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Μεταπτυχιακή Διπλωματική Εργασία

"ΠΕΡΙΕΠΕΜΒΑΤΙΚΗ ΔΙΑΧΕΙΡΙΣΗ ΤΗΣ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗΣ ΑΓΩΓΗΣ ΣΤΙΣ ΕΚΛΕΚΤΙΚΕΣ ΕΠΕΜΒΑΣΕΙΣ ΤΗΣ ΣΠΟΝΔΥΛΙΚΗΣ ΣΤΗΛΗΣ: ΚΡΙΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΜΕ ΤΟ ΕΡΓΑΛΕΙΟ AGREE II ΚΑΙ ΠΕΡΙΛΗΨΗ ΤΩΝ ΚΑΤΕΥΘΥΝΤΗΡΙΩΝ ΟΔΗΓΙΩΝ"

υπό

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Υπεβλήθη για την εκπλήρωση μέρους των

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Μεταπτυχιακού Διπλώματος Ειδίκευσης

«Θρόμβωση και Αντιθρομβωτική Αγωγή»

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"Perioperative antithrombotic therapy in elective spinal procedures.

A critical assessment and summary of the

Clinical Practice Guidelines with the AGREE II tool"

ΕΥΧΑΡΙΣΤΙΕΣ

Στην Καθηγήτρια Αναισθησιολογίας και Μέντορά μου κα Αρναούτογλου Ελ.
για το όμορφο και τόσο διδακτικό, γεμάτο υπέροχες αναμνήσεις, ταξίδι
και την ακούραστη διάθεση να με διδάξει και να με παιδεύσει.

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Abstract in Greek language

Εισαγωγή: Η περιεπεμβατική διαχείριση των ασθενών που λαμβάνουν αντιθρομβωτικούς παράγοντες και υποβάλλονται σε εκλεκτικές επεμβάσεις της σπονδυλικής στήλης αποδεικνύεται άκρως απαιτητική για την ιατρική ομάδα κυρίως λόγω του ενδογενούς αυξημένου αιμορραγικού κινδύνου και της ταυτόχρονης ανάγκης για ελαχιστοποίηση του θρομβοεμβολικού κινδύνου.

Σκοπός: Σκοπό της παρούσας μεταανάλυσης αποτελούν: α) η αναγνώριση των κατευθυντηρίων οδηγιών και συστάσεων για την περιεπεμβατική διαχείριση των ασθενών που λαμβάνουν αντιθρομβωτικούς παράγοντες και υποβάλλονται σε εκλεκτικές επεμβάσεις της σπονδυλικής στήλης και β) η αξιολόγηση της σαφήνειας και της ποιότητας της μεθοδολογίας αυτών με το εργαλείο "Appraisal of Guidelines for Research and Evaluation (AGREE) II".

Μεθοδολογία: Πραγματοποιήθηκε αναζήτηση της υπάρχουσας ιατρικής βιβλιογραφίας στην αγγλική γλώσσα στις βάσεις PubMed, Google Scholar και Scopus μέχρι 31 Απριλίου, 2020. Η προσέγγιση "GRADE" χρησιμοποιήθηκε για την βαθμολόγηση τόσο της ποιότητας της αξιολόγησης των δεδομένων όσο και της σύνοψης των ευρημάτων. Το εργαλείο "AGREE II" χρησιμοποιήθηκε για την αξιολόγηση της σαφήνειας και της μεθοδολογικής ποιότητας των κατευθυντηρίων οδηγιών και συστάσεων.

Αποτελέσματα: Συνολικά 38 κατευθυντήριες οδηγίες και συστάσεις αναγνωρίστηκαν κατά την αρχική έρευνα. Στην τελική ανάλυση και αξιολόγηση συμπεριελήφθησαν συνολικά 16 κατευθυντήριες οδηγίες και συστάσεις. Με βάση το εργαλείο AGREE II και την συμφωνία μεταξύ των κριτών (inter-rater agreement) οι συστάσεις των "Narouze 2018" και "Fleisher 2014" πληρούσαν τόσο τα κριτήρια της υψηλής ποιότητας όσο και της επαρκούς συμφωνίας μεταξύ των κριτών (Cohen's kappa >/= 0.60). Οι τομείς «Σαφήνεια της παρουσίασης» (Clarity of presentation) και «Πεδίο εφαρμογής και σκοπός» (Scope and purpose) συγκέντρωσαν την υψηλότερη βαθμολογία (100%), ενώ ο τομέας «Συμμετοχή των ενδιαφερομένων», (Stakeholder involvement) την χαμηλότερη (48,5%) αντίστοιχα.

Συμπεράσματα: Η περιεπεμβατική διαχείριση των ασθενών που λαμβάνουν αντιθρομβωτικούς παράγοντες και υποβάλλονται σε εκλεκτικές επεμβάσεις της σπονδυλικής στήλης αποδεικνύεται ιδιαίτερα απαιτητική. Εξαιτίας της έλλειψης υψηλής ποιότητας δεδομένων σε αυτόν τον τομέα, εξακολουθεί να υπάρχει αβεβαιότητα όσον αφορά στη βέλτιστη διαχείριση της αντιθρομβωτικής αγωγής για την εξισορρόπηση του κινδύνου της αιμορραγίας και της θρομβοεμβολής.

Λέξεις - Κλειδιά: Αναστολείς της συσσώρευσης των αιμοπεταλίων, διπλή αντιαιμοπεταλιακή θεραπεία, αντιπηκτικά, αναστολείς του παράγοντας Xa, αντιθρομβίνη, χειρουργική της σπονδυλικής στήλης, αιμορραγία, εμβολή και θρόμβωση, ενήλικες,

άνθρωποι, πέρι-επεμβατική περίοδος, περιεπεμβατική φροντίδα, κατευθυντήριες οδηγίες, συστάσεις, αγγλική γλώσσα.

Abstract

Background: The management of patients who are treated with antithrombotic agents and undergo elective spinal procedures proves to be extremely challenging for the perioperative team due to the concurrent increased risk of bleeding and the need to minimize the risk of thrombosis.

Aim: The present meta-analysis identified the clinical practice guidelines (CPGs) and recommendations (CPRs) on this topic and reported and assessed the clarity and quality of methods of the them with the Appraisal of Guidelines for REsearch and Evaluation (AGREE) II instrument.

Methods: A data search of the English Medical Literature was conducted using PubMed, Google Scholar, and Scopus until April 31, 2020. The GRADE approach was used to evaluate the quality of evidence assessment and the summary of findings and the AGREE II to assess the methodological clarity and quality of the CPGs and CPRs respectively.

Results: The initial search identified 38 CPGs and CPRs. The final analysis and critical appraisal with the AGREE II instrument included 16 CPGs and CPRs. Based on the AGREE II tool for CPGs and CPRs assessment and on the interrater agreement "Narouze 2018" and "Fleisher 2014" fulfilled the criteria of high quality and adequate interrater agreement (Cohen's kappa >/= 0.60). The domains "Clarity of presentation" and "Scope and purpose" had the highest scores (100%), while "Stakeholder involvement" the lowest, with an average of 48.5% respectively.

Conclusion: The management of the antithrombotic agents in patients undergoing elective spine surgery may prove challenging. Due to the lack of high quality data, there is still uncertainty when attempting to harmonize the risk of thromboembolism with that of bleeding.

Keywords: Platelet aggregation inhibitors; Dual Anti-Platelet Therapy; Anticoagulants; Factor Xa inhibitors; Antithrombins; Spine surgery; Hemorrhage; Embolism and Thrombosis; Humans; Adults; Perioperative period; Perioperarive care; Guidelines; Recommendations; English language.

Abbreviations

CPGs	Clinical Practice Guidelines
CPRs	Clinical Practice Recommendations
AGREE II	Appraisal of Guidelines for REsearch and Evaluation II
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis statement
DES	Drug - Eluting Stent
BMS	Bare - Metal Stent
DAPT	Dual Antiplatelet Therapy
MACE	Major Cardiovascular Events
ST	Stent Thrombosis
UFH	Unfractioned Heparin
LMWH	Low Molecular Weight Heparin
VKA	Vitamin K Antagonists
WCK	Weighted Cohen’s Kappa

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General Issue

1. Periprocedural management of antiplatelet agents

1.1 Introduction

Over the years, the antiplatelet agents (*appendix, table 1*) have been recognized as the cornerstone for the prevention of the arterial thrombosis. As a matter of fact, the non-optimal perioperative management of the antiplatelet drugs can lead to severe complications such as the myocardial infraction, the thrombosis of both the coronary and the peripheral artery stent and the life-threatening bleeding (1–7).

In order to ensure the best possible management of the antiplatelet therapy perioperatively the co-operation, also known as teamwork, of the medical team (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist) with the medical doctor that has administrated the antithrombotic agent seems mandatory (1,5,6,8). The medical team should also assess the thrombotic and the hemorrhagic risk that is related to both the patient and the invasive procedure and should decide a) if it is safe and absolutely necessary for the patient to undergo the procedure and b) when it is the best time frame for it. The next steps should include the decisions regarding a) the discontinuation or the appropriate modifications of the antiplatelet therapy, b) the need for bridging therapy, c) the optimal time frame for the discontinuati on of the antiplatelet preoperatively and d) for the resumption of the agent postoperatively and e) the available options/antidotes for the reversion of the antiplatelet action in case of bleeding complications. Last but not least, the detailed information of the patient regarding the perioperative risk, including the thromboembolic and the bleeding complications, from a multidisciplinary approach collaboration among the members of the perioperative team (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist) and the written informed consent of the patient is of outmost important (1–9).

1.2 Bleeding risk

The multidisciplinary evaluation of the bleeding risk of the patient *and* the invasive procedure is recommended (1–7,9,10).

Bleeding risk of to the invasive procedure: The bleeding risk that is related to the invasive procedure is stratified in three categories (*appendix, table 2*) (1,3,6,7).

- Low hemorrhagic risk (<1% risk of hemorrhage): sufficient hemostasis can be achieved. The hemorrhage a) does not put in danger the patient's life, b) does not have impact on the outcome of the invasive procedure and c) does not increase the need for transfusion.
- Intermediate hemorrhagic risk: sufficient hemostasis is difficult to be achieved and the hemorrhage does not have impact on the need for transfusion and/or re-intervention.
- High hemorrhagic risk: the hemorrhage a) puts in dangers the patient's life and/or leads to life-threatening bleeding, b) affects the outcome of the invasive procedure.

