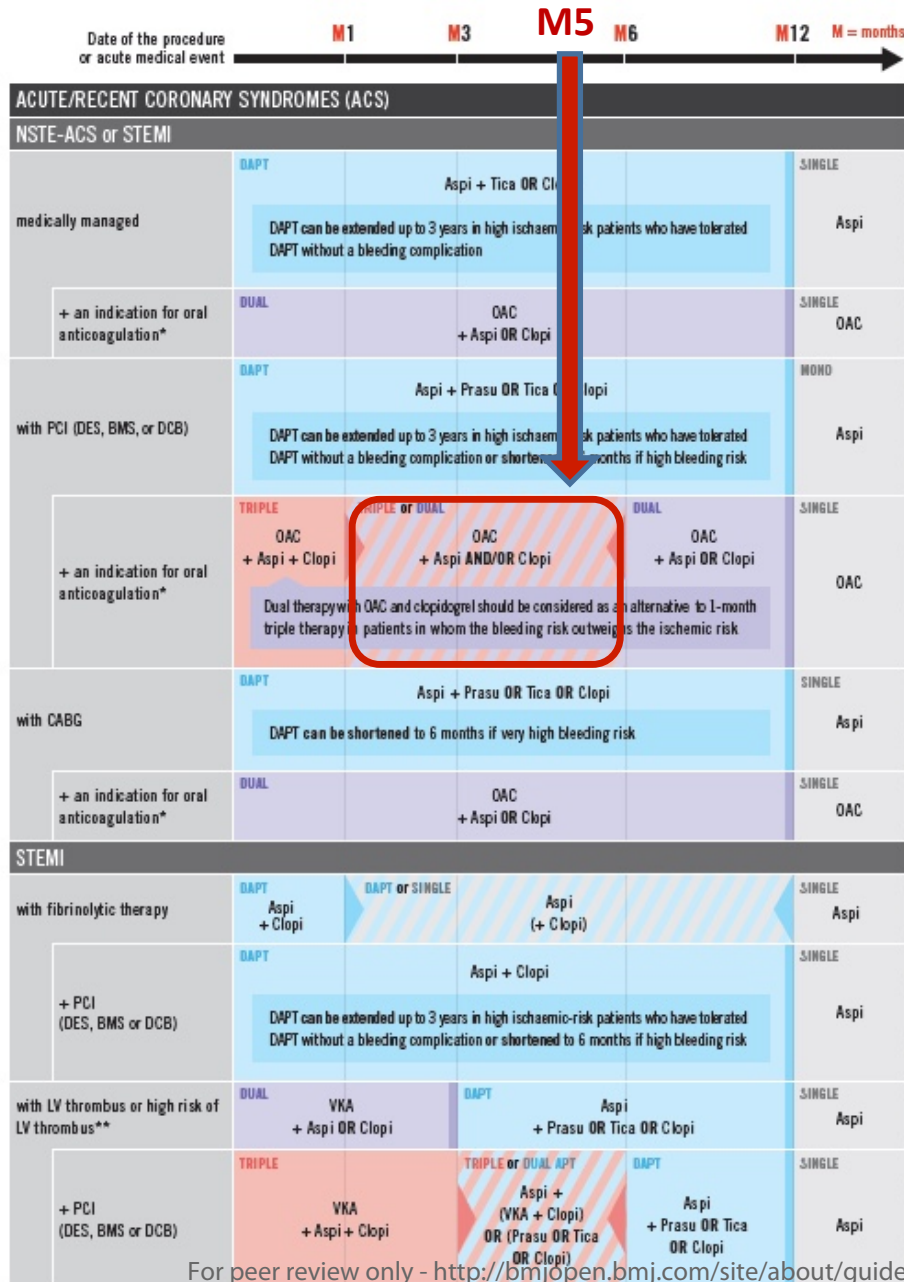
CHA2DS2-VASc score?

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)

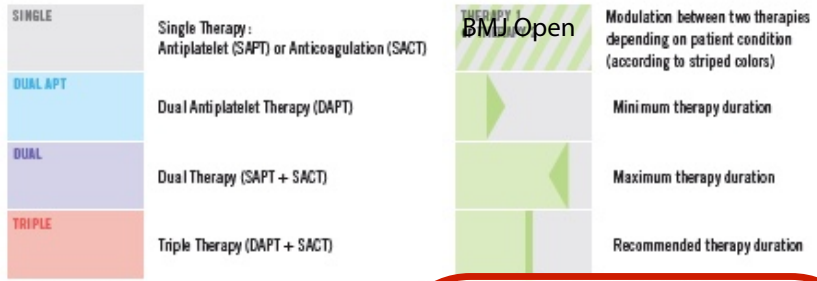
Here, two options are possible according to the ischemic and bleeding risk of your patient:

- 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)

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

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



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
NSTEMI-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
Trifu	Triflusal
TRIPLE	Triple Therapy: DAPT + SACT
VKA	Vitamin K Antagonist Transcatheter Aortic Valve
VTE	Venous Thromboembolism

TARGET INR FOR MECHANICAL PROSTHESE	Patient-related risk factor	
Prosthesis thrombogenicity	None	≥ 1
Low ^a	2.5	3.0
Medium ^b	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 GALT FORMULA (1976)
 $C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight})}{(72 \times S_{Cr})} \times 0.85$ (if female)
 C_{Cr} (creatinine clearance) = mL/minute
 Age = years Weight = kg S_{Cr} (serum creatinine) = mg/dL

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

IF BLEEDING DURING DAPT, follow these recommendations (figure 10)
<https://www.esdof.org/2019/06/06/2019-ESC-Guidelines-Oral-Antiplatelet-Therapy-DAPT/>
<https://open.bmj.com/site/about/guidelines.xhtml>

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)

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/m²). 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

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

- 5
- 6 • 1 month
 - 7 • 6 months
 - 8 • 12 months
 - 9 • For life
- 10

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

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

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

- 21
- 22 • The prescription support-tool helped me answer to the clinical vignettes:../10
 - 23 • The prescription support-tool has modified the answers that I spontaneously made to
 - 24 clinical vignettes:../10
 - 25 • The prescription support-tool is clear:../10
 - 26 • The prescription support-tool is operational:../10
 - 27 • The prescription support-tool is useful for practice:../10
 - 28 • I would be ready to use this prescription support-tool:../10
 - 29 • I would recommend the use of this prescription support-tool:../10
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33 **Notes on the tool: What are the points of the prescription support-tool that could be**
34 **improved: useless information, missing information, presentation, etc:**

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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

1			
2	Objectives	7	Specific objectives or hypotheses
3			→ Lines 102 - 105, page 5
4			
5	Trial design	8	Description of trial design including type of trial (eg, parallel group,
6			crossover, factorial, single group), allocation ratio, and framework (eg,
7			superiority, equivalence, noninferiority, exploratory)
8			
9			

Methods: Participants, interventions, and outcomes

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11			
12			
13	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
14			and list of countries where data will be collected. Reference to where
15			list of study sites can be obtained
16			→ Lines 109 - 110 page 5
17			
18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
20			criteria for study centres and individuals who will perform the
21			interventions (eg, surgeons, psychotherapists)
22			→ Lines 110 - 112 page 5
23			
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
25			including how and when they will be administered
26			→ Lines 113 - 121, page 5 - 6
27			
28			
29		11b	Criteria for discontinuing or modifying allocated interventions for a
30			given trial participant (eg, drug dose change in response to harms,
31			participant request, or improving/worsening disease)
32			
33		11c	Strategies to improve adherence to intervention protocols, and any
34			procedures for monitoring adherence (eg, drug tablet return,
35			laboratory tests)
36			→ Lines 143, page 6
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39		11d	Relevant concomitant care and interventions that are permitted or
40			prohibited during the trial
41			
42	Outcomes	12	Primary, secondary, and other outcomes, including the specific
43			measurement variable (eg, systolic blood pressure), analysis metric
44			(eg, change from baseline, final value, time to event), method of
45			aggregation (eg, median, proportion), and time point for each
46			outcome. Explanation of the clinical relevance of chosen efficacy and
47			harm outcomes is strongly recommended
48			→ Lines 144 - 153, page 7
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51	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
52	timeline		washouts), assessments, and visits for participants. A schematic
53			diagram is highly recommended (see Figure)
54			→ Lines 113 - 143, page 5 - 6
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2 Sample size 14 Estimated number of participants needed to achieve study objectives
3 and how it was determined, including clinical and statistical
4 assumptions supporting any sample size calculations
5 → **Lines 196 – 198, page 9**
6
7 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
8 target sample size
9 → **Lines 113 - 114 page 5**
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12 **Methods: Assignment of interventions (for controlled trials)**

13 Allocation:

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16 Sequence 16a Method of generating the allocation sequence (eg, computer-
17 generation generated random numbers), and list of any factors for stratification.
18 To reduce predictability of a random sequence, details of any planned
19 restriction (eg, blocking) should be provided in a separate document
20 that is unavailable to those who enrol participants or assign
21 interventions
22 **Lines 86 - 189 page 8**
23
24
25 Allocation 16b Mechanism of implementing the allocation sequence (eg, central
26 concealment telephone; sequentially numbered, opaque, sealed envelopes),
27 mechanism describing any steps to conceal the sequence until interventions are
28 assigned
29 **Lines 86 - 189 page 8**
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32 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
33 and who will assign participants to interventions
34 **Lines 86 - 189 page 8**
35
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37 Blinding 17a Who will be blinded after assignment to interventions (eg, trial
38 (masking) participants, care providers, outcome assessors, data analysts), and
39 how
40
41 17b If blinded, circumstances under which unblinding is permissible, and
42 procedure for revealing a participant's allocated intervention during
43 the trial
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46 **Methods: Data collection, management, and analysis**

- 47
48 Data collection 18a Plans for assessment and collection of outcome, baseline, and other
49 methods trial data, including any related processes to promote data quality (eg,
50 duplicate measurements, training of assessors) and a description of
51 study instruments (eg, questionnaires, laboratory tests) along with
52 their reliability and validity, if known. Reference to where data
53 collection forms can be found, if not in the protocol
54 → **Lines 190 – 194 page 8 - 9**
55
56
57 18b Plans to promote participant retention and complete follow-up,
58 including list of any outcome data to be collected for participants who
59 discontinue or deviate from intervention protocols
60

1			
2	Data	19	Plans for data entry, coding, security, and storage, including any
3	management		related processes to promote data quality (eg, double data entry;
4			range checks for data values). Reference to where details of data
5			management procedures can be found, if not in the protocol
6			→ Lines 190 – 194 page 8 - 9
7			
8	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
9	methods		Reference to where other details of the statistical analysis plan can be
10			found, if not in the protocol
11			→ Lines 202 - 205, page 9
12			
13		20b	Methods for any additional analyses (eg, subgroup and adjusted
14			analyses)
15		20c	Definition of analysis population relating to protocol non-adherence
16			(eg, as randomised analysis), and any statistical methods to handle
17			missing data (eg, multiple imputation)
18			
19			
20			
21			
22	Methods: Monitoring		
23			
24	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
25			and reporting structure; statement of whether it is independent from
26			the sponsor and competing interests; and reference to where further
27			details about its charter can be found, if not in the protocol.
28			Alternatively, an explanation of why a DMC is not needed
29		21b	Description of any interim analyses and stopping guidelines, including
30			who will have access to these interim results and make the final
31			decision to terminate the trial
32			
33			
34			
35	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
36			spontaneously reported adverse events and other unintended effects
37			of trial interventions or trial conduct
38			
39			
40	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
41			whether the process will be independent from investigators and the
42			sponsor
43			
44			
45	Ethics and dissemination		
46			
47	Research ethics	24	Plans for seeking research ethics committee/institutional review board
48	approval		(REC/IRB) approval
49			→ Lines 223 - 233 page 10
50			
51	Protocol	25	Plans for communicating important protocol modifications (eg,
52	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
53			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
54			regulators)
55			
56			
57	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
58			participants or authorised surrogates, and how (see Item 32)
59			
60			

1			
2		26b	Additional consent provisions for collection and use of participant data
3			and biological specimens in ancillary studies, if applicable
4			
5	Confidentiality	27	How personal information about potential and enrolled participants will
6			be collected, shared, and maintained in order to protect confidentiality
7			before, during, and after the trial
8			→ Lines 192 - 193, page 8 - 9
9			
10	Declaration of	28	Financial and other competing interests for principal investigators for
11	interests		the overall trial and each study site
12			→ Line 241, page 11
13			
14			
15	Access to data	29	Statement of who will have access to the final trial dataset, and
16			disclosure of contractual agreements that limit such access for
17			investigators
18			
19	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
20	post-trial care		compensation to those who suffer harm from trial participation
21			
22			
23	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
24	policy		participants, healthcare professionals, the public, and other relevant
25			groups (eg, via publication, reporting in results databases, or other
26			data sharing arrangements), including any publication restrictions
27			→ Lines 232 - 233, page 10
28			
29			
30		31b	Authorship eligibility guidelines and any intended use of professional
31			writers
32			
33		31c	Plans, if any, for granting public access to the full protocol, participant-
34			level dataset, and statistical code
35			
36			
37	Appendices		
38			
39	Informed consent	32	Model consent form and other related documentation given to
40	materials		participants and authorised surrogates
41			
42	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
43	specimens		specimens for genetic or molecular analysis in the current trial and for
44			future use in ancillary studies, if applicable
45			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Complete List of Authors:	<p>ZERAH, Lorene; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique Bonnet-Zamponi, Dominique; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique Ile de France, OMEDIT Frappé, Paul; Institut de recherche en médecine générale; University of Saint-Etienne, Department of General Practice Hauguel-Moreau, Marie; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de cardiologie De Rycke, Yann; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi) Magnier, Anne-Marie; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de médecine générale Pautas, Eric; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de gériatrie Charles, Pierre; Institut Mutualiste Montsouris, Médecine Interne Collet, Jean-philippe; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de cardiologie Dechartres, Agnes; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; APHP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi) Tubach, Florence; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; APHP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p>
Primary Subject Heading:	Pharmacology and therapeutics

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



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3 **Evaluation of a prescription support-tool for chronic management of oral**
4 **antithrombotic combinations in adults using clinical vignettes: protocol of a randomized**
5 **controlled trial**
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12 Zerah L¹, Bonnet-Zamponi D^{1,2}, Frappé P^{3,4}, Hauguel-Moreau M⁵, De Rycke Y^{1,6}, Magnier
13 AM⁷, Pautas E⁸, Charles P⁹, Collet JP⁵, Dechartres A^{1,6}, Tubach F^{1,6}
14
15

- 16 1. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
17 Publique, F-75013 Paris, France
- 18 2. Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique
19 Ile de France (OMEDIT), Paris, France
- 20 3. Institut de recherche en médecine générale, Paris, France
- 21 4. Département de médecine générale, Université de Saint-Etienne, Saint-Etienne, France
- 22 5. Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix,
23 Département de Cardiologie, F-75013 Paris, France
- 24 6. AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département
25 Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie
26 (Cephepi), F-75013 Paris, France
- 27 7. Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix,
28 Département de Médecine Générale, F-75013 Paris, France
- 29 8. Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix,
30 Département de Gériatrie, F-75013 Paris, France
- 31 9. Institut Mutualiste Montsouris, Département de Médecine Interne, F-75014 Paris, France

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42
43
44 *** Corresponding author: Dr Lorene Zerah**

45 Correspondence to: lorene.zerah@inserm.fr

46
47 Address: Département Biostatistique Santé Publique et Information Médicale, Centre de
48 Pharmacoépidémiologie (Cephepi), Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l'hôpital,
49 75013, Paris, France

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Tel: +33 1 42 16 03 47

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

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2
3 combinations were numerous (n=70) and none encompassed all the clinical situations
4
5 requiring oral AT combinations. This review highlighted the difficulty for a physician to
6
7 quickly find the most up-to-date recommendation and the one most relevant to the patient's
8
9 clinical situation. These findings agreed with clinical experience and led us to synthesize all
10
11 the recommendations into a prescription support-tool (**Figure 1**)[9] to help physicians
12
13 prescribe oral AT combinations.
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16
17 Our hypothesis is that this prescription support-tool would improve the prescription of oral
18
19 AT prescriptions to comply with guidelines. Our primary objective is to assess the impact of
20
21 this tool on improving the prescription of oral ATs to comply with guidelines (in terms of
22
23 number of drugs, drug class, duration and dosage at the same time).
24
25

26 27 28 **METHODS AND ANALYSIS**

29 30 **Study design, study setting and eligibility criteria**

31
32 A web-based, open randomized controlled trial involving clinical vignettes will be performed
33
34 in France via an online survey. This study will be conducted among French general
35
36 practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive
37
38 hospital practice will not be eligible.
39
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41
42 Physicians will be identified and contacted to participate in the online survey by email via
43
44 physician associations, social networks or word of mouth. The survey will gather
45
46 informations on physicians' characteristics, including age, sex, medical specialty (cardiologist
47
48 or general practitioner), place of exercise (hospital or ambulatory setting), years of medical
49
50 practice, approximate proportion of patients prescribed oral AT combinations in their practice
51
52 ($\leq 5\%$, 6 – 10%, 11-20% or $\geq 21\%$), whether physicians feel comfortable or not with
53
54 management of oral AT prescriptions (totally, partially, rarely, never), and whether physicians
55
56 know where to find the most recent guidelines on oral AT prescriptions. Then, physicians will
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3 be randomized to 2 arms: the experimental arm, having access to the prescription support-tool
4 **(Figure 1),**[9] and the control arm, with no prescription support-tool. For physicians in the
5
6 **(Appendix 1),**[9] both downloaded (or just viewed) online in pdf format. Then, participants
7
8 from both arms will be presented 3 different clinical vignettes illustrating outpatient clinical
9
10 situations and will be asked to propose prescriptions for each clinical vignette (oral AT or not,
11
12 number of oral ATs, type, duration and dosage of each oral AT) by answering 4 multiple-
13
14 choice questions (each question on a separate web page). Question 5 will evaluate the degree
15
16 of confidence of physicians have that their prescription of ATs complies with guidelines on a
17
18 scale of 0 to 10. Physicians in the experimental arm will answer each question with the help
19
20 of the tool, downloadable (or viewable on each page). At the end, we will ask to physicians of
21
22 the experimental arm to rate, on a scale from 0 and 10, the usefulness of the prescription
23
24 support-tool, how much they would be willing to use this prescription support-tool in their
25
26 practice and if they would recommend its use. Physicians in the control arm will be asked to
27
28 answer according to their actual clinical practice as closely as possible. Once the answer is
29
30 given, physicians cannot go back or change their answer. Physicians must answer the
31
32 questions consecutively; however, they will be allowed to stop and continue at any time (on
33
34 the same computer). Physicians from the control arm will be able to download the
35
36 prescription support-tool once they have completed their answers for the 3 clinical vignettes.
37
38
39 The scientific and expert committee have created and validated 30 clinical vignettes. To
40
41 ensure that each clinical vignette will be read the same number of times in both arms, we
42
43 created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical
44
45 vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm
46
47 in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized,
48
49 all clinical vignettes will be read once. The randomization unit will be the physician and the
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3 unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle
4
5 ground to ensure the feasibility of the study considering both participants' availability
6
7 (acceptable time to complete the clinical vignettes) and statistical need (number of clinical
8
9 vignettes needed). To maximize the participation rate, physicians will be sent reminders every
10
11
12 20 days.

13 14 **Outcomes**

15
16 The primary outcome is prescription of oral ATs that comply with guidelines in terms of
17
18 number of drugs, drug class, duration and dosage at the same time, which will be termed fully
19
20 appropriate prescription. An expert committee will determine the correct answer, based on the
21
22 prescription support-tool (**Figure 1**)[9]. Secondary outcomes are (1) prescription of oral ATs
23
24 that comply with guidelines in terms of number of drugs, drug class, duration and dosage,
25
26 each assessed separately; (2) prescription of oral ATs that comply with guidelines (fully
27
28 appropriate prescription, number of drugs, drug class, duration and dosage each assessed
29
30 separately) by medical specialty of physicians responding (cardiologist or general
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32 practitioner); (3) the degree of confidence of physicians have that their prescription of ATs
33
34 complies with guidelines; 4) for physicians allocated to receive the prescription support-tool
35
36 only, the overall usefulness of the tool.
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41

42 **Intervention**

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44 We developed, from a systematic review of international guidelines published between 2012
45
46 and 2018 (n=70),[9] a prescription support-tool to help physicians prescribe oral AT
47
48 combinations for complying with guidelines. This prescription support-tool synthesizes, on a
49
50 double-sided page, selected international guidelines on chronic management (at least 1
51
52 month) of oral AT combinations (indication, drugs, dosages and duration) in adults, without
53
54 considering in-hospital management, bridging therapy and primary prevention (**Figure 1**).[9].
55
56 We excluded particular clinical situations that require inevitably specialist medical advice:
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3 active cancer, autoimmune diseases, haemophilia, HIV, paediatrics and pregnancy. The
4 following pathologies were included in this tool because they are the main causes leading to
5 the prescription of ATs (single, dual or triple therapy) in adults[1]: non-valvular atrial
6 fibrillation, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery
7 disease and venous thromboembolism. Our tool also specifies the type of oral ATs that should
8 never be combined (combinations of oral anticoagulants [OACs], combinations of P2Y12
9 inhibitors or combining one OAC with one potent P2Y12 inhibitor, namely ticagrelor or
10 prasugrel), the clinical situations in which oral AT combinations are never indicated and the
11 contraindications of ATs. This prescription support-tool aims to give physicians quick access
12 to the recommendation that fits most of their patient's clinical situation. The prescription
13 support-tool is accompanied by an explanatory guide (how to read and use the tool, with
14 examples, **Appendix 1**).[9]

30 **Clinical vignettes**

31
32 The clinical vignettes illustrating plausible clinical situations have been developed to reflect
33 clinical practice.[10,11] Such an approach has been found valid in measuring quality of
34 care.[12,13] Each clinical vignette corresponds to a specific situation for which physicians
35 will have to indicate, by answering a multiple-choice question, whether they would prescribe
36 oral ATs, with the number, type, duration and dosage. All answers to clinical vignettes'
37 questions can be found in the prescription support-tool. An example of a clinical vignette is
38 presented in **Appendix 2**. Two physicians (1 cardiologist and 1 internist-geriatrician) from the
39 scientific committee have created 30 clinical vignettes covering most outpatient clinical
40 situations (without considering in-hospital management, bridging therapy and primary
41 prevention) for which the long-term use of oral ATs (single, dual or triple therapy) is
42 recommended or needs to be stopped according to the guidelines.

58 **Randomization**

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3 Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated
4 randomization scheme implemented in the online survey (1:1 ratio), then stratified by their
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7
8 medical specialty.
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10 **Data collection methods and data management**

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12 Data from physicians' answers will be automatically integrated in a database for statistical
13
14 analysis. The data will be completely anonymous. In particular, neither the physician's name
15
16 nor email address will be collected (there will be no login for participants). There is no
17
18 planned follow-up in this trial.
19

20 **Sample size and statistical considerations**

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22
23 Considering that 85% of AT prescriptions fully comply with guidelines in the control arm,[8]
24
25 to demonstrate an increase in this proportion up to 90% in the experimental arm, we need to
26
27 include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per arm.
28
29 To obtain a multiple of 10 physicians (because each physician will complete 3 of 30 clinical
30
31 vignettes and to have all clinical vignettes completed the same number of times in each arm),
32
33 we plan to include at least 230 physicians per arm. However, if more physicians participate,
34
35 all collected data will be considered. For each clinical vignette, we will consider that
36
37 prescription is fully appropriate (versus inappropriate) if answers to each of the first four
38
39 questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To
40
41 compare the percentage of fully appropriate prescriptions between the two randomized arms,
42
43 taking into account that each participant intends to complete 3 clinical vignettes, we will use a
44
45 logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial
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47 arm. We will use the same method to compare the percentage of prescriptions of oral ATs that
48
49 comply with guidelines in terms of number of drugs, drug class, duration and dosage, each
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51 assessed separately, between the two randomized arms (secondary analyses). To compare the
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53 degree of confidence that physicians have that their prescription of oral AT combinations
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3 complies with guidelines (quantitative variable: scale from 0 and 10), taking into account that
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5 each participant intends to complete 3 clinical vignettes, we will use a linear mixed model
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7 with a clinical-vignette effect and a physician-effect nested in the trial arm. A sub-group
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9 analysis for general practitioners and for cardiologist will be done. Finally, to assess the
10
11 overall usefulness of the tool, we will describe the data of the experimental arm (mean \pm SD,
12
13 median (25–75 interquartile range)). All analyses will involve use of R v3.5.2 ([www.cran.r-](http://www.cran.r-project.org)
14
15 [project.org](http://www.cran.r-project.org)).
16
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18 19 **Scientific and expert committees**

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21 Our study involves a scientific committee and an expert committee. The scientific committee
22
23 consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2
24
25 epidemiologists. The scientific committee designed the study protocol, created and validated
26
27 the clinical vignettes and will be responsible for data analysis and writing of the manuscript.
28
29 The expert committee consists of a cardiologist, a geriatrician, an internist and 2 general
30
31 practitioners (medical specialties that often deal with patients needing chronic oral AT
32
33 prescriptions). The expert committee had to review all clinical vignettes with the prescription
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35 support-tool (external validation) to confirm the agreement of the clinical vignettes with
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37 clinical practice and their readability. The committee estimated the time needed to complete 3
38
39 clinical vignettes at 10 minutes.
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44 **Patient and Public Involvement**

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46 Patients and/or the public have not been involved in the development of the research or in the
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48 study design because only physicians are enrolled and they will not care for patients in the
49
50 context of this trial; they just complete clinical vignettes. The main objective of this study is
51
52 to evaluate a tool for physicians to help with prescribing AT combinations.
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58 **ETHICS AND DISSEMINATION**

1
2
3 The ethics evaluation committee of Inserm, the *Institutional Review Board* (IRB00003888)
4 approved our research project (no. 18-492). If the prescription support-tool is associated with
5 improving the prescription of oral ATs to comply with guidelines, it will be disseminated to
6 help improve ATs prescriptions. We will create an interactive web tool to improve the
7 ergonomics of the tool and to facilitate the updates. We will assess the impact of this
8 interactive web tool in terms of clinical outcomes in real life. This will be the second step, but
9 we feel that we must first demonstrate that the use of the prescription support-tool (on paper)
10 is associated with better prescription appropriateness before launching a trial involving
11 patients with clinical outcomes. Results of this trial will be disseminated in a paper submitted
12 to a peer-reviewed journal and presentations at relevant conferences.
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28 **Figure 1 legend:** 2019 synthesis of recommendations for chronic management of
29 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.