The bleeding risk related to several procedures such as the dental, the invasive coronary artery and the radiological interventions has not yet been stratified as both the primary hemostasis and the direct compression of the bleeding areas are not always possible (1,3,6,7).

Bleeding risk related to patient: Factors such as: the age > 65 years, the renal and/or liver failure, the atrial fibrillation, the acute coronary syndrome, the quantity and quality platelet abnormalities, the non-discontinuation of the antiplatelet agents and/or the concomitant administration of agents with antithrombotic action, the history of spontaneous bleeding during the last three months and/or in previous invasive procedure increase the bleeding risk that is related to the patient (6).

Of note, the non-discontinuation of the antiplatelet agents perioperatively was found to be responsible for increased bleeding risk. However, with the exception of the neurosurgical and the urological procedures, the reported bleeding cases were self-limited and they did not affect the outcome of the procedure or the patient (7,11).

1.3 Thrombotic risk

For the optimal and complete evaluation of the thrombotic risk experts suggest the multidisciplinary evaluation of the risk of thrombosis the patient *and* the invasive procedure (1,5,12,13).

Thrombotic risk of the invasive procedure: Table 3 (*appendix, figure 1*), as published in the 2014 ESC/ESA guidelines proves to be quite useful (13).

Thrombotic risk related to patient: Factors such as: the advanced age, the medical history of acute coronary syndrome, of diabetes mellitus and of renal and/or heart failure, the resistance in the antiplatelet action of clopidogrel and the early/premature discontinuation of antiplatelet agents in patients with coronary or peripheral artery stents increase the thrombotic risk that is related to the patient (1,5,13). Furthermore, the patients that had suffered from an acute cerebrovascular event are facing an increased thrombotic risk during the first month after the thrombotic event and the risk is further increased if they discontinue early the dual antiplatelet therapy (5).

Table 3 (appendix) presents the main characteristics of high-thrombotic risk after coronary or peripheral artery stent implantation (1). *Table 4 (appendix)* demonstrates the clinical and angiographic characteristics of increased ischemic risk in patients who are treated with coronary artery stents (5).

For the thorough evaluation of the risk of thrombosis in patients who are treated with antiplatelet agents for secondary prevention (ischemic cerebrovascular event, carotid artery disease, coronary artery disease, peripheral artery disease) the following should be also taken under consideration;

- The indications of the antiplatelet therapy.
- The characteristics and the course of the disease (i.e. stable, unstable).

- The time that has passed from the initiation of the antiplatelet therapy.
- The need for any type of invasive therapy – such as stent – in addition to the antiplatelet therapy.
- The time that has passed from the invasive therapy.

However, it should be highlighted that the above – mentioned suggestions are mostly based on experts opinions due to the lack of randomized controlled studies (*appendix, table 5, table 6, table 7, table 8*) (1–3,6).

To conclude, for the assessment of the cardiovascular risk in patients treated with antiplatelets *table 9 (appendix)* proves quite useful (2,6).

1.4 The idea of "combined ischemic risk"

As stated above, the decisions for the periprocedural management of antiplatelet therapy should be balanced with:

- The thrombotic risk of the patient.
- The build – in thrombotic risk of the invasive procedure.
- The anticipated hemorrhagic risk based on patient characteristics.
- The bleeding risk that arises from the individual features of the procedure (2,9,14).

When it comes to patients with coronary artery stents important challenges and safety concerns arise perioperatively (5,9,13,14). Nowadays, drug – eluting stents (DES) have successfully replaced the older types of stents (bare – metal stents, BMS) (5). Following DES implantation, dual antiplatelet therapy (DAPT), for the predefined duration as stated on the updated guidelines (*appendix, figure 2*), is of outmost importance to prevent the major cardiovascular events (MACE), such as stent thrombosis (ST), myocardial infraction and cardiovascular death during the vascular healing and the endothelialization process of the stent (5,15). However, up to 25% of patients with coronary artery stents require some type of intervention within this essential time frame (5). Moreover, invasive procedures may lead to the early discontinuation of DAPT quite often and along with anesthesia they are well-recognized triggers of inflammation and thrombotic response that attenuate the pathogenesis of MACE (*figure 3)* (5,16).

The estimated incidence of MACE in patients treated with coronary artery stents who have non-cardiac surgery is up to 11%(5). Experts suggest that the interplay between the time-frame, the need for DAPT and the combined thrombotic and hemorrhagic risk are the main determents of the perioperative outcome in patients treated with coronary artery stents (5). Moreover, several independent factors may increase the risk of MACE (5,17,18). These include:

- The time from stent implantation to the invasive procedure.
- The early discontinuation of DAPT.
- The clinical and angiographic characteristics of the stent/stents.
- The stent/stents type.

The time from stent to the invasive procedure and the early discontinuation of DAPT have been recognized as the leading modifiable determinants of the ischemic risk. (2,6).

On this background the idea of "combined ischemic risk" (*appendix, figure 4*) was introduced based on the aforementioned independent risk factors in an attempt to highlight the uniqueness and the special characteristics of every patient with stent, as well as the urgency of the multidisciplinary approach collaboration among the members of the perioperative team, also known as "bleeding team" (5,8,9,15).

1.5 Elective procedures

- The decisions about the management of antiplatelet agents perioperatively should be made from a multidisciplinary team of experts in Thrombosis and Antithrombotic Therapy (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist), the "bleeding team" based on the assessment of the hemorrhagic and the thrombotic risk against the consequences that arise from the postponement of the procedure. The "bleeding team" should inform the patient in depth regarding the perioperative risk, including the thromboembolic and the bleeding complications and a written informed consent of the patient should be obtained. A singed copy of the consent should be kept in the medical file of the patient (1,4,5,7,8,9,19).
- *Figure 5 (appendix)* demonstrates the basic steps for the management of the antiplatelet agents perioperatively in a simple algorithm (6).
- *Table 10 (appendix)* introduces the basic principles for the DAPT (3).
- *Figure 2 (appendix)* (see above, chapter 1.5) demonstrates the management of DAPT in coronary artery disease, while *figure 6 (appendix)* summarizes the recommendations on DAPT in patients who undergo non-cardiac surgery and suffer from coronary artery disease (15).
- *Figure 7 (appendix)* and *figure 8 (appendix)* represent the proposals for the patients with peripheral arterial disease (20). *Figure 9 (appendix)* demonstrates the recommendations for the carotid artery stenosis (20).
- In case that it is not possible to determine the hemorrhagic risk and/or the thrombotic risk experts suggest the formation of a thorough and detailed individualized plan (for the exact patient and the exact procedure) from the "bleeding team" (1,9).

1.6 Bridging therapy

- There is a lack of high quality randomized studies regarding the bridging therapy (*appendix, table 11 and figure 10 and figure 11*) in patients treated with antiplatelet and undergo invasive procedures. Consequently, experts suggest that this kind of intervention is suitable only for patients with high/very high thrombotic risk and intermediate or high bleeding risk who should undergo a nondeferrable procedure at all costs (1,3,6,9,15).

- Bridging therapy should only be administrated in Intensive Care Unit and in hospitals with functional catheterization laboratory 24/7 (1,3,6,9,15).
- For the bridging therapy of antiplatelet agents any kind of heparin and any kind of non-steroidal anti-inflammatory drugs should not be used (1,3,6,9,15).

1.7 Platelet function tests

- The use of platelet function tests (*appendix, table 12*) is recommended preoperatively in order to determine the decreased platelet function due to the action of antiplatelet agents (IIB) (4,7).
- In case that the platelet function tests are used outside from the laboratories (point of care tests) experts suggest that they should be assessed by the appropriate trained personnel, based on the updated guidelines (7).

1.8 Means of neutralizing the effect of antiplatelet agents

- Up until the writing of the present Thesis there were not any available agents for the reversal of the action of the antiplatelet agents (antidotes) (7).
- For the neutralization of the effect of the antiplatelet agents the type of the antiplatelet along with the time that has passed from the last dose should be taken into consideration (7).
- For the neutralization of the effect of aspirin experts suggest the transfusion with platelets (adult dose: 0.5 – 0.7 x 10 ^11/10 kg of body weight) (4,7).
- For the neutralization of the effect of clopidogrel or prasugrel experts suggest the transfusion with platelets in higher doses than those suggested for the neutralization of aspirin. For the neutralization of the effect of prasugrel the dose should be at least doubled, compared to that suggested for the neutralization of aspirin (4,7).
- For the neutralization of the effect of ticagrelor if the last dose of ticagrelor was < 24 hours experts suggest to withhold the platelet transfusion. When > 24 hours have passed since the last dose of ticagrelor the dose of platelet transfusion should be at least doubled, compared to that suggested for the neutralization of aspirin (4,7).

2. Periprocedural management of anticoagulant agents

2.1 Introduction

Anticoagulant agents (*appendix, table 13*) are the cornerstone for the treatment of thrombosis and a variety of thromboembolic complications (2,4,6,9,21–23). The non-optimal perioperative management of the anticoagulants may lead to life-threatening thromboembolic and bleeding complications (2,4,6,9,21–23).

In order to ensure the best possible management of the antiplatelet therapy perioperatively the co-operation, also known as teamwork, of the medical team (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist) with the medical doctor that has administrated the antithrombotic agent seems mandatory (1,6–8,14). The medical team should also assess the thrombotic and the hemorrhagic risk that is related to both the patient and the invasive procedure and should decide a) if it is safe and absolutely necessary for the patient to undergo the procedure and b) when it is the best time frame for it. The next steps should include the decisions regarding a) the discontinuation or the appropriate modifications of the antiplatelet therapy, b) the need for bridging therapy, c) the optimal time frame for the discontinuation of the antiplatelet preoperatively and d) for the resumption of the agent postoperatively and e) the available options/antidotes for the reversion of the antiplatelet action in case of bleeding complications. Last but not least, the detailed information of the patient regarding the perioperative risk, including the thromboembolic and the bleeding complications, from a multidisciplinary approach collaboration among the members of the perioperative team (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist) and the written informed consent of the patient is of outmost important (1–9).

2.2 Bleeding risk

The assessment of the bleeding risk should follow a multidisciplinary approach and should include the evaluation of the bleeding risk of the invasive procedure ***and*** the patient (2,4,6,23,24).

Bleeding risk of the invasive procedure: The hemorrhagic risk, that is related to the invasive procedure is stratified in three categories (*appendix, figure 12*) (9,24).

- Low hemorrhagic risk (<1% risk of hemorrhage): sufficient hemostasis can be achieved. The hemorrhage a) does not put in danger the patient's life, b) does not have impact on the outcome of the invasive procedure and c) does not increase the need for transfusion.
- Intermediate hemorrhagic risk: sufficient hemostasis is difficult to be achieved and the hemorrhage does not have impact on the need for transfusion and/or re-intervention.
- High hemorrhagic risk: the hemorrhage a) puts in dangers the patient's life and/or leads to life-threatening bleeding, b) affects the outcome of the invasive procedure.

The bleeding risk related to several procedures such as the dental, the invasive coronary artery and the radiological interventions has not yet been stratified as both the primary hemostasis and the direct compression of the bleeding areas are not always possible (1,3,6,7).

Bleeding risk related to patient: *Figure 13* (*appendix*) demonstrates the risk factors that should be examined during the assessment of the bleeding risk that is related to patient (25). Of note, it is recommended that the "HAS - BLED" score should be used as a tool a) to identify the factors that may increase the bleeding risk, b) in an attempt to optimize any of them when possible in an attempt to decrease the bleeding risk (25).

2.3 Thromboembolism risk

For the optimal and complete evaluation of the thrombotic risk experts suggest the multidisciplinary evaluation of the risk of thrombosis the patient ***and*** the invasive procedure (9,17,24–28).

Thromboembolism risk related to patient: The multidisciplinary assessment of the patient from the members of the "bleeding team" is recommended based on *table 14*, *table 15* and *table 16* (*appendix*) (9,17,25,27,28).

Thromboembolism of the invasive procedure: For the complete thromboembolic risk the estimation of the thrombotic risk of the procedure is recommended (24,26,27). The laparoscopic procedures, especially the ones that are performed in Trendelenburg position, along with those that are classified as major operations are accompanied by a strong pre-thrombotic effect and an increased risk for venous thromboembolism (24,26). Furthermore, patients with atrial fibrillation are at increased risk for ischemic cerebrovascular events when they undergo neurosurgical or vascular procedures. On the other hand, it seems that the abdominal and the pelvic operations have lower risk for thromboembolism perioperatively (27).

2.4 Elective procedures

- The decisions about the management of the anticoagulant agents perioperatively should be made from a multidisciplinary team of experts in thrombosis and antithrombotic therapy (surgeon, anesthetist, vascular surgeon, hematologist, cardiologist), the "bleeding team" based on the assessment of the hemorrhagic and the thrombotic risk against the consequences that arise from the postponement of the procedure. The "bleeding team" should inform in depth the patient regarding the perioperative risk, including the thromboembolic and the bleeding complications and a written informed consent of the patient should be obtained. A singed copy of the consent should be kept in the medical file of the patient (6,9,24,25).
- *Figure 14 (appendix)* demonstrates the basic steps for the management of the anticoagulant agents perioperatively in a simple pathway decision algorithm (25).

- If the members of the bleeding team decide that bridging therapy is necessary it should only be administrated in Intensive Care Unit and in hospitals with functional catheterization laboratory 24/7 (6).

2.4.1 Unfractioned Heparin

- In patients treated with Unfractionated Heparin (UFH) due to high risk of thromboembolism experts suggest:
  - UFH should be discontinued at least for 6 hours before the invasive procedure, if the values of aPTT are within therapeutic range. The values of aPTT should be checked one hour before the procedure and if they are within normal range the patient may undergo the procedure.
  - If the values of aPTT are beyond the therapeutic range, the procedure should be postponed for at least 6 hours and ideally until the values of aPTT are within the therapeutic range (9,17,25).
  - Postoperatively the reinstitution of UFH should be a multidisciplinary decision of the members of the bleeding team and always after the estimation of the risk of bleeding. In case of high bleeding risk the administration of UFH should start after 24 - 48 hours, while in non - high bleeding risk at 6 - 8 hours postoperatively, without a loading dose (9).

2.4.2 Low Molecular Weight Heparin

- When Low Molecular Weight Heparin (LMWH) is administrated in therapeutic dose experts suggest:
  - The last dose of LMWH should be administrated at least 24 hours before the procedure (9,17).
  - In case of high bleeding risk the need for administration of half the last dose preoperatively should be considered(4,9,17).
  - In high bleeding risk procedures the administration of UFH should start after thorough consultation with the surgical team, 48 hours postoperatively (9,17).

2.4.3 Vitamin K Antagonists

- *Figure 19 and tables 17, 18 and 19 (appendix)* demonstrate a basic algorithm for the management of Vitamin K Antagonists (VKA) perioperatively (9).

2.4.4 Direct oral anticoagulants

- For the management of the patients who are treated with Direct Oral Anticoagulants (DOACs) perioperatively the estimation of the procedural bleeding risk *(figure 12, appendix)* in conjunction with the following proves to be mandatory:
  - The time since the last dose of the DOAC.
  - The plasma half-life adapted to the creatinine clearance (CrCl, Cockcroft-Gault) (4,9,22,29).

- *Table 20 (appendix)* provides some information regarding the effect of DOACs on anticoagulants tests (29).

- For a number of minimal or low bleeding risk procedures the discontinuation of DOACs may not be required. If the decision to withhold the therapy is made *tables 21, 22 and 23 (appendix)* present the current guidelines. Bridging therapy is generally not required (9,29).
- The decision for reinstitution of DOACs postoperative should be also made from the bleeding team. *Table 24 (appendix)* demonstrates a simple guidance (9,29).

2.4.5 Dual Antithrombotic therapy

- For the optimal management of patients with Lower Extremity Artery Disease who require dual antithrombotic therapy please refer to chapter 1.5 and *figure 8 (appendix)* (20).

Special Issue

Perioperative antithrombotic therapy in elective spinal procedures: A critical assessment and summary of the Clinical Practice Guidelines with the AGREE II tool

3. Introduction

The long-term use of antithrombotic (antiplatelet or anticoagulant) agents continues to rise, mainly due to the aging of the population (30,31). Every year almost 250,000 patients who are treated with antithrombotic agents undergo surgery in North America (9,17,32,33). Antiplatelet agents remain the essential treatment for the coronary artery or peripheral vascular disease. Anticoagulants are the cornerstone for the prevention of stroke due to atrial fibrillation and for the management of the venous thromboembolism (9,19,23,31).

The foundation of the optimal perioperative management entails for the risk of perioperative blood loss to be balanced against the risk of thromboembolism (9,17,23,32,34). Consequently, before any invasive spinal procedure the evaluation of both the patient and the procedural specific factors for hemorrhage and thrombosis, along with the special characteristics of the antithrombotic agents should be assessed and risk - stratified (9,17,23,32,34). In addition, the multidisciplinary patient-centered approach is of utmost importance for the arrangement of the antithrombotic treatment perioperatively (8,39,40). Therefore, the collaboration between the members of the perioperative team, along with the open communication and the transparency with the patients and the caregivers proves to be mandatory for the escalation of the quality of care and the optimization of patients' safety (32).

However, the perioperative management of the antiplatelet and anticoagulant agents represents an extremely challenging clinical problem for patients that undergo spinal procedures (9,17,19,33,37). To begin with, there is lack of high-quality data, such as large randomized control clinical trials. Therefore the current available recommendations are mostly based on experts' opinion (34). In addition, the vast majority of spinal procedures - with the exception of the spinal embolization - are classified as high bleeding risk procedures *(figure 15, appendix)* (9,25,34). Last of all, the basic principles of teamwork and patient-centered care, such as cooperation, communication, shared goals and decision - making require continuous medical education and training. Hence, there are quite time consuming, making the risk of failure to comply with the basic standards of teamwork (38).

To the best of our knowledge, the available recommendations on the perioperative management of patients treated with antithrombotic (antiplatelet or anticoagulant) agents in elective spinal procedures has not been systematically reviewed and methodologically assessed yet. The aims of this meta - analysis are: 1) to identify the clinical practice

guidelines (CPGs) and clinical practice recommendations (CPRs) on the management of antithrombotic (antiplatelet or anticoagulant) agents in the elective spinal procedures and 2) to report and assess the clarity and quality of methods of the CPGs and CPRs with the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

4. Material and methods

We performed an electronic literature search looking for published guidelines or recommendations. The search involved three databases (PubMed, Google Scholar, and Scopus) using the strategy depicted in *table 25, (appendix)*. Additional CPGs were traced in the reference list of the gathered records. In our current review we included CPGs focusing on the management of patients who are treated with antithrombotic agents and undergo elective spinal procedures. We excluded CPGs on elective spinal procedures that did not comment on the use of antithrombotic agents. However, we included general CPGs on the periprocedural use of antithrombotic agents, even if they did not focus on elective spinal procedures.

For the study selection, two authors (MPNt and AGB) assessed the titles and abstracts to eliminate records based on study design. Additional CPGs were discarded studies after reading the full - text document. For the appraisal process, the full – texts and the updated versions of the gathered recommendations, including their supplements were examined, in depth. Two reviewer authors, an experienced anesthesiologist (MPNt) and a neurosurgeon experienced with Bioinformatics and Biostatistics (AGB), worked together. Both reviewers completed the AGREE II online training (36,39,40). None of them had participated in the writing or the development of any of the gathered records.

The AGREE II tool consists of 23 items organized in five domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence) and two additional items (overall assessment). Each item was rated on a 7 - point Likert scale (1, strongly disagree; 7, strongly agree). Final domain scores were calculated according to the AGREE II tutorial and sample test practice guideline. The two reviewers rated each domain, independently (39,40). The results were then visualized in bar plots side – by - side. At present there is no specific quality thresholds in order to determine the quality of the guidelines as high or low (39,40). The domain scores were categorized as high (≥ 80%), medium (60 – 79%), low (40 – 59%), or very low (≤ 40%). The degree of agreement between reviewers was determined by the measurement of weighted Cohen's kappa (WCK). A value between 0 - 0.20 corresponded to "No agreement", 0.21 - 0.39 to "Minimal agreement", 0.40 - 0.59 to "Weak agreement", 0.60 - 0.79 to "Moderate agreement", 0.80 - 0.90 to "Strong agreement", and above 0.90 to "Almost perfect agreement".