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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

2019 SYNTHESIS OF RECOMMENDATIONS FOR CHRONIC MANAGEMENT OF ANTITHROMBOTIC COMBINATIONS INDICATIONS, DURATION AND DOSAGE IN ADULTS

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

Abbreviations

ABCD² score for TIA
 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
Aspl 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 (+1)
 V Vascular disease (+1) A Age 65-74 (+1)

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamol: 25/200 mg twice a day
Aspirin/ticlopidogrel: 75 mg/day
Aspirin/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
Ticlopidogrel: 90 mg twice a day
 Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds.
Rivaroxaban: 600 mg/day
 3 for NV-AF, VTE, LV thrombus

! 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:
 - ischaemic 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
- Embolism ischaemic stroke
- Recurrent stroke despite SAPT
- Mitral stenosis and previous stroke or left atrial thrombus
- 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)

Indications for SACT

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

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

Combinations of antithrombotic drugs NEVER recommended

Recommended dosages for each drug

Abbreviations used in the tool

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

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 (+1) or liver function (+2) Hypertension (+1) Stroke history (+1) Prior major Bleeding or predisposition to bleeding (+1) Labile INR (+1) Elderly > 65 (+1) Drugs (concomitant Aspl, Clopi, NSAIDs (+1)) or alcohol (+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 Anticoagulation: VKA or DOA
PCI	Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu	Prasugrel
SAPT	Single Antiplatelet Therapy
SACT	Single Anticoagulation Therapy
SIHD	Stable Ischaemic Heart Disease
STEMI	ST-Elevation Myocardial Infarction
TAVR	Transcatheter Aortic Valve Replacement
TIA	Transient Ischaemic Attack
Tica	Ticagrelor
Trifu	Trifluralin
TRIPLE	Triple Therapy: DAPT + SACT
VKA	Vitamin K Antagonist Transcatheter Aortic Valve
VTE	Venous Thromboembolism

Target INR for mechanical valves

TARGET INR FOR MECHANICAL PROSTHESE Patient-related risk factor*

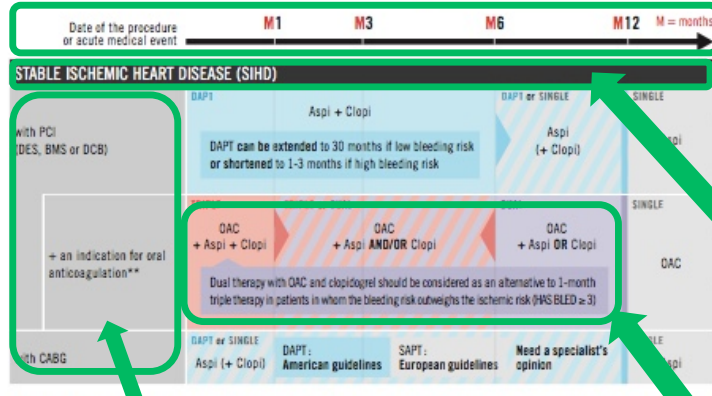
Prosthesis thromboembolism	None	≥1
Low [†]	2.5	3.0
Medium [‡]	3.0	3.5
High [§]	3.5	4.0

INR = international normalized ratio, DEF = left ventricular ejection fraction
 * Mitral or tricuspid valve replacement, previous thrombotic atrial fibrillation, mitral stenosis of any degree, LVF, etc.
 † Carbomedics, Medtronic Hall, AFS, Medtronic Pro, St-Jude Medical, On-X, Sorin Bicarbon
 ‡ Other bileaflet valve with insufficient antithrombotic treatment
 § Lillehei-Kaster, Omniscience, Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves

THE COCKCROFT AND GAULT FORMULA (1973)
 $CrCl = \frac{[(140 - \text{Age}) \times \text{Weight}] / (72 \times Sc_{Cr}) \times 0.85 \text{ (if female)}}{1}$
 CrCl (creatinine clearance) = mL/minute
 Age = years Weight = kg Sc_{Cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations (Aureus, https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2019-2020/antithrombotic-therapy-in-atrial-fibrillation)

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 disease)



Timeline (in months) since diagnosis or beginning of treatment

Pathology

Time dependant recommended treatments

* 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, 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.

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

Link for recommendations if bleeding during DAPT

Specific conditions not included in the tool

Cockcroft and Gault formula

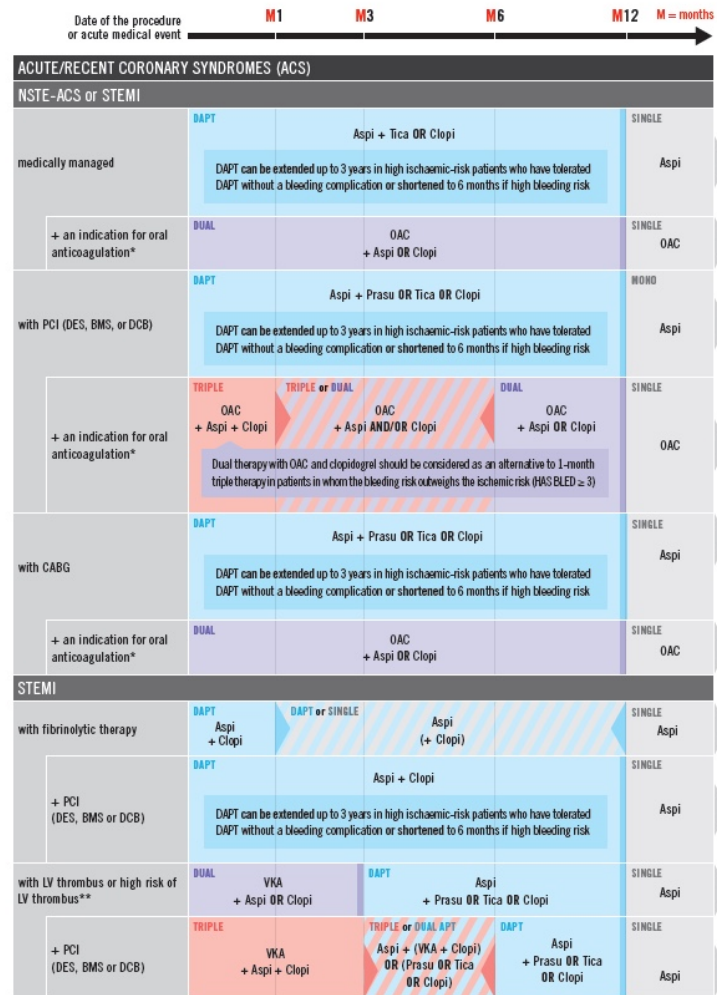
In practice

Example 1: one cardiovascular disease

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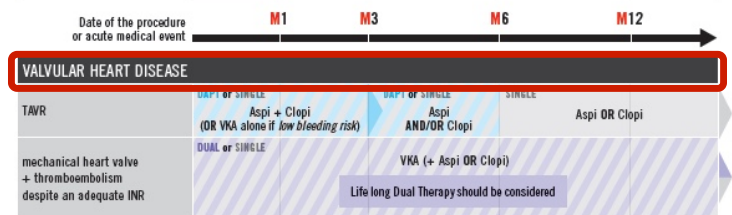
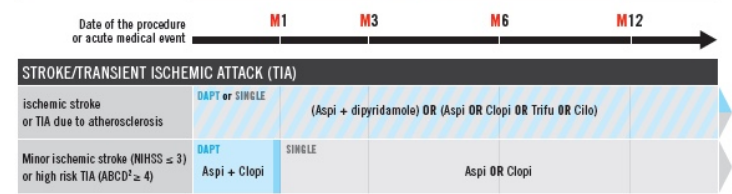
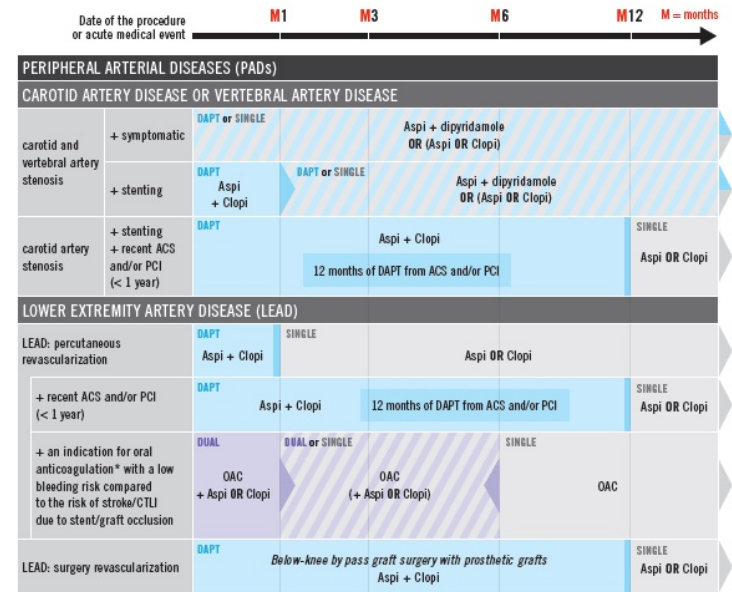
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- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m²).
 - Medical history: arterial hypertension and Parkinson disease
 - He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve 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.

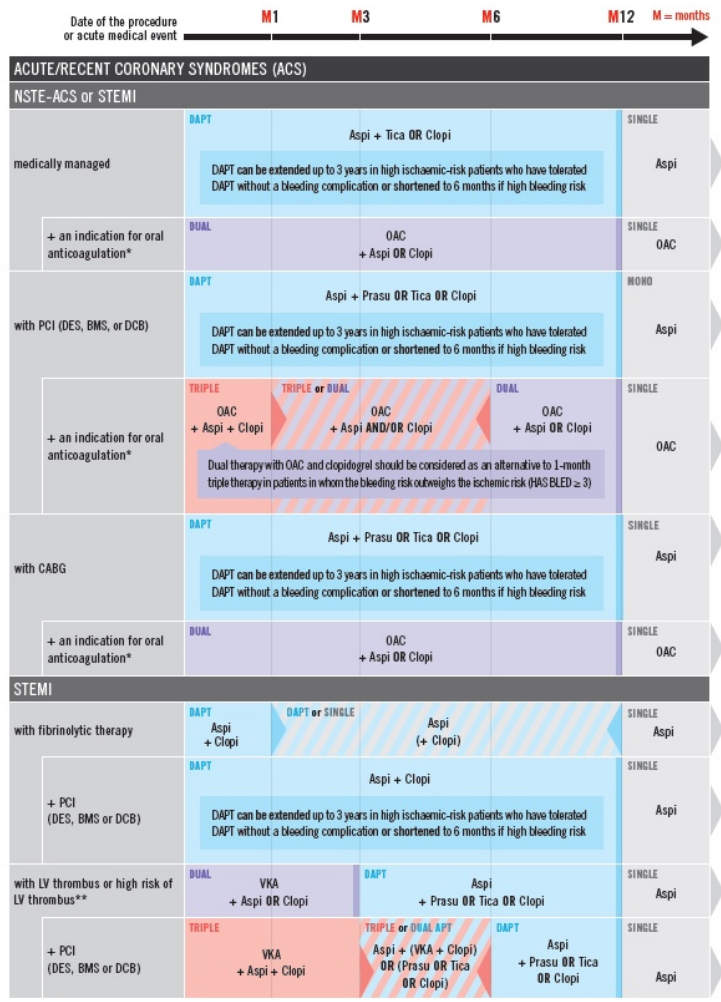
** High risk for LV thrombus: Ejection Fraction < 40%, Anteroseptal wall motion abnormality.



*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.

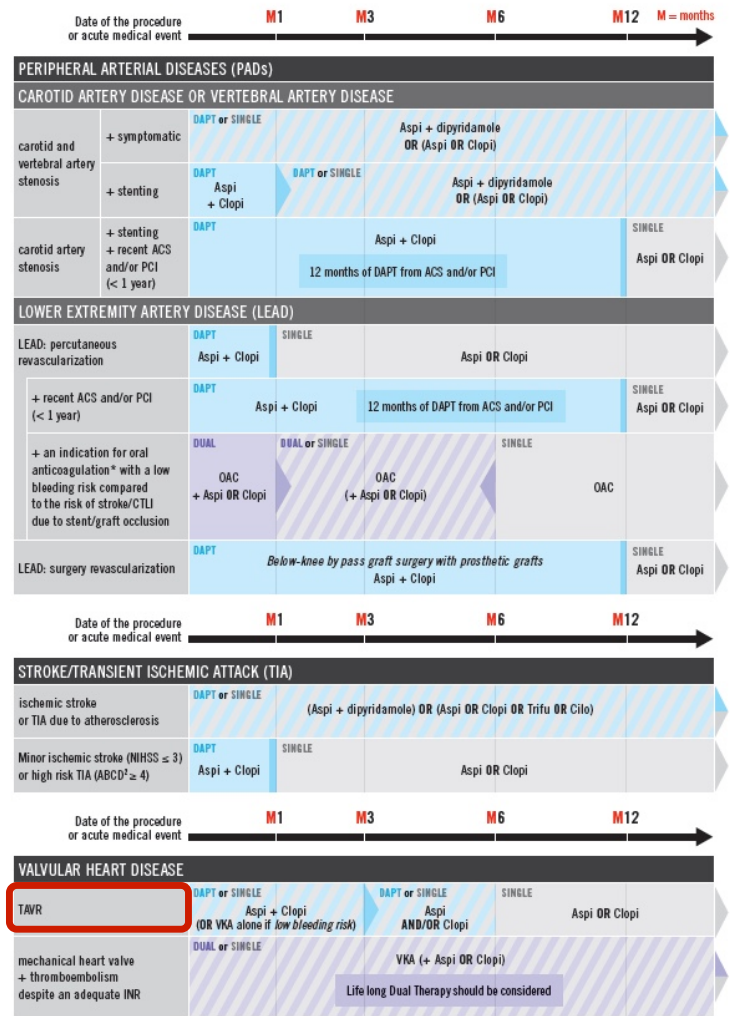
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2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



*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.