In anticipation of deviation from the normal distribution, the results were summarized using median values along with their interquartile range, and visualized in bar plots and boxplots, accordingly. Comparisons of mean group values was realized using Kruskal - Wallis non - parametric ANOVA tests, followed by Dwass - Steel - Critchlow -

Fligner pairwise comparisons. All statistical analyses were performed using Excel, R - statistical environment, and the Real Statistics package. Statistical significance was considered for p - values of less than 0.05.

5. Results

5.1 Search of the literature

The search of the literature resulted in 38 unique CPGs. Twelve records were discarded with respect to their abstract and additional 10 records after reading their full text respectively. The remaining 16 CPGs were included in our review *(figure 16, appendix)*.

5.2 CPGs scores

As depicted in *table 26 (appendix)*, the list of the top - 5 scores included the CPGs were reported by Kozek et al., (88%), Narouze et al., (81%), CEC et al., (81%), Armstrong et al., (81%), and Madhugiri et al., (81%). The CPS with the lowest scores were those reported by Albaladejo et al., (50%), Goldier et al., (63%), Rossini et al., (63%) and Steffel et al., (63%) *(figure 17, appendix)*.

5.3 Overall AGREE-II domain scores

The highest scores were recorded in the "Clarity of presentation" and "Scope and purpose" domains *(table 27, appendix)*, reaching as high as 100%. On the contrary, the lowest scores were registered in the "Stakeholder involvement", "Rigor of development", and the "Applicability" domains, with an average of 48.5%, 57%, and 58%, respectively *(figure 18, appendix)*. The differences between the domain scores were frequently significant, particularly when comparing the high- and low-score domains *(table 28, appendix)*.

5.4 Interrater agreement

The mean interobserver agreement was as high as 84% (IQR: 66.5 - 98.2%), corresponding to "Strong agreement" between the two reviewers *(table 29, appendix)*. However, large variations were noted among the individual CPGs, ranging from as low as 19% for the CPGs by Rossini et al., to as high as 100% for the CPGs by Douketis et al., and Armstrong et al., *(figure 19, appendix)*.

6. Discussion

Several disorders of the spine mandate the elective surgical treatment in a notable number of patients annually (34,41). On the other hand, more than a few medical conditions require the administration of antithrombotics in order to outweigh the risk of thrombosis (23,34,37). Perioperatively the decisions regarding the antithrombic therapy in patients undergoing spine procedures remain challenging , in the terms of the lack of high quality data (1,5,42). Spine procedures are accompanied by high - bleeding risk *(table 30, appendix)* and hence, the discontinuation of the antithrombotic therapy perioperatively may be required (5,42). However, maintaining the antiplatelet or the anticoagulant agents may lead to hemorrhagic incidents (5,7). Thus, any decision should be made by a team of experts based on the current available guidelines (8,9,43).

6.1 Methodological aspects

Following our literature search with the provided search terms, 16 CPGs and CPRs were published since 2009 and met our inclusion criteria. With respect to the methodological quality of the CPGs and CPRs from which the data were extracted, certain crucial aspects need to be analyzed. To begin with, the methodological framework of the included guidelines varies significantly. Hence, the processes with which the available evidences were merged into the provided recommendations is not the same between the CPGs and CPRs that were used in our analysis. Furthermore, the level of evidences and the strength of recommendations was graded in the guidelines using different grading systems and might not be exactly the same as the Guidelines organizations. Consequently, the interpretation of the statements and the direct comparison of the guidelines, based on their strength, proves to be quite challenging and should be addressed with utmost caution.

Although the AGREE II is a validated tool it indicates a broad assessment of the methodological quality of the guideline synthesis (39,40). Hence, no pre-defined thresholds exists to define high, moderate or low-quality CPGs (31). An arbitrary threshold of < 30% to define low quality and > 70% to define high quality can be used for the AGREE II instrument (31). In addition, with respect to the AGREE II manual, guidelines should be considered of high quality if the domain “Rigour of development” scored at least 70% and the remaining domains along with the overall assessment scored at least 50% (39,40,44). Thus, the use of the overall score of the AGREE II instrument as a sole indicator of the methodological quality is discouraged. Moreover, with respect to the primary research aim of the CPGs and CPRs, certain domains may have a higher influence (e.g. “applicability”, “stakeholder involvement”) and so their rates will require discrete analysis. Therefore, physicians are discouraged from preferring to follow or disapproving a specific guideline

over another one based merely on the AGREE results. On the other hand, AGREE II could prove to be a valuable asset during the development of the guidelines with respect to the key domains that are vital for a robust guideline.

The guidelines that fulfil the aforementioned criteria are; "Narouze 2018", "Fleisher 2014", "Valgimigli 2018" and "de Hert 2018" *(table 26, appendix)*. However, experts suggest that "little confidence should be placed in the study results for any kappa below 0.60, as it indicates inadequate experts' agreement". Therefore, based on the results of the interrater agreement and the Cohen's kappa (with a threshold of 0.60) only "Narouze 2018" and "Fleisher 2014" seem to fulfil the criteria of high and adequate interrater agreement.

In our study "Scope and purpose" and "Clarity of presentation" had the higher scores, reaching as high as 100% in terms of quality. "Editorial independence" had medium to high scores, while "Stakeholder involvement" and "Applicability" had the lower scores. In "Scope and purpose" and "Clarity of presentation" Narouze had high scores (94%, 97%) respectively. On the other hand, in "Stakeholder involvement" and "Applicability" Narouze had low scores (58% and 56%). In addition, in "Scope and purpose" and "Clarity of presentation" Fleisher had perfect scores (100%) and moderate (67%) in "Stakeholder involvement" and in "Applicability" (65%) respectively. The most impressive scores range was detected in "Stakeholder involvement" with Madhugiri and Armstrong scoring very low (0%), and Valgimigli and de Hert medium to almost high (78% and 75%) respectively.

It is worth mentioning that either the lack of time or the financial burdens could be a possible explanation for the poor scores (40). The low scores of "Stakeholder involvement" could be the result of the exclusion of some of the stakeholders such as the patients, payers and other physicians. Their involvement could potentially improve the quality of the recommendations. Moreover, the reflection on potential barriers for the implementation of the guidelines in the authors' clinical practice could improve the low scores on "Applicability". As a matter of fact, that way the authors could also manage to broaden the applicability of their guidelines to the rest of the healthcare systems. Last but not least, the guideline developers should be aware of the limitations during the implementation of the suggested guidelines within the healthcare systems (39,40).

Regarding the scores of the "Editorial independence" domain it should be highlighted that it can prove difficult to find members for the review process during the guideline development who are being acknowledged as experts in a specific field, yet they are not included to the editors. This is quite important when it comes to topics that we lack high-quality data, such as in the management of the antithrombotic therapy perioperatively, especially in high-bleeding risk environment. However, it proves to be of outmost importance to maintain the editorial independence, since the interference with that process could bias the results. Hence, the transparency in the "disclosures" may

mitigate this conflict. In our study the medium to high scores of "Editorial independence" indicate that the available guidelines lack bias in this domain. More specifically, Albaladejo had the lower scores (46%), however there was a disclosure of interest, regarding unrestricted grants from various medical companies. On the contrary, Madhugiri, Douketis and de Hert had the higher scores (100%) in this domain.

It seems mandatory for the CPGs and CPRs to identify the obstacles during the application of their recommendations and to demonstrated how they could be implemanted in the everyday clinical routine. Likewise, in order to upgrade the "Applicability" domain scores the auditing criteria should be demonstrated in the guidelines. Moreover, detailed information of the target users of the CPGs and CPRs and more information regarding the implementation of the views and the preferences of the patients could improve the "Stakeholder involvement" domain. Based on the results of this meta - analysis it seems that additional modifications may improve the quality of the recommendations and methods of the available CPGs and CPRs

6.2 Key features and summary of the CPGs and CPRs

Fleisher et al, 2014

With respect to the patient that undergoes elective noncardiac surgery these guidelines focused on patients treated with antiplatelet agents (45). The recommendations are mostly based on consensus of experts' opinion, small or retrospective studies and registries and were rated as "level of evidence C" (45). The guideline panel consists of 17 physicians mainly from cardiovascular specialties and their conflict of interests were displayed.

The key clinical settings discussed are the perioperative management of monotherapy and DAPT. The authors highlight the importance of a consensus decision among treating clinicians as to the relative periprocedural risks and the maintaining against the discontinuation of the antiplatelet therapy. The consensus between the treating physician and the patient with respect to the perioperative plan is also emphasized (45).

The authors address the importance of the continuation of the antiplatelet therapy when the increased cardiovascular risk cardiac outweighs the risk of hemorhage. Moreover, the significance of the maintenance of the DAPT for the first 4 to 6 weeks, according to the type of stent is highlighted. Last but not least, the authors point out the value of the consensus among the surgeon, the anaesthesiologist and the cardiologist who should evaluate the relative risk of bleeding against the risk of thrombosis perioperatively (45).

Narouze et al, 2018 (second edition)

With respect to the patient that undergo interventional spine procedures these guidelines focus on patients treated with both antiplatelet and anticoagulant agents (42). The guideline panel include 124 physicians. Eighty four percent of the members are

anaesthesiologists, while the rest of them are neurological surgeons, orthopaedic surgeons, neurologists and physical medicine and rehabilitation physicians (42). Conflicts of all authors are listed in the publication.

The challenge of the classification of the interventional pain spine procedures, with respect to the potential risk of bleeding complications, is exceptionally acknowledged. Moreover, attention is drawn to the patient related bleeding risks. The authors recommend that the patients with high risk of bleeding (e.g. advanced age, bleeding tendency, concurrent use of antithrombotic agents, liver or renal diseases) that are presented for low- and/or intermediate-bleeding risk procedures should be treated as intermediate or high bleeding risk respectively (42). *Table 30 (appendix)* provides proposed classification of the invasive spine procedures according to the potential risk of serious bleeding and the summary of the proposed recommendations respectively.

Worth mentioning is that the authors affirm the lack of high quality, randomized, data regarding the management of procedures with high bleeding risk in patients receiving antithrombotic agents. Therefore, they acknowledge that it is not possible to provide strength and grading although the recommendations were extracted based on the current best available quality data (42).