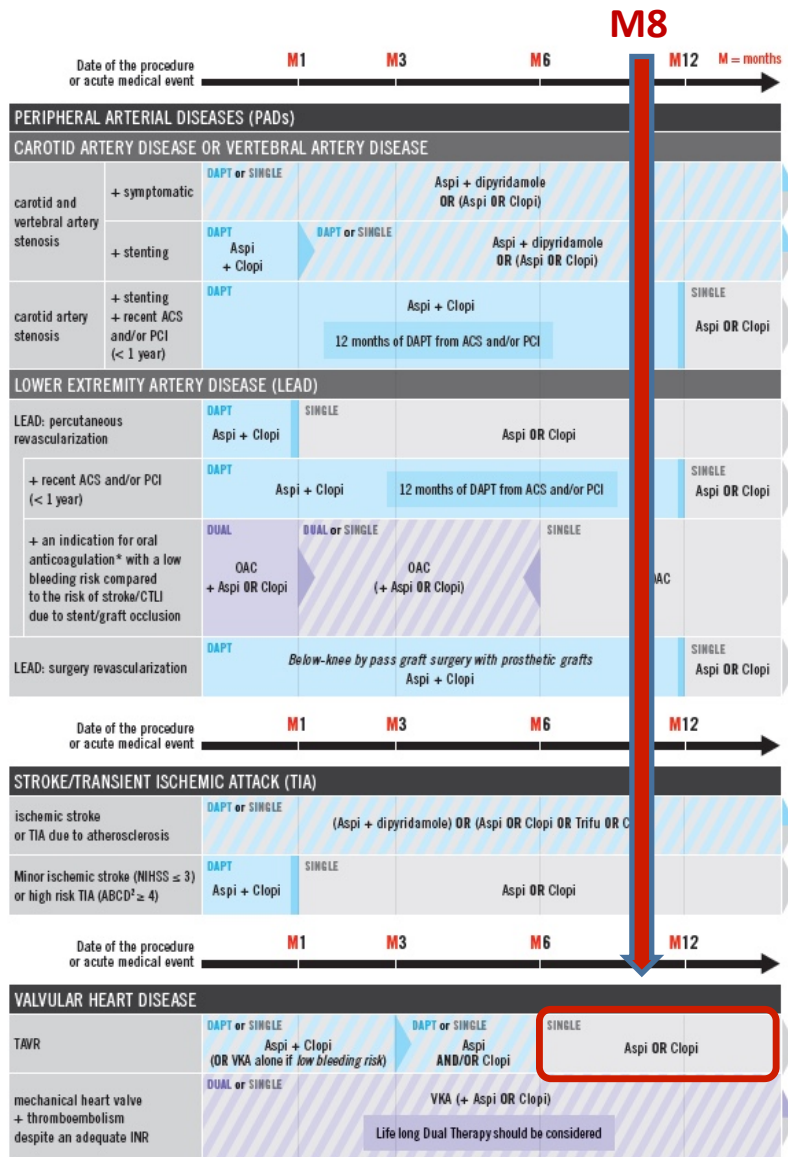
** High risk for LV thrombus: Ejection Fraction < 40%, Anteroseptal wall motion abnormality.



*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.

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



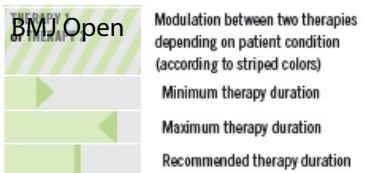
Long-term single antithrombotic therapy is recommended:
1) Aspirin
2) Clopidogrel

*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.

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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)



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)
Prasugr 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

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

THE COCKCROFT AND GAULT FORMULA (1973)

$$C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight})}{(72 \times S_{Cr})} \times 0.85 \text{ (if female)}$$

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, Four-Blade
^c Other bileaflet valve with insufficient data
^d Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

review only - <http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt>

In practice

Example 2: two cardiovascular diseases

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- At your medical consultation, you meet Mr V, 55 years old (weight: 81 kg, body mass index: 24 kg/m²).
 - 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?

Date of the procedure or acute medical event **M1** **M3** **BMJ Open** **M12** **M = months**

ACUTE/RECENT CORONARY SYNDROMES (ACS)					
NSTE-ACS or STEMI					
medically managed		DAPT	Aspi + Tica OR Clopi		SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE	OAC
with PCI (DES, BMS, or DCB)		DAPT	Aspi + Prasu OR Tica OR Clopi		MONO
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			
+ an indication for oral anticoagulation*	TRIPLE	TRIPLE or DUAL	OAC + Aspi AND/OR Clopi	DUAL	SINGLE
	OAC + Aspi + Clopi			OAC + Aspi OR Clopi	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 (HAS BLED ≥ 3)					
with CABG		DAPT	Aspi + Prasu OR Tica OR Clopi		SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE	OAC
STEMI					
with fibrinolytic therapy		DAPT Aspi + Clopi	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			
+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi		SINGLE	Aspi
with LV thrombus or high risk of LV thrombus**		DUAL	VKA + Aspi OR Clopi	DAPT	SINGLE
				Aspi + Prasu OR Tica OR Clopi	Aspi
+ PCI (DES, BMS or DCB)	TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL DAPT	DAPT	SINGLE
			Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	Aspi

* 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 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.

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

ACUTE/RECENT CORONARY SYNDROMES (ACS)		M1	M3	BMJ Open	M12	M = months
NSTE-ACS or STEMI						
medically managed		DAPT	Aspi + Tica OR Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
with PCI (DES, BMS, or DCB)		DAPT	Aspi + Prasu OR Tica OR Clopi			MONO
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				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 (HAS BLED ≥ 3)						
with CABG		DAPT	Aspi + Prasu OR Tica OR Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
STEMI						
with fibrinolytic therapy		DAPT Aspi + Clopi	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE	
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi			SINGLE
with LV thrombus or high risk of LV thrombus**		DUAL VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi		SINGLE
		TRIPLE VKA + Aspi + Clopi	TRIPLE or DUAL APT Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	DAPT	Aspi + Prasu OR Tica OR Clopi	

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

* 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.

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3 **2bis- Locate the**
4 **precise clinical**
5 **situation of your**
6 **patient**
7 **(treatment**
8 **already**
9 **performed,**
10 **associated**
11 **pathologies etc.)**

Date of the procedure or acute medical event	M1	M3	M6	M12	M = months
ACUTE/RECENT CORONARY SYNDROMES (ACS)					
NSTE-ACS or STEMI					
medically managed	DAPT	Aspi + Tica OR Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE
					OAC
with PCI (DES, BMS, or DCB)	DAPT	Aspi + Prasu OR Tica OR Clopi			MONO
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	TRIPLE	TRIPLE or DUAL	OAC + Aspi AND/OR Clopi	DUAL	SINGLE
	OAC + Aspi + Clopi	OAC + Aspi	OAC + Aspi OR Clopi	OAC + Aspi OR Clopi	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 (HAS BLED ≥ 3)				
with CABG	DAPT	Aspi + Prasu OR Tica OR Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE
					OAC
STEMI					
with fibrinolytic therapy	DAPT	DAPT or SINGLE	Aspi (+ Clopi)		SINGLE
	Aspi + Clopi				Aspi
+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
with LV thrombus or high risk of LV thrombus**	DUAL	VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi	SINGLE
					Aspi
+ PCI (DES, BMS or DCB)	TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL APT	DAPT	SINGLE
			Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	Aspi

ABBREVIATIONS

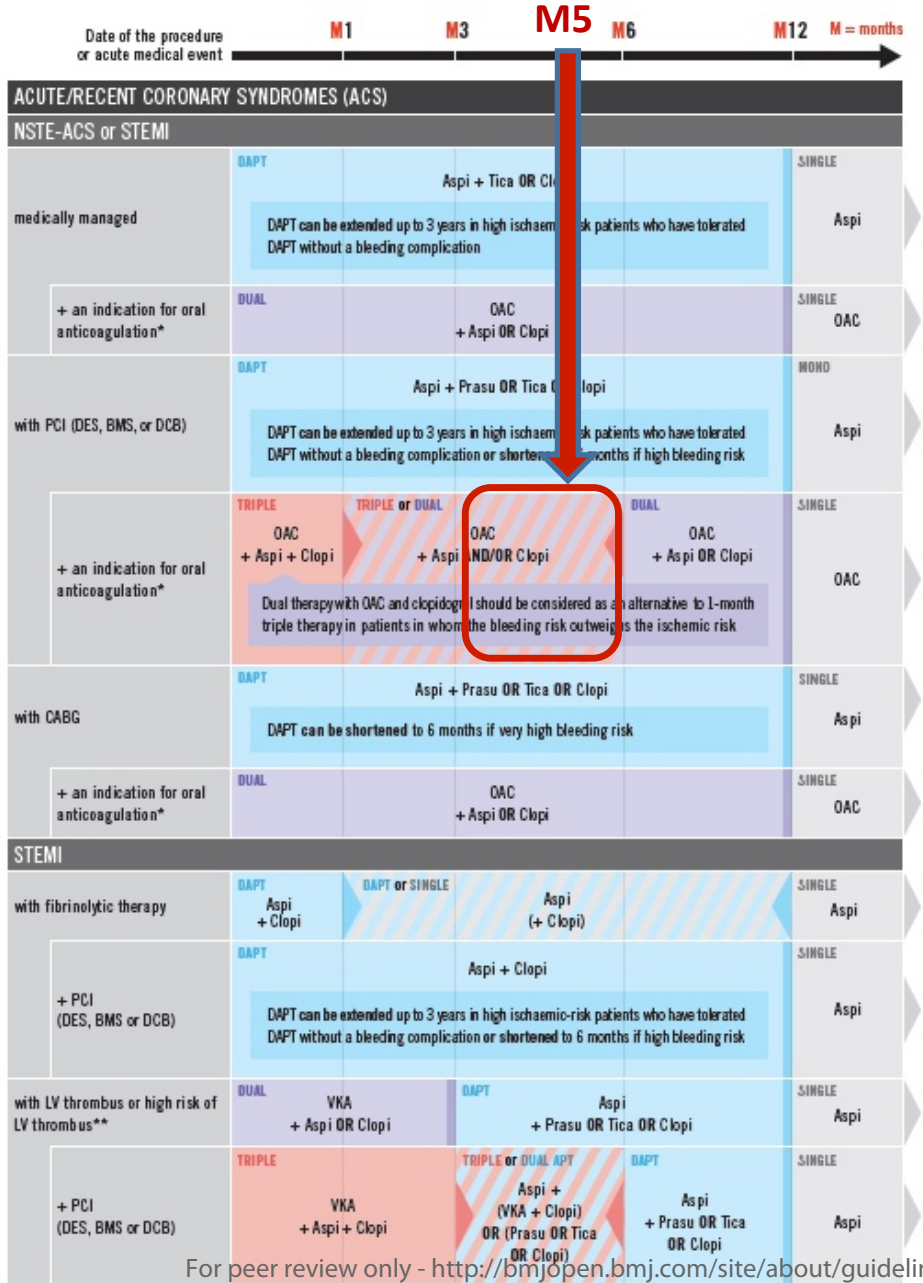
- CHA2DS2-VASc** C Congestive Heart failure (+1)
- H Hypertension (+1) A2 Age ≥ 75 (+2)
- D Diabetes Mellitus (+1) S2 Prior stroke or TIA thromboembolism (+2)
- V Vascular disease (+1) A Age 65-74 (+1)
- Sc Sex category (i.e.: female sex) (+1)

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 Bleeding or predisposition to bleeding (+1)
- Labile INR (+1) Elderly > 65 (+1)
- Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)

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

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37* **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**
38 **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**
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19 **3- In the**
20 **recommended**
21 **treatment, find**
22 **out where your**
23 **patient is**
24 **currently**
25 **(here: 5**
26 **months)**

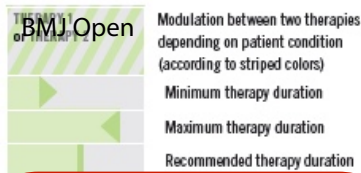
Here, two options are possible according to the ischemic and bleeding risk of your patient:

- 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)

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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.