Summary of the CPGs and CPRs

Table 31 (appendix) provides a summary of the proposed elective spinal procedure classification according to the potential risk of serious bleeding. Table 31 provides a summary of the proposed recommendations for the periprocedural management of the antithrombotic agents in the elective spinal settings.

Antiplatelet agents

As far as the the management of antiplatelets is concerned, the guidelines focus on aspirin and clopidogrel. However, there are specific recommendations regarding the rest of the antiplatelet agents, including the P2Y12 inhibitors, the phosphodiesterase inhibitors and the non-ASA NSAIDS. It is noteworthy that all guidelines emphasize the imperative value of the balance of the risk of bleeding against that of thromboembolic complications and the need for shared and patient centered decisions along with the neurosurgeons, the anaesthesiologists, the cardiologists and the prescribing physician.

In general, the need for the discontinuation of all antiplatelet agents preoperatively in intermediate and high bleeding risk elective spinal procedures is highlighted. Especially when ASA is being prescribed for primary prophylaxis in the aforementioned settings it should be discontinued for at least 6 days. However, in secondary prophylaxis a shared and individualized assessment and risk stratification management of the antithrombotics, especially in high thrombotic risk is strongly advised. As far as the challenging management of DAPT it is concerned, it is advised that the elective spinal procedures should be deferred until the completion of the DAPT course and the that the decisions

should not be made from junior doctors. Resumption of antiplatelet therapy is recommended at least 28 hours postoperatively without a loading dose with respect to shared assessment and risk stratification.

Anticoagulant agents

The VKA, the LMWH and the DOACs are being discussed. Regarding the VKA the discontinuation of both the coumadins and acenocoumarol perioperatively for high and intermediate bleeding risk procedures is highly advised for at least 5 and 3 days respectively and until normal INR values have been achieved in the time of the spinal procedure. The reinstitution of the VKA therapy is advised at least 48 hours postoperatively and always after the adequate haemostasis has been confirmed by the neurosurgeon. Moving on to LMWHs, enoxaparin in prophylactic dose should be discontinued for at least 12 hours, while when therapeutic doses are being used a 24 hours interval is strongly advised, along with the halfling of the last preoperative dose. The same recommendations as the therapeutic dose of enoxaparin are applied for dalteparin. Postoperatively, in intermediate and high bleeding risk procedures the reinstitution of LMHWs should be delayed for at least 48-72 hours and LMWHs should only be administrated after the adequate haemostasis has been confirmed and in half dose based on shared assessment if there are any concerns regarding the risk of bleeding. Lastly, at least a 5-half-life interval, adjusted for renal function, between discontinuation of any one of the DOACs in medium- and high-risk elective spinal interventionss is advised. Of note, for patients treated with any of the above mentioned anticoagulants and undergo low bleeding risk surgery the guidelines advise the shared assessment and risk stratification by a multidisciplinary experts' team for the anticoagulants.

6.3 Limitations and strengths

A limitation of our meta - analysis could be the fact that we followed a more inclusive approach and a more extensive literature search. Our attempt was to present a comprehensive overview of the literature regarding the management of the antiplatelet and the anticoagulant agents in a predominantly high - bleeding risk environment. Therefore, we decided to include the 16 articles that our literature search produced with the search terms that was provided. Additionally, we decided to describe the key features of the two guidelines that fulfilled the criteria for the higher quality along with the higher interrater agreement. However, both percent agreement and Cohen's kappa have strength and limitations. Cohen's kappa was designed to exclude the possibility that ratters guessed on scores and thus it may lower the estimate of the agreement excessively as the assumptions it makes are not well supported (46). Nonetheless, experts suggest that "little confidence should be placed in the study results for any kappa below 0.60, as it indicates inadequate experts' agreement". In addition, the different background of the reviewers

(anaesthesia, neurosurgery) could strengthen the results in terms of a more multidisciplinary approach and increases patient safety.

The AGREE II tool has also a number of limitations. Experts support that it is highly subjective and thus there is a chance for the score to be the lowest possible (1/7) for this key item if the answer is not clearly mentioned in the evaluated guidelines. Lastly, its domains are not weighted and due to the lack of clear threshold it may prove quite challenging for the appraiser to come to a unbiased conclusion regarding the accuracy of the CPGs and CPRs.

To the best of our knowledge this is the first meta - analysis to summarize and critically assess the evidences on the management of the antiplatelet and anticoagulant agents in the elective spine surgery. Based on both a clinical and a methodological perspective we ought to emphasize the limitations and the strengths of the available evidences/recommendations in the field of the perioperative management of antiplatelet and anticoagulant agents in elective spine surgery.

7. Conclusions

The perioperative management of antiplatelet and anticoagulant agents in elective spinal surgery proves to be challenging. Due to the lack of high quality data in this field, there is still uncertainty as to the optimal practices to balance the risk of thromboembolism against that of bleeding. Therefore, it is imperative to continue to develop level I evidences and use it to form methodologically sound guidelines with a rigorous, balanced and evidence – based process that involves all relevant stakeholders. To conclude with, the decisions regarding the complicated and challenging perioperative management of antithrombotic agents should be based on a multidisciplinary patient - centered approachs and should be made by a team of experts based on the current available guidelines.

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Appendix

Table 1. Basic characteristics of the antiplatelet agents (47)								
	Aspirin	**Clopidogrel**	**Prasugrel**	**Ticagrelor**	**Cangrelor**	**Eptifibatide**	**Tirofiban**	**Abciximab**
Administration	Oral	Oral	Oral	Oral	Intravenous	Intravenous	Intravenous	Intravenous
Bioavailability	68%	50%	80%	36%				
Plasma peak concentration	30-40 minutes	1 hour	30 minutes	1.5 hours	Seconds	Dose dependent	Dose dependent	Dose dependent
Plasma half - life	15-30 minutes	8 hours	7 hours	7 hours	2-5 minutes	10-15 minutes	2.5 hours	2 hours
Plasma protein binding	Strong	Strong	Strong	Strong				
Reversibility of platelet inhibition	No	No	No	Yes	Yes	Yes	Yes	Yes

Table 2. Bleeding risk of procedures (48)		
Low	**Intermediate**	**High**
General - Orthopaedic - Urologic procedures		
• Hernioplasty, plastic surgery of incisional hernias • Cholecystectomy, appendectomy, colectomy, gastric resection, intestinal resection • Breast surgery • Hand surgery, arthroscopy • Cystoscopy, stereoscopy	• Hemorrhoidectomy, splenectomy, gastrectomy, bariatric surgery, rectal resection, thyroidectomy • Prosthetic shoulder, knee, foot surgery • Major spine surgery • Prostate biopsy, orchiectomy	• Hepatic resection, duodenocefalo-pancreasectomy • Hip and proximal femur fracture surgery • Major pelvic surgery • Nephrectomy, cystectomy, TURP, TURBT, prostatectomy
Vascular procedures		
• Carotid endarterectomy • Bypass or endarterectomy of lower extremity • EVAR, TEVAR • Limb amputation	Open abdominal aorta surgery	Open thoracic and thoracoabdominal surgery
Cardiac procedures		
	• Mini-thoracotomy • TAVR (apical approach), OPCAB, CABG • Valve replacement	• Re-intervention • CABG in PCI failure • Endocarditis • Aortic dissection

Table 3 Surgical risk estimate according to type of surgery or intervention[a,b]

Low-risk: <1%	Intermediate-risk: 1–5%	High-risk: >5%
• Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynaecology: minor • Orthopaedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate)	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant

CAS, carotid artery stenting; CEA, carotid endarterectomy. [a]Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention without considering the patient's comorbidities. [b]Adapted from Glance *et al.*[11]

Figure 1. Thrombotic risk of the invasive procedure (50)

Table 3. Features of high - thrombotic risk after stent implantation (1)
• Chronic renal disease (Clearance of creatinine <60 mL/min)
• Diffuse atherosclerotic disease especially in patients suffering from diabetes mellitus
• History of stent thrombosis even under treatment with adequate antiplatelet therapy
• Placement of a stent on the last patent coronary vessel
• At least 3 lesions treated
• At least 3 stents implanted
• Two stents implanted in a bifurcation
• Stents implantation with total length > 60 mm
• Treatment of a chronic total occlusion

Table 4. Increased Ischemic Risk Factors following Coronary Artery Stents implantation (50)
Clinical risk factors
• Acute Coronary Syndrome during the PCI
• Multiple previous myocardial infraction
• History of stent thrombosis even under treatment with adequate antiplatelet therapy
• Ejection fraction of the left ventricular < 35%
• Chronic renal disease
• Diabetes mellitus
Angiographic risk factors
• More than one or long stents (at least 3 stents or three lesions treated or total stent length >60 mm)
• Stents that overlap
• Diameter of stents <2.5 mm
• Two stents implanted in a bifurcation
• Extensive coronary artery disease
• Incomplete revascularization
• Treatment of chronic total occlusion

Table 5. Risk of thrombosis in Acute Coronary Syndrome * (51)							
Low <1%		**Intermediate 1-5%**			**High >5%**		
Duration of Antiplatelet Therapy (months)							
>12	**>6**	**>12**	**6-12**	**3-6**	**<12**	**<6**	**<3**
• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment	• PCI + BMS/DES/ DEB or CABG and risk factors** • PCI + 1st generation DED (rapamycin, paclitacel) + bioasborbable vascular scaffold	• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment	• PCI + BMS/DES/ DEB or CABG and risk factors** • PCI + 1st generation DED (rapamycin, paclitacel) + bioasborbable vascular scaffold	• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment

BMS: bare metal stent; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; CRF: chronic renal failure; DEB: drug - eluting balloon; DES: drug - eluting stent DM: diabetes mellitus; HF: heart failure; LVEF: Left ventricular ejection fraction; TIA: transient ischemic attack.

* Particular high risk of cardiovascular death and myocardial infraction during the first 30 days.