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



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 (+1)
	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
NIBSS	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

TARGET INR FOR MECHANICAL PROSTHESES	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, Sorbus
^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)

$C_{Cr} = \left(\frac{140 - \text{Age}}{72} \times \text{Weight} \right) \times 0.85$ (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)

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 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/m²). 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

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

- 5
- 6 • 1 month
 - 7 • 6 months
 - 8 • 12 months
 - 9 • For life
- 10

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

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

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

- 21
- 22 • The prescription support-tool helped me answer to the clinical vignettes:../10
 - 23 • The prescription support-tool has modified the answers that I spontaneously made to
 - 24 clinical vignettes:../10
 - 25 • The prescription support-tool is clear:../10
 - 26 • The prescription support-tool is operational:../10
 - 27 • The prescription support-tool is useful for practice:../10
 - 28 • I would be ready to use this prescription support-tool:../10
 - 29 • I would recommend the use of this prescription support-tool:../10
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33 **Notes on the tool: What are the points of the prescription support-tool that could be**
34 **improved: useless information, missing information, presentation, etc:**

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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

1			
2	Objectives	7	Specific objectives or hypotheses
3			→ Lines 99 - 102, page 5
4			
5	Trial design	8	Description of trial design including type of trial (eg, parallel group,
6			crossover, factorial, single group), allocation ratio, and framework (eg,
7			superiority, equivalence, noninferiority, exploratory)
8			
9			
10			
11	Methods: Participants, interventions, and outcomes		
12			
13	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
14			and list of countries where data will be collected. Reference to where
15			list of study sites can be obtained
16			→ Lines 106 - 107 page 5
17			
18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
19			criteria for study centres and individuals who will perform the
20			interventions (eg, surgeons, psychotherapists)
21			→ Lines 107 - 109 page 5
22			
23			
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
25			including how and when they will be administered
26			→ Lines 110 - 136, page 5 - 6
27			
28			
29		11b	Criteria for discontinuing or modifying allocated interventions for a
30			given trial participant (eg, drug dose change in response to harms,
31			participant request, or improving/worsening disease)
32			
33		11c	Strategies to improve adherence to intervention protocols, and any
34			procedures for monitoring adherence (eg, drug tablet return,
35			laboratory tests)
36			
37			
38		11d	Relevant concomitant care and interventions that are permitted or
39			prohibited during the trial
40			
41	Outcomes	12	Primary, secondary, and other outcomes, including the specific
42			measurement variable (eg, systolic blood pressure), analysis metric
43			(eg, change from baseline, final value, time to event), method of
44			aggregation (eg, median, proportion), and time point for each
45			outcome. Explanation of the clinical relevance of chosen efficacy and
46			harm outcomes is strongly recommended
47			→ Lines 148 - 159, page 7
48			
49			
50	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
51	timeline		washouts), assessments, and visits for participants. A schematic
52			diagram is highly recommended (see Figure)
53			→ Lines 110 - 136, page 5 - 6
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2 Sample size 14 Estimated number of participants needed to achieve study objectives
3 and how it was determined, including clinical and statistical
4 assumptions supporting any sample size calculations
5 → **Lines 201 – 208, page 9**
6
7 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
8 target sample size
9 → **Lines 146-147, page 7**
10
11

12 **Methods: Assignment of interventions (for controlled trials)**

13 Allocation:

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16 Sequence generation 16a Method of generating the allocation sequence (eg, computer-
17 generated random numbers), and list of any factors for stratification.
18 To reduce predictability of a random sequence, details of any planned
19 restriction (eg, blocking) should be provided in a separate document
20 that is unavailable to those who enrol participants or assign
21 interventions
22 **Lines 137 – 143, page 6-7**
23 **Lines 192 - 195 page 8-9**
24
25
26 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central
27 telephone; sequentially numbered, opaque, sealed envelopes),
28 describing any steps to conceal the sequence until interventions are
29 assigned
30 **Lines 192 - 195 page 8-9**
31
32
33 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
34 and who will assign participants to interventions
35 **Lines 192 - 195 page 8-9**
36
37
38 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial
39 participants, care providers, outcome assessors, data analysts), and
40 how
41
42 17b If blinded, circumstances under which unblinding is permissible, and
43 procedure for revealing a participant's allocated intervention during
44 the trial
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47 **Methods: Data collection, management, and analysis**

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

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- 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

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
→ **Lines 243 - 252 page 11**

1			
2	Protocol	25	Plans for communicating important protocol modifications (eg,
3	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
4			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
5			regulators)
6			
7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
8			participants or authorised surrogates, and how (see Item 32)
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10		26b	Additional consent provisions for collection and use of participant data
11			and biological specimens in ancillary studies, if applicable
12			
13	Confidentiality	27	How personal information about potential and enrolled participants will
14			be collected, shared, and maintained in order to protect confidentiality
15			before, during, and after the trial
16			→ Lines 198 - 199, page 9
17			
18	Declaration of	28	Financial and other competing interests for principal investigators for
19	interests		the overall trial and each study site
20			→ Line 265, page 12
21			
22	Access to data	29	Statement of who will have access to the final trial dataset, and
23			disclosure of contractual agreements that limit such access for
24			investigators
25			
26	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
27	post-trial care		compensation to those who suffer harm from trial participation
28			
29	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
30	policy		participants, healthcare professionals, the public, and other relevant
31			groups (eg, via publication, reporting in results databases, or other
32			data sharing arrangements), including any publication restrictions
33			→ Lines 251 - 252, page 11
34			
35		31b	Authorship eligibility guidelines and any intended use of professional
36			writers
37			
38		31c	Plans, if any, for granting public access to the full protocol, participant-
39			level dataset, and statistical code
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45	Appendices		
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47	Informed consent	32	Model consent form and other related documentation given to
48	materials		participants and authorised surrogates
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50	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
51	specimens		specimens for genetic or molecular analysis in the current trial and for
52			future use in ancillary studies, if applicable
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Complete List of Authors:	<p>ZERAH, Lorene; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique Bonnet-Zamponi, Dominique; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique Ile de France, OMEDIT Frappé, Paul; Institut de recherche en médecine générale; University of Saint-Etienne, Department of General Practice Hauguel-Moreau, Marie; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de cardiologie De Rycke, Yann; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi) Magnier, Anne-Marie; Sorbonne Université, Département de médecine générale Pautas, Eric; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de gériatrie Charles, Pierre; Institut Mutualiste Montsouris, Médecine Interne Collet, Jean-philippe; Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département de cardiologie Dechartres, Agnes; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; APHP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi) Tubach, Florence; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique; APHP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi)</p>
Primary Subject Heading:	Pharmacology and therapeutics

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



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3 **Evaluation of a prescription support-tool for chronic management of oral**
4 **antithrombotic combinations in adults using clinical vignettes: protocol of a randomized**
5 **controlled trial**
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12 Zerah L¹, Bonnet-Zamponi D^{1,2}, Frappé P^{3,4}, Hauguel-Moreau M⁵, De Rycke Y^{1,6}, Magnier
13 AM⁷, Pautas E⁸, Charles P⁹, Collet JP⁵, Dechartres A^{1,6}, Tubach F^{1,6}
14
15

- 16 1. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
17 Publique, F-75013 Paris, France
- 18 2. Observatoire du Médicament des Dispositifs Médicaux et de l'Innovation Thérapeutique
19 Ile de France (OMEDIT), Paris, France
- 20 3. Institut de recherche en médecine générale, Paris, France
- 21 4. Département de médecine générale, Université de Saint-Etienne, Saint-Etienne, France
- 22 5. Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix,
23 Département de Cardiologie, F-75013 Paris, France
- 24 6. AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix, Département
25 Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie
26 (Cephepi), F-75013 Paris, France
- 27 7. Sorbonne Université, Département de Médecine Générale, F-75013 Paris, France
- 28 8. Sorbonne Université, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix,
29 Département de Gériatrie, F-75013 Paris, France
- 30 9. Institut Mutualiste Montsouris, Département de Médecine Interne, F-75014 Paris, France

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36
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38
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40
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42 *** Corresponding author: Dr Lorene Zerah**

43
44 Correspondence to: lorene.zerah@inserm.fr

45
46 Address: Département Biostatistique Santé Publique et Information Médicale, Centre de
47 Pharmacoépidémiologie (Cephepi), Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l'hôpital,
48 75013, Paris, France

49
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51 Tel: +33 1 42 16 03 47
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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

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3 AT combinations were numerous (n=70) and none encompassed all the clinical situations
4 requiring oral AT combinations. This review highlighted the difficulty for a physician to
5 quickly find the most up-to-date recommendation and the one most relevant to the patient's
6 clinical situation. These findings, agreed with clinical experience, led us to synthesize all the
7 recommendations into a prescription support-tool (**Figure 1**)[9] to help physicians prescribe
8 oral AT combinations.
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12 Our hypothesis is that this prescription support-tool would improve the prescription of oral
13 ATs to comply with guidelines. Our primary objective is to assess the impact of this tool on
14 improving the prescription of oral ATs to comply with guidelines (in terms of number of
15 drugs, drug class, dosage and duration at the same time).
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28 **METHODS AND ANALYSIS**

29 **Study design, study setting and eligibility criteria**

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32 A web-based, open randomized controlled trial involving clinical vignettes will be performed
33 in France via an online survey. This study will be conducted among French general
34 practitioners and cardiologists involved in outpatient settings. Physicians with an exclusive
35 hospital practice will not be eligible.
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42 Physicians will be identified and contacted to participate in the online survey by email via
43 physician associations, social networks or word of mouth. The survey will gather
44 informations on physicians' characteristics, including age, sex, medical specialty (cardiologist
45 or general practitioner), place of exercise (hospital or ambulatory setting), years of medical
46 practice, approximate proportion of patients prescribed oral AT combinations in their practice
47 ($\leq 5\%$, 6 – 10%, 11-20% or $\geq 21\%$), whether physicians feel comfortable or not with
48 management of oral AT prescriptions (totally, partially, rarely, never), and whether physicians
49 know where to find the most recent guidelines on oral AT prescriptions. Then, physicians will
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3 be randomized to 2 arms: the experimental arm, having access to the prescription support-tool
4 **(Figure 1),**[9] and the control arm, with no prescription support-tool. For physicians in the
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6 **(Appendix 1),**[9] both downloaded (or just viewed) online in pdf format. Then, participants
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8 from both arms will be presented 3 different clinical vignettes illustrating outpatient clinical
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10 situations and will be asked to propose prescriptions for each clinical vignette (oral AT or not,
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12 number of oral ATs, type of oral ATs, dosage of each oral AT and duration of the
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14 prescription) by answering 4 multiple-choice questions (each question on a separate web
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16 page). Question 5 will evaluate the degree of confidence of physicians have that their
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18 prescription of ATs complies with guidelines on a scale of 0 to 10. Physicians in the
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20 experimental arm will answer each question with the help of the tool, downloadable (or
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22 viewable on each page). At the end, we will ask to physicians of the experimental arm to rate,
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24 on a scale from 0 and 10, the usefulness of the prescription support-tool, how much they
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26 would be willing to use this prescription support-tool in their practice and if they would
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28 recommend its use. Physicians in the control arm will be asked to answer according to their
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30 actual clinical practice as closely as possible. Once the answer is given, physicians cannot go
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32 back or change their answers. Physicians must answer the questions consecutively; however,
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34 they will be allowed to stop and continue at any time (on the same computer). Physicians
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36 from the control arm will be able to download the prescription support-tool once they have
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38 completed their answers for the 3 clinical vignettes.
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49 The scientific and expert committee have created and validated 30 clinical vignettes. To
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51 ensure that each clinical vignette will be read the same number of times in both arms, we
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53 created 2 randomized lists of clinical vignettes in blocks of 30 (one list per trial arm). Clinical
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55 vignettes will then be allocated consecutively 3 by 3 to each physician, according to the arm
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57 in which he/she was randomized. Therefore, in each arm, for every 10 physicians randomized,
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3 all clinical vignettes will be read once. The randomization unit will be the physician and the
4 unit of analysis the clinical vignette. Three clinical vignettes per physician was a middle
5 ground to ensure the feasibility of the study considering both participants' availability
6 (acceptable time to complete the clinical vignettes) and statistical need (number of clinical
7 vignettes needed). To maximize the participation rate, physicians will be sent reminders every
8 20 days.
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16 **Outcomes**

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

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46 We developed, from a systematic review of international guidelines published between 2012
47 and 2018,[9] a prescription support-tool to help physicians prescribe oral AT combinations
48 for complying with guidelines. This prescription support-tool synthesizes, on a double-sided
49 page, selected international guidelines on chronic management (at least 1 month) of oral AT
50 combinations (indication, drugs, dosages and duration) in adults, without considering in-
51 hospital management and bridging therapy (**Figure 1**).[9] We excluded particular clinical
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3 situations that require inevitably specialist medical advice: active cancer, autoimmune
4 diseases, haemophilia, HIV, paediatrics and pregnancy. The following pathologies were
5 included in this tool because they are the main causes leading to the prescription of ATs
6 (single, dual or triple therapy) in adults[1]: non-valvular atrial fibrillation, coronary artery
7 disease, ischemic stroke, valvular heart disease, peripheral artery disease and venous
8 thromboembolism. Therefore, this tool covers prevention of ischemic and /or embolic events
9 in patients with a history of coronary disease (stable coronary disease or acute coronary
10 syndrome), non-valvular atrial fibrillation, peripheral artery disease, venous
11 thromboembolism disease, ischemic stroke (and transient ischemic attack) and/or valvular
12 heart disease (bioprosthesis, mechanical valve and transcatheter aortic valve replacement).
13 It does not cover primary prevention in other scenarios such as patients without those
14 conditions but at low or high-risk for ischemic events (**Figure 1**).[9] Our tool also specifies
15 the type of oral ATs that should never be combined (combinations of oral anticoagulants
16 [OACs], combinations of P2Y12 inhibitors or combining one OAC with one potent P2Y12
17 inhibitor, namely ticagrelor or prasugrel), the clinical situations in which oral AT
18 combinations are never indicated and the contraindications of ATs. This prescription support-
19 tool aims to give physicians quick access to the recommendation that fits most of their
20 patient's clinical situation. The prescription support-tool is accompanied by an explanatory
21 guide (how to read and use the tool, with examples, **Appendix 1**).[9]