** Risk factors: as stated above

Table 6. Risk of thrombosis in Stable Coronary Artery Disease * (51)							
Low <1%		**Intermediate 1-5%**			**High >5%**		
Duration of Antiplatelet Therapy (months)							
>12	**>6**	**>12**	**6-12**	**3-6**	**<12**	**<6**	**<3**
• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment	• PCI + BMS/DES/ DEB or CABG and risk factors** • PCI + 1st generation DED (rapamycin, paclitacel) + bioasborbable vascular scaffold	• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment	• PCI + BMS/DES/ DEB or CABG and risk factors** • PCI + 1st generation DED (rapamycin, paclitacel) + bioasborbable vascular scaffold	• PCI + BMS/ DES/DEB OR • CABG	Medical Treatment
BMS: bare metal stent; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; CRF: chronic renal failure; DEB: drug - eluting balloon; DES: drug - eluting stent DM: diabetes mellitus; HF: heart failure; LVEF: Left ventricular ejection fraction; TIA: transient ischemic attack.							
* Particular high risk of cardiovascular death and myocardial infraction during the first 30 days.							
** Risk factors: as stated above							

Table 7. Risk of thrombosis in Cerebrovascular Disease * (51)							
Low <1%		**Intermediate 1-5%**			**High >5%**		
Duration of Antiplatelet Therapy (months)							
>12	**>6**	**>12**	**6-12**	**3-6**	**<12**	**<6**	**<3**
	• Ischemic stroke • Carotid artery stenting			• Ischemic stroke • Carotid artery stenting			• Ischemic stroke • Carotid artery stenting

* Particular high risk of thrombosis during the first month (cardiovascular death and myocardial infraction).

Table 7. Risk of thrombosis in Peripheral Artery Disease * (51)							
Low <1%		**Intermediate 1-5%**			**High >5%**		
Duration of Antiplatelet Therapy (months)							
>12	**>6**	**>12**	**6-12**	**3-6**	**<12**	**<6**	**<3**
	Acute peripheral vascular event + revascularization with DES OR in chronic occlusions			Acute peripheral vascular event + revascularization with DES OR in chronic occlusions			Acute peripheral vascular event + revascularization with DES OR in chronic occlusions
DES: drug - eluting stent. * Particular high risk of cardiovascular death and myocardial infraction during the first 30 days.							

Table 9. Cardiovascular risk in patients treated with antiplatelet agents (47, 51)		
Low - moderate	**Intermediate - high**	**High - very high**
• All the patients that do not fit to the "moderate to high" and high to very high" categories	• ACS more 12 months before the procedure • PCI/DES >6 months before the procedure • PCI/BMS >1 month before the procedure • CABG >6 weeks before the procedure • CVA/TIA >1 month before the procedure • Peripheral vascular disease	• ACS <12 months before the procedure • PCI/DES <6 months before the procedure • PCI/BMS <1 month before the procedure • CABG <6 weeks before the procedure • CVA/TIA <1 month before the procedure
ACS: acute coronary syndrome; BMS: bare metal stent; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; DES: drug - eluting stent; CVA: cerebrovascular accident; TIA: transient ischemic attack.		

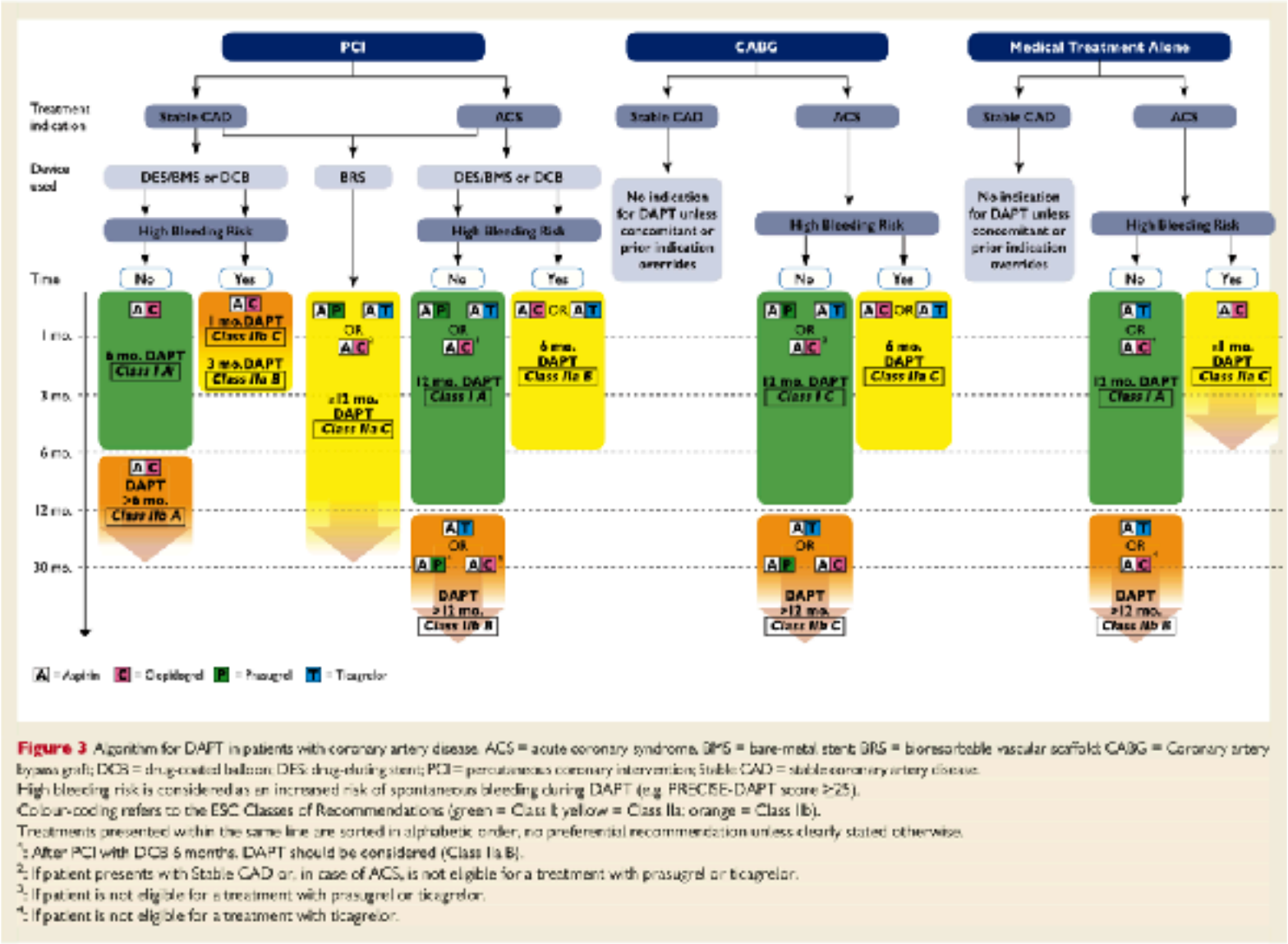

Figure 3 Algorithm for DAPT in patients with coronary artery disease. ACS = acute coronary syndrome; BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = Coronary artery bypass graft; DCB = drug-coated balloon; DES: drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD = stable coronary artery disease.
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
Treatments presented within the same line are sorted in alphabetic order; no preferential recommendation unless clearly stated otherwise.
[1]: After PCI with DCB 6 months. DAPT should be considered (Class IIa B).
[2]: If patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
[3]: If patient is not eligible for a treatment with prasugrel or ticagrelor.
[4]: If patient is not eligible for a treatment with ticagrelor.

Figure 2. DAPT in coronary artery disease (52)

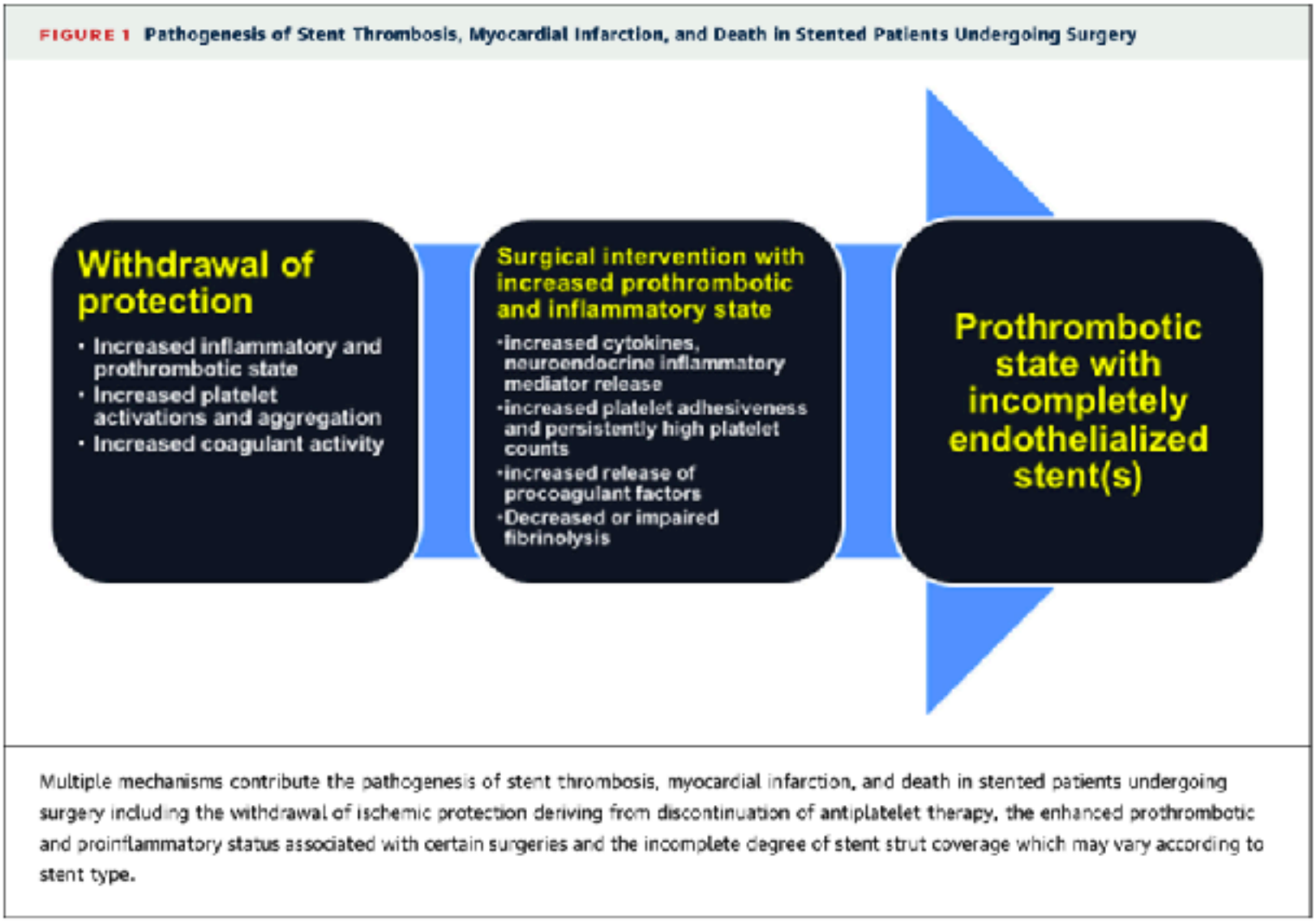

Figure 3. The pathogenesis of coronary artery stent thrombosis perioperatively (50)