46 **Clinical vignettes**

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

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

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18 Physicians will be allocated to the two arms in blocks of 4 by use of a computer-generated
19 randomization scheme implemented in the online survey (1:1 ratio), then stratified by their
20 medical specialty.
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26 **Data collection methods and data management**

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

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39 Considering that 85% of AT prescriptions fully comply with guidelines in the control arm,^[8]
40 to demonstrate an increase in this proportion up to 90% in the experimental arm, we need to
41 include (for a power of 80% and an alpha risk of 5%) a minimum of 229 physicians per arm.
42 To obtain a multiple of 10 physicians (because each physician will complete 3 of 30 clinical
43 vignettes and to have all clinical vignettes completed the same number of times in each arm),
44 we plan to include at least 230 physicians per arm. However, if more physicians participate,
45 all collected data will be considered. For each clinical vignette, we will consider that
46 prescription is fully appropriate (versus inappropriate) if answers to each of the first four
47 questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To
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3 compare the percentage of fully appropriate prescriptions between the two randomized arms,
4 taking into account that each participant intends to complete 3 clinical vignettes, we will use a
5 logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial
6 arm. We will use the same method to compare the percentage of prescriptions of oral ATs that
7 comply with guidelines in terms of number of drugs, drug class, duration and dosage, each
8 assessed separately, between the two randomized arms (secondary analyses). To compare the
9 degree of confidence that physicians have that their prescription of oral AT combinations
10 complies with guidelines (quantitative variable: scale from 0 and 10), taking into account that
11 each participant intends to complete 3 clinical vignettes, we will use a linear mixed model
12 with a clinical-vignette effect and a physician-effect nested in the trial arm. A sub-group
13 analysis for general practitioners and for cardiologist will be done. Finally, to assess the
14 overall usefulness of the tool, we will describe the data of the experimental arm (mean \pm SD,
15 median (25–75 interquartile range)). All analyses will involve use of R v3.5.2 ([www.cran.r-](http://www.cran.r-project.org)
16 [project.org](http://www.cran.r-project.org)).

35 **Scientific and expert committees**

37 Our study involves a scientific committee and an expert committee. The scientific committee
38 consists of a cardiologist, 2 internist-geriatricians, a general practitioner and 2
39 epidemiologists. The scientific committee designed the study protocol, created and validated
40 the clinical vignettes and will be responsible for data analysis and writing of the manuscript.
41 The expert committee consists of a cardiologist, a geriatrician, an internist and 2 general
42 practitioners (medical specialties that often deal with patients needing chronic oral AT
43 prescriptions). The expert committee had to review all clinical vignettes with the prescription
44 support-tool (external validation) to confirm the agreement of the clinical vignettes with
45 clinical practice and their readability. The committee estimated the time needed to complete 3
46 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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2
3 **Acknowledgements:** We thank Sebastien Zerah who designed the online survey. We thank
4
5 Laura Smales (BioMedEditing) for English editing
6

7 **Authors' contributions:** LZ, DBZ, AD and FT designed the study. YDR designed the
8
9 statistical analysis. LZ and MHM designed the clinical vignettes. PF, AMM, EP, PC and JPC
10
11 reviewed the clinical vignettes. LZ, DBZ, MHM, AD and FT validated the clinical vignettes.
12
13 LZ drafted and prepared the manuscript for publication. All authors re-read and corrected the
14
15 manuscript. All authors approved the final manuscript.
16
17

18
19 **Funding statement:** This work was supported by Sorbonne Université (PhD grant).
20

21 **Competing interests:** None.
22

23
24 **Ethics approval:** The ethics evaluation committee of Inserm, the *Institutional Review Board*
25
26 (IRB00003888) reviewed and approved our research project on 06/12/2018 (no. 18-492). The
27
28 ethics evaluation committee of Inserm reviewed and approved a revised version of the
29
30 protocol on 10/03/18 (no. 18-492 bis) to allow us to communicate our trial via social networks
31
32 or word of mouth.
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35 **Trial registration:** ClinicalTrials.gov ID: NCT03630874.
36

37 **The study start date is November 2018.**
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40 **Data sharing statement:** The manuscript is a protocol for a randomized controlled trial,
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42 which does not include data.
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53 given, any changes made indicated, and the use is non-commercial. See:
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55 <http://creativecommons.org/licenses/by-nc/4.0/>.
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3 13. Peabody JW, Luck J, Glassman P, *et al.* Measuring the quality of physician practice by
4 using clinical vignettes: a prospective validation study. *Ann Intern Med* 2004;**141**:771-
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For peer review only

How to use the prescription support tool

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General presentation of the prescription support tool

Colour codes for single, dual or triple therapy

Codes for duration of treatments

2019 SYNTHESIS OF RECOMMENDATIONS FOR CHRONIC MANAGEMENT OF ANTITHROMBOTIC COMBINATIONS INDICATIONS, DURATION AND DOSAGE IN ADULTS

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

Abbreviations

ABCD² score for TIA
 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
Aspl 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 (+1)
 V Vascular disease (+1) A Age 65-74 (+1)

Dosage of antithrombotic drugs

Aspirin: 75-100 mg/day
Aspirin/dipyridamol: 25/200 mg twice a day
Aspirin/ticlopidogrel: 75 mg/day
Aspirin/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
Ticlopidogrel: 90 mg twice a day
 Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds.
Rivaroxaban: 600 mg/day
 3 for NV-AF, VTE, LV thrombus

! 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:
 - ischaemic 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 bioprostheses
- Embolism ischaemic stroke
- Recurrent stroke despite SAPT
- Mitral stenosis and previous stroke or left atrial thrombus
- Carotid or vertebral stenosis (except with stent) } Indications for SAPT
- Carotid or vertebral dissection } SAPT or SACT. 3-6 month
- Valvular bioprostheses } 3-6 months of SACT (SAPT for patients with aortic bioprostheses at high risk of bleeding)

Indications for SACT

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

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

Combinations of antithrombotic drugs NEVER recommended

Recommended dosages for each drug

Abbreviations used in the tool

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

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 (+1) or liver function (+2) Hypertension (+1) Stroke history (+1) Prior major Bleeding or predisposition to bleeding (+1) Labile INR (+1) Elderly > 65 (+1) Drugs (concomitant Aspl, Clopi, NSAIDs (+1)) or alcohol (+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 Anticoagulation: VKA or DOA
PCI	Percutaneous coronary intervention (= DES, BMS or DCB)
Prasu	Prasugrel
SAPT	Single Antiplatelet Therapy
SACT	Single Anticoagulation Therapy
SIHD	Stable Ischaemic Heart Disease
STEMI	ST-Elevation Myocardial Infarction
TAVR	Transcatheter Aortic Valve Replacement
TIA	Transient Ischaemic Attack
Tica	Ticagrelor
Trifu	Trifluralin
TRIPLE	Triple Therapy: DAPT + SACT
VKA	Vitamin K Antagonist Transcatheter Aortic Valve
VTE	Venous Thromboembolism

Target INR for mechanical valves

TARGET INR FOR MECHANICAL PROSTHESE Patient-related risk factor*

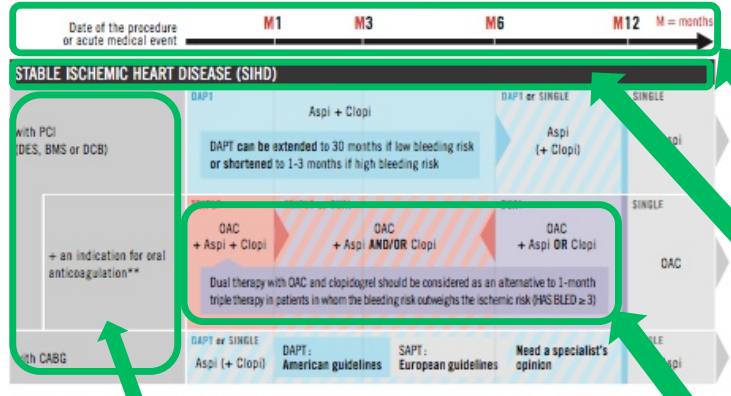
Prosthesis thromboembolism	None	≥1
Low [†]	2.5	3.0
Medium [‡]	3.0	3.5
High [§]	3.5	4.0

INR = international normalized ratio, DEF = left ventricular ejection fraction
 * Mitral or tricuspid valve replacement, previous thrombotic atrial fibrillation, mitral stenosis of any degree, LVF, etc.
 † Carbomedics, Medtronic Hall, AFS, Medtronic Pro, St-Jude Medical, On-X, Sorin Bicarbon
 ‡ Other bileaflet valve with insufficiently closed AVA
 § Lillehei-Kaster, Omniscience, Edwards (ball-cage), Björk-Shiley and other tilting-disc valves

THE COCKCROFT AND GAULT FORMULA (1973)
 $Cr_{cl} = \frac{[(140 - \text{Age}) \times \text{Weight}] / (72 \times S_{cr}) \times 0.85 \text{ (if female)}}{1.73}$
 Cr_{cl} (creatinine clearance) = mL/minute
 Age = years Weight = kg S_{cr} (serum creatinine) = mg/dL

IF BLEEDING DURING DAPT, follow these recommendations (Aurep, 2019):
<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2019-2020/antithrombotic-therapy-in-atrial-fibrillation>

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 disease)



Timeline (in months) since diagnosis or beginning of treatment

Pathology

Time dependant recommended treatments

Link for recommendations if bleeding during DAPT

Specific conditions not included in the tool

Cockcroft and Gault formula

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

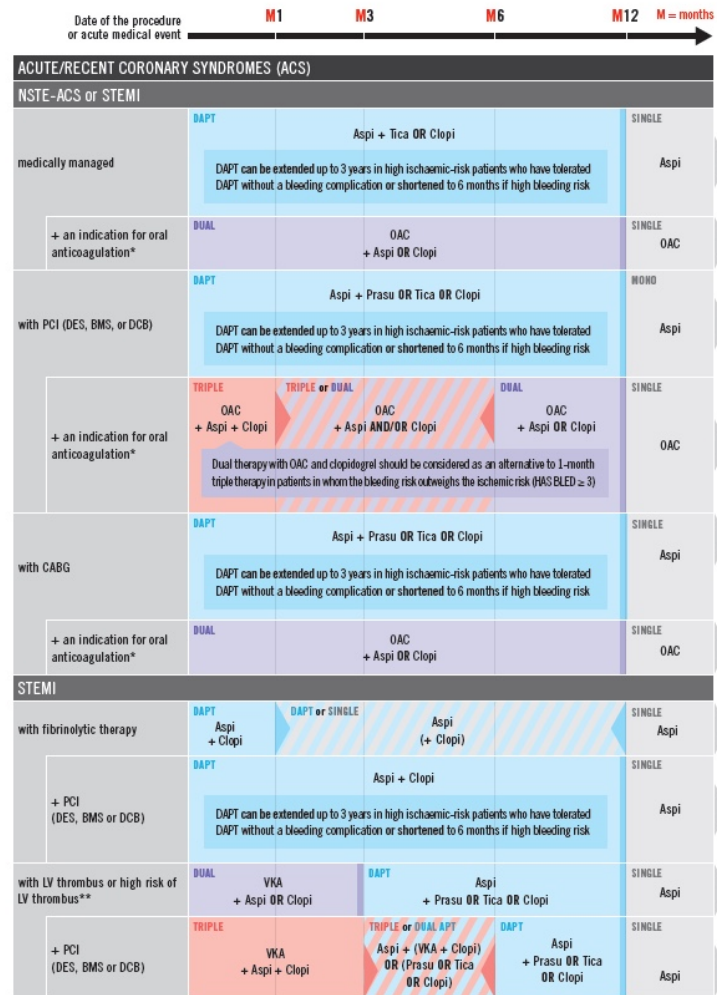
In practice

Example 1: one cardiovascular disease

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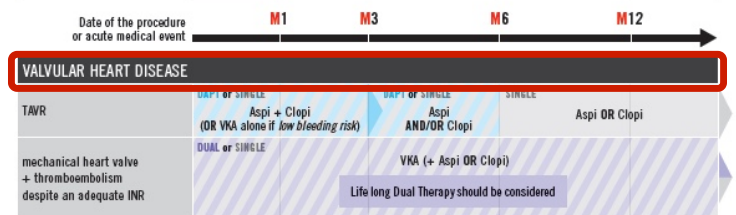
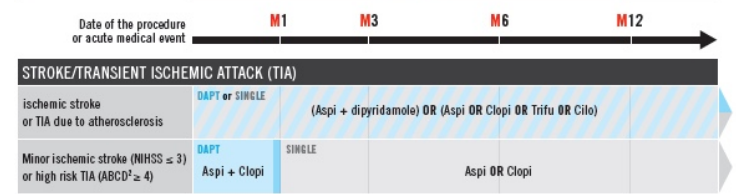
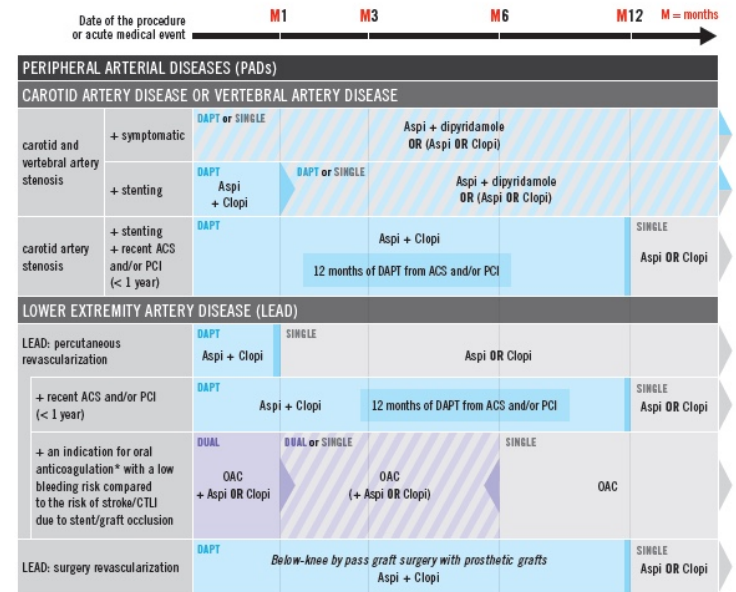
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- At your medical consultation, you meet Mr R, 85 years old (weight: 81 kg, body mass index: 24 kg/m²).
 - Medical history: arterial hypertension and Parkinson disease
 - He had surgery 8 months ago for an aortic stenosis: transcatheter aortic valve 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.

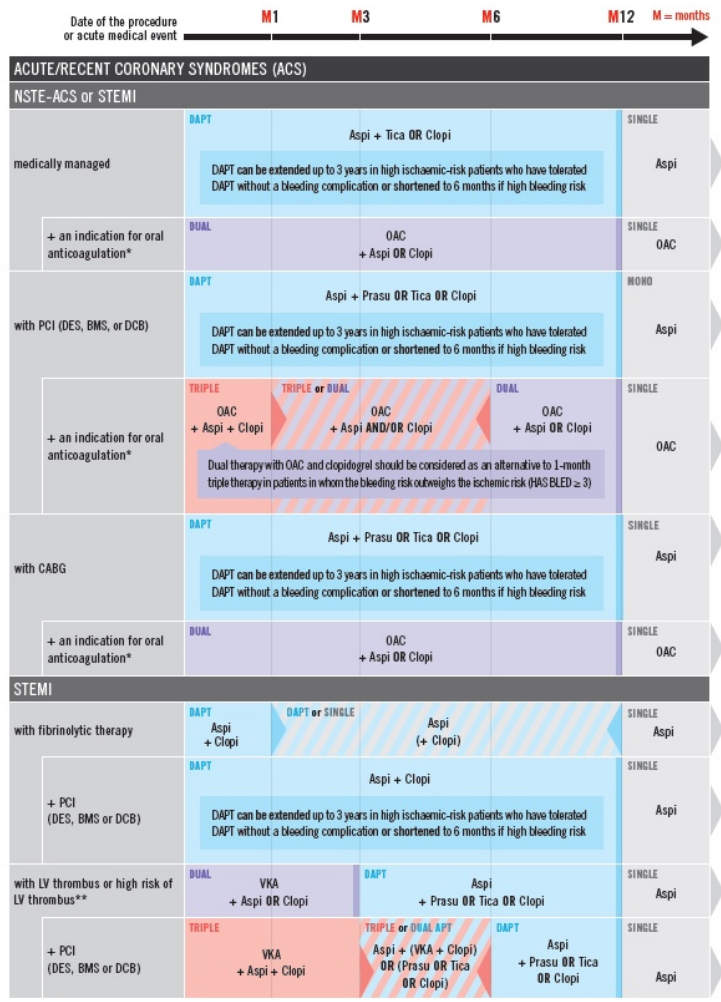
** High risk for LV thrombus: Ejection Fraction < 40%, Anteroapical wall motion abnormality.



*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.

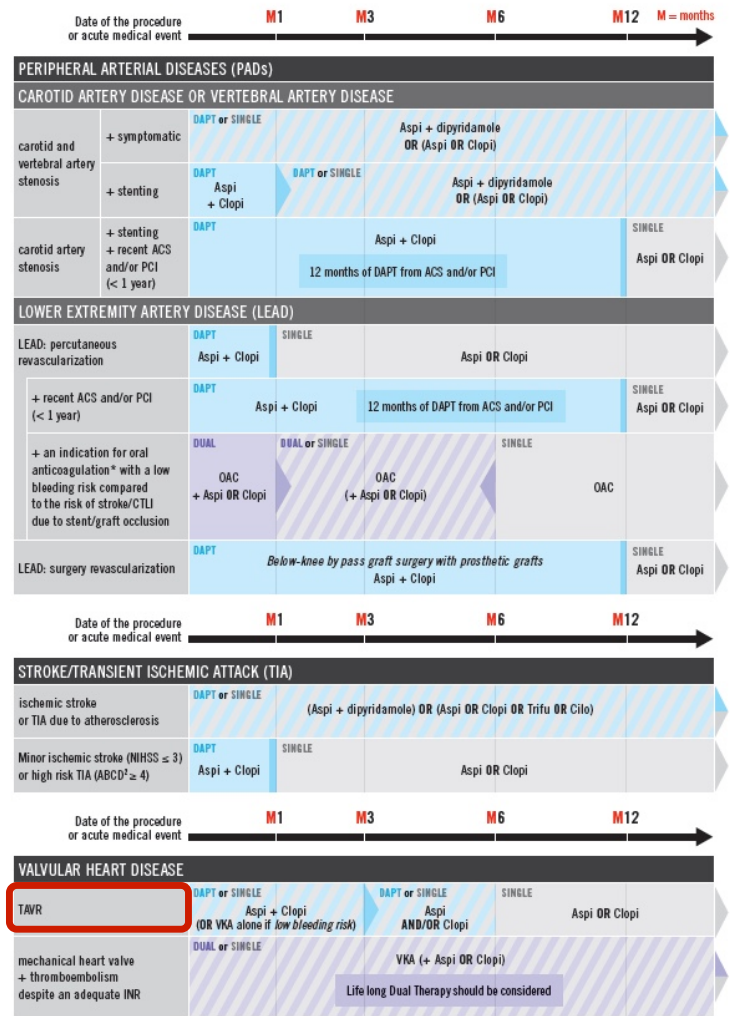
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2- Locate the precise clinical situation of your patient (treatment already performed, associated pathologies etc.)



*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.

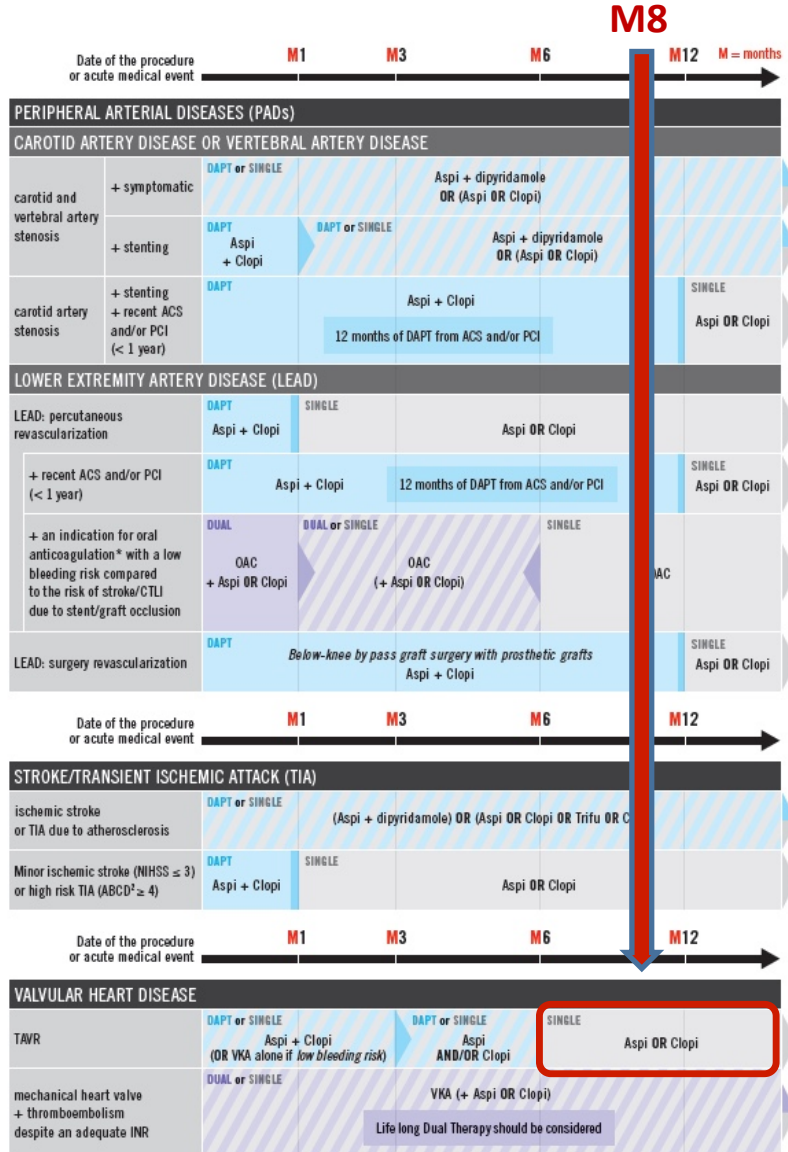
** High risk for LV thrombus: Ejection Fraction < 40%, Anteroseptal wall motion abnormality.



*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.

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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

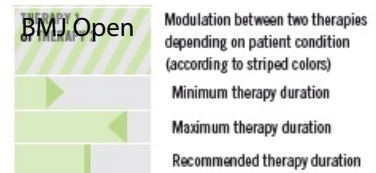
*Indication for OAC: Mechanical heart valve prosthesis, NV-AF or flutter with CHA2DS2-VASC score ≥ 2 for men and ≥ 3 for female. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASC score of 1 and in female AF patients with a CHA2DS2-VASC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

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

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

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



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)
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

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

THE COCKCROFT AND GAULT FORMULA (1973)

$$C_{Cr} = \frac{((140 - \text{Age}) \times \text{Weight})}{(72 \times S_{Cr})} \times 0.85 \text{ (if female)}$$

$$C_{Cr} \text{ (creatinine clearance)} = \text{mL/minute}$$

$$\text{Age} = \text{years} \quad \text{Weight} = \text{kg} \quad S_{Cr} \text{ (serum creatinine)} = \text{mg/dL}$$

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 PROSTHESES	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, Four-Blade
^c Other bileaflet valve with insufficient data
^d Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork Shiley and other tilting-disc valves

In practice

Example 2: two cardiovascular diseases

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- At your medical consultation, you meet Mr V, 55 years old (weight: 81 kg, body mass index: 24 kg/m²).
 - 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?

Date of the procedure or acute medical event **M1** **M3** **BMJ Open** **M12** **M = months**

ACUTE/RECENT CORONARY SYNDROMES (ACS)				
NSTE-ACS or STEMI				
medically managed		DAPT	Aspi + Tica OR Clopi	SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk		
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
with PCI (DES, BMS, or DCB)		DAPT	Aspi + Prasu OR Tica OR Clopi	MONO
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk		
+ an indication for oral anticoagulation*	TRIPLE	TRIPLE or DUAL	DUAL	SINGLE
	OAC + Aspi + Clopi	OAC + Aspi AND/OR Clopi	OAC + Aspi OR Clopi	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 (HAS BLED ≥ 3)				
with CABG		DAPT	Aspi + Prasu OR Tica OR Clopi	SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk		
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi		SINGLE OAC
STEMI				
with fibrinolytic therapy		DAPT Aspi + Clopi	DAPT or SINGLE	SINGLE
		Aspi (+ Clopi)		
+ PCI (DES, BMS or DCB)		DAPT	Aspi + Clopi	SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk			Aspi
with LV thrombus or high risk of LV thrombus**		DUAL	VKA + Aspi OR Clopi	SINGLE
		Aspi + Prasu OR Tica OR Clopi		
+ PCI (DES, BMS or DCB)	TRIPLE	TRIPLE or DUAL	DAPT	SINGLE
	VKA + Aspi + Clopi	Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	Aspi

* 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 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.

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

ACUTE/RECENT CORONARY SYNDROMES (ACS)		M1	M3	BMJ Open	M12	M = months
NSTE-ACS or STEMI						
medically managed		DAPT	Aspi + Tica OR Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
with PCI (DES, BMS, or DCB)		DAPT	Aspi + Prasu OR Tica OR Clopi			MONO
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				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 (HAS BLED ≥ 3)						
with CABG		DAPT	Aspi + Prasu OR Tica OR Clopi			SINGLE
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE OAC
STEMI						
with fibrinolytic therapy		DAPT Aspi + Clopi	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE	
		DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
	+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi			SINGLE
with LV thrombus or high risk of LV thrombus**		DUAL VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi		SINGLE
		TRIPLE VKA + Aspi + Clopi	TRIPLE or DUAL APT Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	DAPT	Aspi + Prasu OR Tica OR Clopi	

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

* 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.