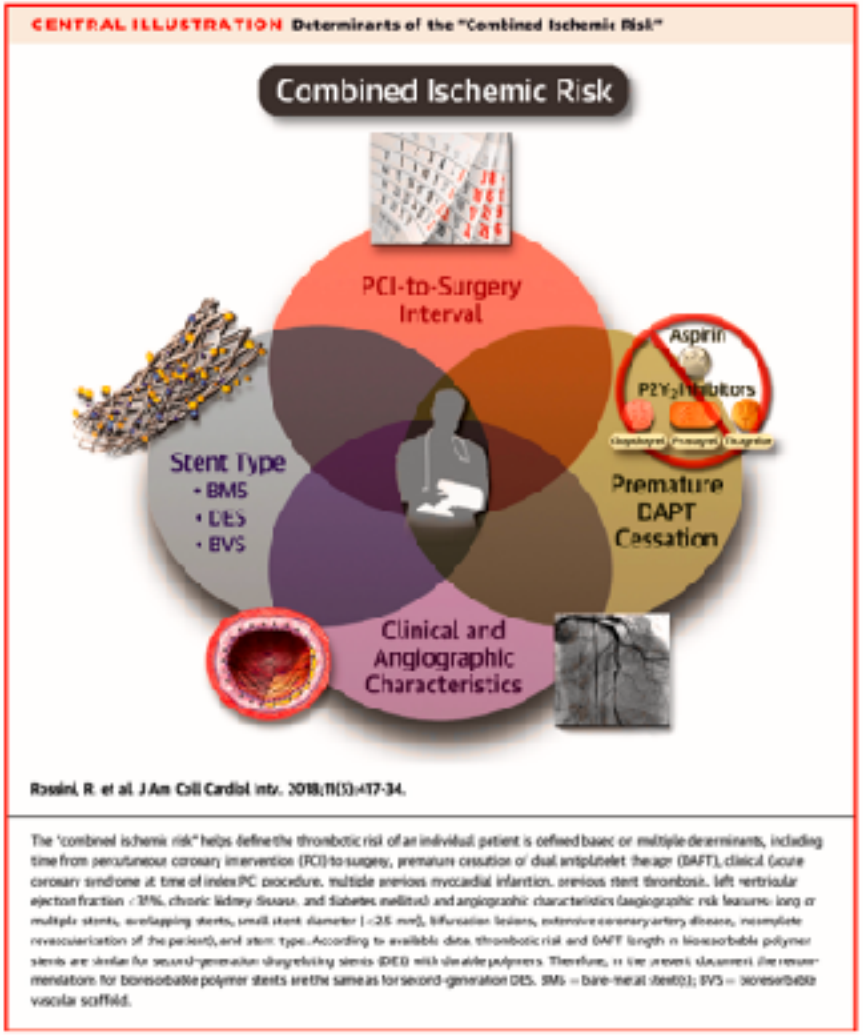

Figure 4. "Combined ischemic risk" (50)

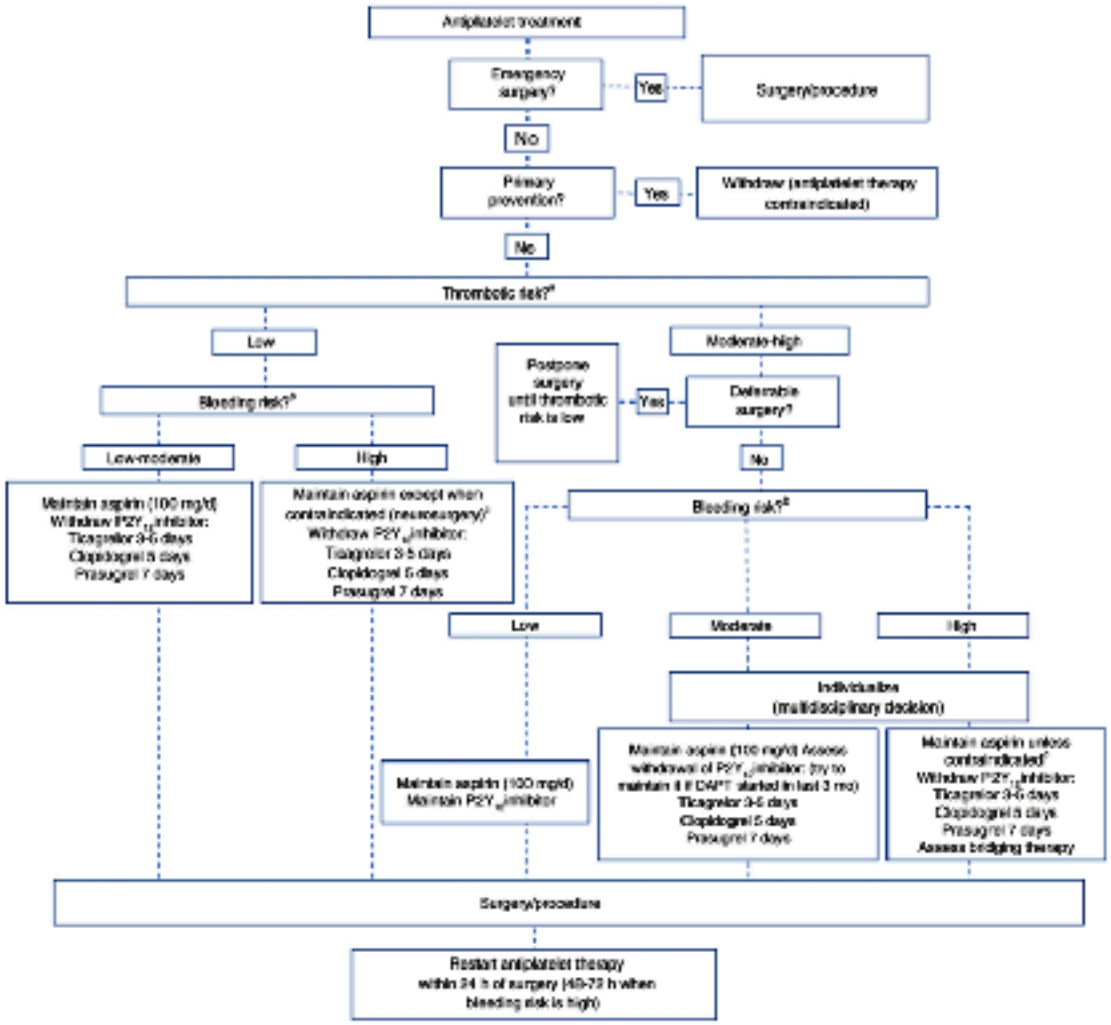

Figure 5. Perioperative management of antiplatelet therapy - General algorithm (51)

Table 10. Perioperative management of Dual Antiplatelet Therapy (DAPT) - Basic Principles (48)			
Risk	**Thrombotic**		
Haemorrhagic	**Low <1%**	**Intermediate 1-5%**	**High >5%**
Low	• Continue ASA • Stop P2Y12 receptor inhibitors • Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred: ✓Continue ASA ✓Stop P2Y12 receptor inhibitors Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred; continue ASA and P2Y12 receptor inhibitors perioepratively
Intermediate	• Continue ASA • Stop P2Y12 receptor inhibitors • Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred: ✓Continue ASA ✓Stop P2Y12 receptor inhibitors ✓Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred: ✓Continue ASA ✓Stop P2Y12 receptor inhibitors ✓Reinstitute APT (24-72 hours) with a loading dose ✓Consider the need to bridge with short - acting IV APT
High	• Continue ASA • Stop P2Y12 receptor inhibitors • Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred: ✓Continue ASA ✓Stop P2Y12 receptor inhibitors ✓Reinstitute APT (24-72 hours) with a loading dose	• Do not continue with elective procedures • If the surgery cannot be deferred: ✓Continue ASA ✓Stop P2Y12 receptor inhibitors ✓Reinstitute APT (24-72 hours) with a loading dose ✓Consider the need to bridge with short - acting IV APT
APT: antiplatelet therapy ASA: aspirin IV: intravenous			

Dual antiplatelet therapy in patients undergoing elective non-cardiac surgery

Recommendations	Class[a]	Level[b]
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.[232 236]	I	B
After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period.[277]	IIa	B
Discontinuation of $P2Y_{12}$ inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel, and at least 7 days for prasugrel.[152,153,160]	IIa	B
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C
In patients with recent MI or other high ischaemic risk features[c] requiring DAPT, elective surgery may be postponed for up to 6 months.[17,214,215,234]	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.[229,237–239]	IIb	C
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.[203]	III	B

DAPT = dual antiplatelet therapy; MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]High ischaemic risk features are provided in Table 5.