<https://www.bmj.com/site/about/guidelines.xhtml>

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3 **2bis- Locate the**
4 **precise clinical**
5 **situation of your**
6 **patient**
7 **(treatment**
8 **already**
9 **performed,**
10 **associated**
11 **pathologies etc.)**

Date of the procedure or acute medical event	M1	M3	M6	M12	M = months
ACUTE/RECENT CORONARY SYNDROMES (ACS)					
NSTE-ACS or STEMI					
medically managed	DAPT	Aspi + Tica OR Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE
					OAC
with PCI (DES, BMS, or DCB)	DAPT	Aspi + Prasu OR Tica OR Clopi			MONO
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	TRIPLE	TRIPLE or DUAL	OAC + Aspi AND/OR Clopi	DUAL	SINGLE
	OAC + Aspi + Clopi	OAC + Aspi	OAC + Aspi OR Clopi	OAC + Aspi OR Clopi	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 (HAS BLED ≥ 3)				
with CABG	DAPT	Aspi + Prasu OR Tica OR Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
+ an indication for oral anticoagulation*	DUAL	OAC + Aspi OR Clopi			SINGLE
					OAC
STEMI					
with fibrinolytic therapy	DAPT	DAPT or SINGLE	Aspi (+ Clopi)	SINGLE	
	Aspi + Clopi			Aspi	
+ PCI (DES, BMS or DCB)	DAPT	Aspi + Clopi			SINGLE
	DAPT can be extended up to 3 years in high ischaemic-risk patients who have tolerated DAPT without a bleeding complication or shortened to 6 months if high bleeding risk				Aspi
with LV thrombus or high risk of LV thrombus**	DUAL	VKA + Aspi OR Clopi	DAPT	Aspi + Prasu OR Tica OR Clopi	SINGLE
				Aspi	
+ PCI (DES, BMS or DCB)	TRIPLE	VKA + Aspi + Clopi	TRIPLE or DUAL APT	DAPT	SINGLE
			Aspi + (VKA + Clopi) OR (Prasu OR Tica OR Clopi)	Aspi + Prasu OR Tica OR Clopi	Aspi

ABBREVIATIONS

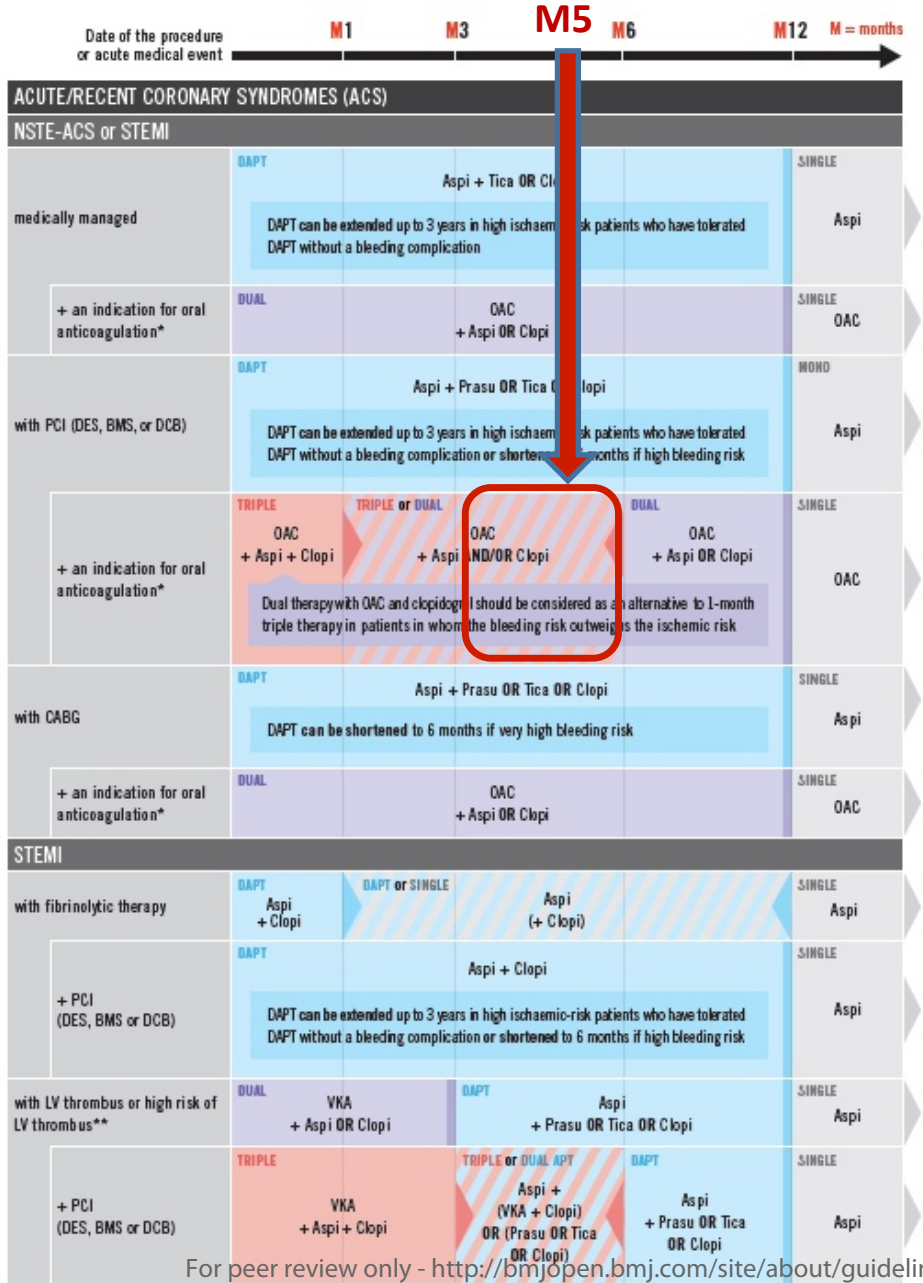
- CHA2DS2-VASc** C Congestive Heart failure (+1)
- H Hypertension (+1) A2 Age ≥ 75 (+2)
- D Diabetes Mellitus (+1) S2 Prior stroke or TIA thromboembolism (+2)
- V Vascular disease (+1) A Age 65-74 (+1)
- Sc Sex category (i.e.: female sex) (+1)

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 Bleeding or predisposition to bleeding (+1)
- Labile INR (+1) Elderly > 65 (+1)
- Drugs (concomitant aspirin, clopidogrel, NSAIDs) or alcohol (+1 or +2)

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

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37* **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**
38 **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**
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19 **3- In the**
20 **recommended**
21 **treatment, find**
22 **out where your**
23 **patient is**
24 **currently**
25 **(here: 5**
26 **months)**

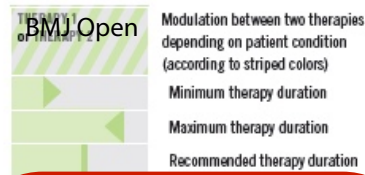
Here, two options are possible according to the ischemic and bleeding risk of your patient:

- 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)

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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.

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



Abbreviations

ABC² 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 (+1) 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 BLEED	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
NIBSS	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

TARGET INR FOR MECHANICAL PROSTHESES		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, Sorbus
^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)
 $C_{Cr} = \{((140 - \text{Age}) \times \text{Weight}) / (72 \times S_{Cr})\} \times 0.85$ (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

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11 **4- Check the**
12 **recommended**
13 **dosage for the**
14 **drugs you**
15 **want to**
16 **prescribe**

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/m²). 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

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

- 5
- 6 • 1 month
 - 7 • 6 months
 - 8 • 12 months
 - 9 • For life
- 10

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

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

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

- 21
- 22 • The prescription support-tool helped me answer to the clinical vignettes:../10
 - 23 • The prescription support-tool has modified the answers that I spontaneously made to
 - 24 clinical vignettes:../10
 - 25 • The prescription support-tool is clear:../10
 - 26 • The prescription support-tool is operational:../10
 - 27 • The prescription support-tool is useful for practice:../10
 - 28 • I would be ready to use this prescription support-tool:../10
 - 29 • I would recommend the use of this prescription support-tool:../10
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33 **Notes on the tool: What are the points of the prescription support-tool that could be**
34 **improved: useless information, missing information, presentation, etc:**

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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

1			
2	Objectives	7	Specific objectives or hypotheses
3			→ Lines 98 - 101, page 5
4			
5	Trial design	8	Description of trial design including type of trial (eg, parallel group,
6			crossover, factorial, single group), allocation ratio, and framework (eg,
7			superiority, equivalence, noninferiority, exploratory)
8			
9			
10			
11	Methods: Participants, interventions, and outcomes		
12			
13	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
14			and list of countries where data will be collected. Reference to where
15			list of study sites can be obtained
16			→ Lines 106 - 108 page 5
17			
18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
19			criteria for study centres and individuals who will perform the
20			interventions (eg, surgeons, psychotherapists)
21			→ Lines 106 - 108 page 5
22			
23			
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
25			including how and when they will be administered
26			→ Lines 109 - 136, page 5 - 6
27			
28			
29		11b	Criteria for discontinuing or modifying allocated interventions for a
30			given trial participant (eg, drug dose change in response to harms,
31			participant request, or improving/worsening disease)
32			
33		11c	Strategies to improve adherence to intervention protocols, and any
34			procedures for monitoring adherence (eg, drug tablet return,
35			laboratory tests)
36			
37			
38		11d	Relevant concomitant care and interventions that are permitted or
39			prohibited during the trial
40			
41	Outcomes	12	Primary, secondary, and other outcomes, including the specific
42			measurement variable (eg, systolic blood pressure), analysis metric
43			(eg, change from baseline, final value, time to event), method of
44			aggregation (eg, median, proportion), and time point for each
45			outcome. Explanation of the clinical relevance of chosen efficacy and
46			harm outcomes is strongly recommended
47			→ Lines 148 - 159, page 7
48			
49			
50	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
51	timeline		washouts), assessments, and visits for participants. A schematic
52			diagram is highly recommended (see Figure)
53			→ Lines 109 - 136, page 5 - 6
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2 Sample size 14 Estimated number of participants needed to achieve study objectives
3 and how it was determined, including clinical and statistical
4 assumptions supporting any sample size calculations
5 → **Lines 208 – 213, page 9**
6
7 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
8 target sample size
9 → **Lines 146-147, page 7**
10
11

12 **Methods: Assignment of interventions (for controlled trials)**

13 Allocation:

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16 Sequence generation 16a Method of generating the allocation sequence (eg, computer-
17 generated random numbers), and list of any factors for stratification.
18 To reduce predictability of a random sequence, details of any planned
19 restriction (eg, blocking) should be provided in a separate document
20 that is unavailable to those who enrol participants or assign
21 interventions
22 **Lines 137 – 143, page 6-7**
23 **Lines 198 - 201 page 9**
24
25
26 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central
27 telephone; sequentially numbered, opaque, sealed envelopes),
28 describing any steps to conceal the sequence until interventions are
29 assigned
30 **Lines 198 - 201 page 9**
31
32
33 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
34 and who will assign participants to interventions
35 **Lines 198 - 201 page 9**
36
37
38 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial
39 participants, care providers, outcome assessors, data analysts), and
40 how
41
42 17b If blinded, circumstances under which unblinding is permissible, and
43 procedure for revealing a participant's allocated intervention during
44 the trial
45
46

47 **Methods: Data collection, management, and analysis**

- 48
49 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other
50 trial data, including any related processes to promote data quality (eg,
51 duplicate measurements, training of assessors) and a description of
52 study instruments (eg, questionnaires, laboratory tests) along with
53 their reliability and validity, if known. Reference to where data
54 collection forms can be found, if not in the protocol
55 → **Lines 202 – 206 page 9**
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- 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

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- 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

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- 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**

1			
2	Protocol	25	Plans for communicating important protocol modifications (eg,
3	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
4			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
5			regulators)
6			
7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
8			participants or authorised surrogates, and how (see Item 32)
9			
10		26b	Additional consent provisions for collection and use of participant data
11			and biological specimens in ancillary studies, if applicable
12			
13	Confidentiality	27	How personal information about potential and enrolled participants will
14			be collected, shared, and maintained in order to protect confidentiality
15			before, during, and after the trial
16			→ Lines 204 - 205, page 9
17			
18	Declaration of	28	Financial and other competing interests for principal investigators for
19	interests		the overall trial and each study site
20			→ Line 269, page 12
21			
22	Access to data	29	Statement of who will have access to the final trial dataset, and
23			disclosure of contractual agreements that limit such access for
24			investigators
25			→ Lines 277 – 278, page 12
26			
27	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
28	post-trial care		compensation to those who suffer harm from trial participation
29			
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
31	policy		participants, healthcare professionals, the public, and other relevant
32			groups (eg, via publication, reporting in results databases, or other
33			data sharing arrangements), including any publication restrictions
34			→ Lines 256 - 257, page 11
35			
36		31b	Authorship eligibility guidelines and any intended use of professional
37			writers
38		31c	Plans, if any, for granting public access to the full protocol, participant-
39			level dataset, and statistical code
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47	Appendices		
48	Informed consent	32	Model consent form and other related documentation given to
49	materials		participants and authorised surrogates
50			
51	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
52	specimens		specimens for genetic or molecular analysis in the current trial and for
53			future use in ancillary studies, if applicable
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*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

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