Figure 6. DAPT in elective non-cardiac procedures (52)

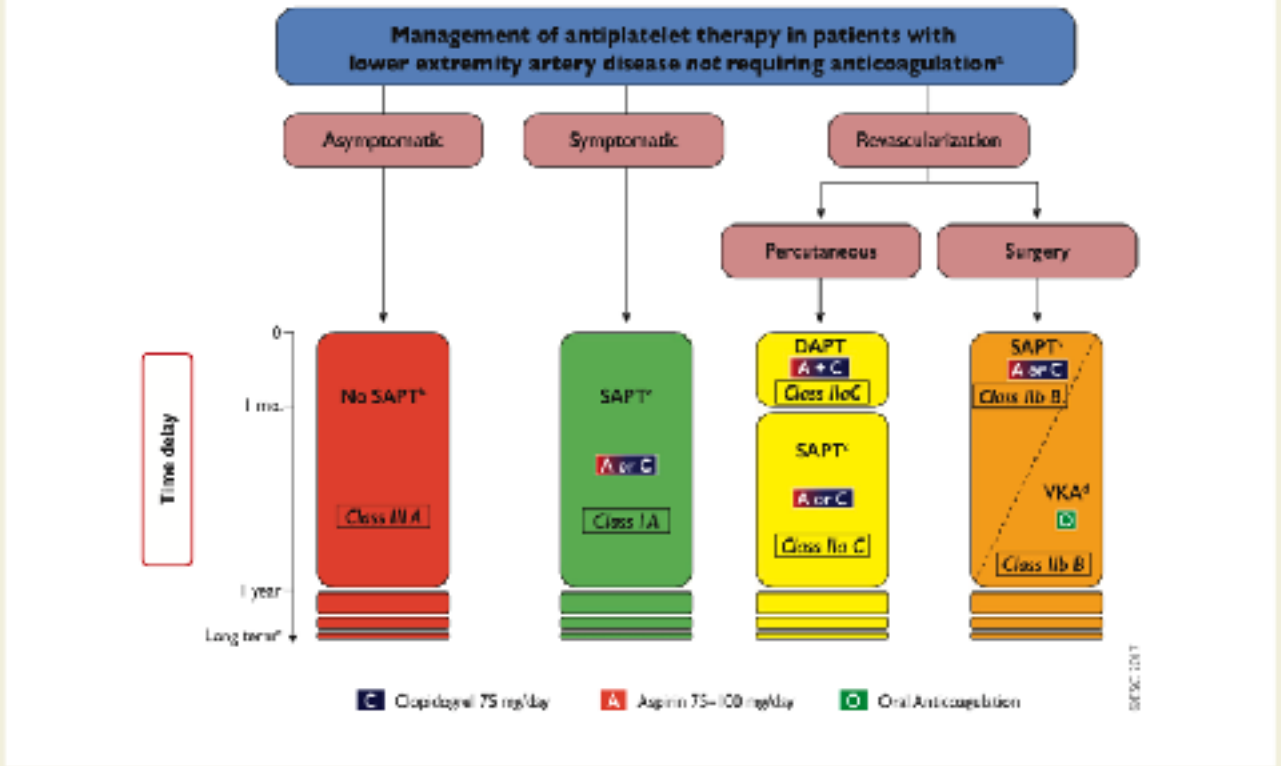

Figure 2 Antiplatelet therapy in patients with lower extremity artery disease. DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.
[a]e.g. concomitant AF or mechanical valve prosthesis.
[b]SAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease).
[c]DAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease,in diabetic patients with incomplete revascularization.
[d]Evidence is weak and bleeding doubles as compared to SAPT.
[e]Stands for as long as it is well tolerated.

Figure 7. Antiplatelets in lower extremity disease (A) (52)

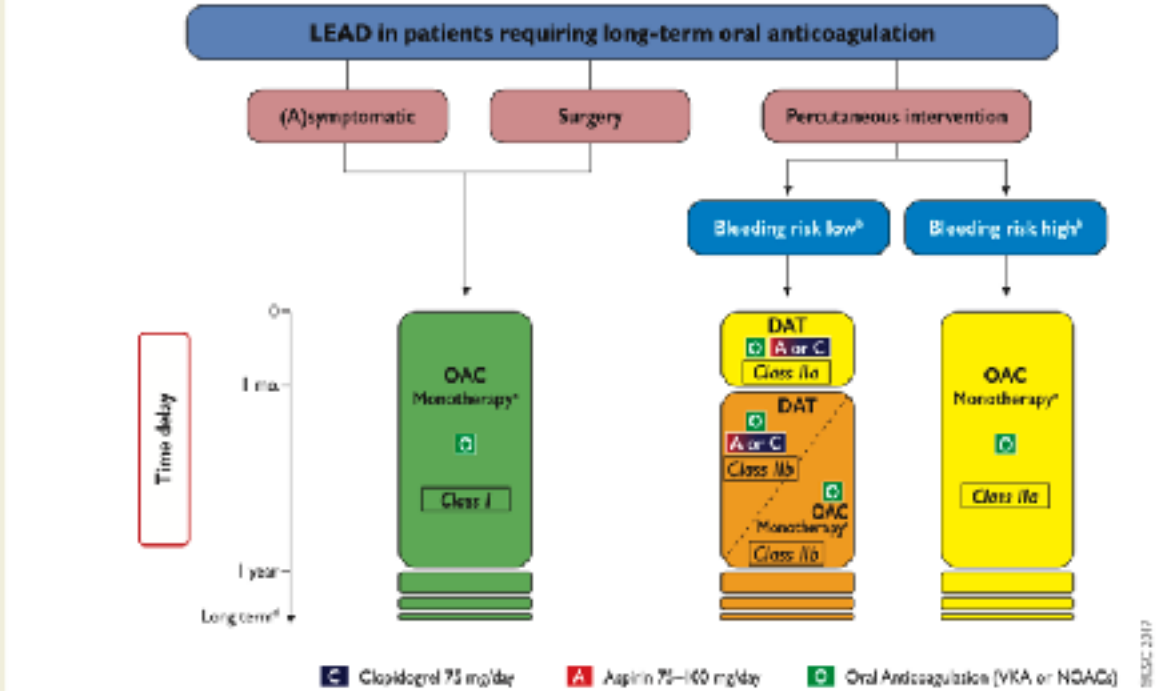

Figure 3 Antithrombotic therapy in patients with LEAD requiring oral anticoagulation. ACS = acute coronary syndrome; CAD = coronary artery disease; CLTI: chronic limb-threatening ischaemia; DAT = dual antithrombotic therapy; LEAD = lower extremity artery disease; NOACs = non-vitamin K oral anticoagulants; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]DAT may be considered in high ischaemic risk patients defined as prior stent thrombosis, acute limb ischaemia on OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization).
[b]Compared to the risk for stroke/CLTI due to stent/graft occlusion.
[c]Stands for as long as it is well tolerated.

Figure 8. Antiplatelets in lower extremity disease (B) (52)

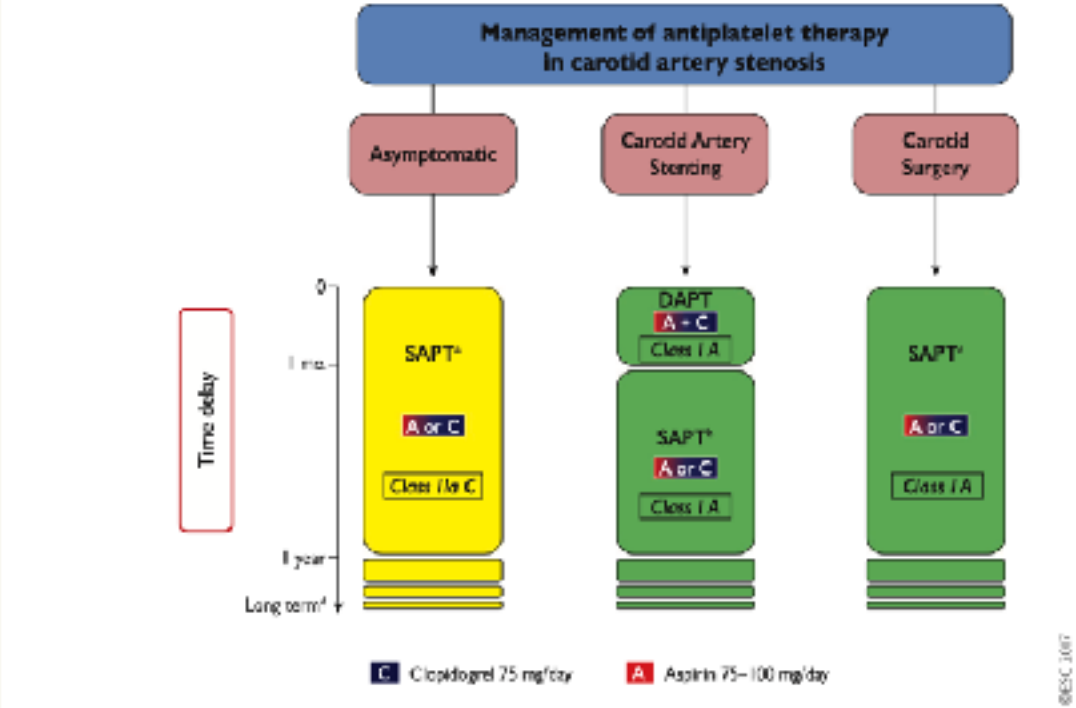

Figure 1 Management of antithrombotic treatment in patients with carotid artery stenosis. DAPT = dual antiplatelet therapy, a daily combination of aspirin (75–100 mg) and clopidogrel (75 mg); CAS = carotid artery stenting; SAPT = single antiplatelet therapy; TIA = transient ischaemic attack.
[a]At the exception of patient at very high bleeding risk.
[b]DAPT may be used if another indication supersedes that of carotid artery stenting such as acute coronary syndrome or percutaneous coronary intervention of less than 1 year.
[c]In case of recent minor stroke or TIA. A loading dose of aspirin (300 mg) and/or clopidogrel (300/600 mg) is recommended at the acute phase of stroke/TIA or during CAS.
[d]Stands for as long as it is well tolerated.

Figure 9. Antiplatelets in carotid artery stenosis (52)

Table 11. Short - acting intravenous bridging antiplatelet agents (48)			
	Tirofiban	**Eptifibatide**	**Cangrelor**
Onset of action	Immediate	Immediate	Immediate
Platelet inhibition	Potent	Potent	Potent
Half - life	120 minutes	150 minutes	3-5 minutes
Offset of action	4-6 hours	4-6 hours	1 hour
	P2Y12 specific	P2Y12 specific	Not P2Y12 specific
Dose (no bolus)	0.1 μg/kg/min (0.05 μg/kg/min if the clearance of creatinine is < 50 mL/min)	2.0 μg/kg/min (0.1μg/kg/min if the clearance of creatinine is < 50 mL/min)	0.75 μg/kg/min (Dose adjustment for impaired renal function is not required)

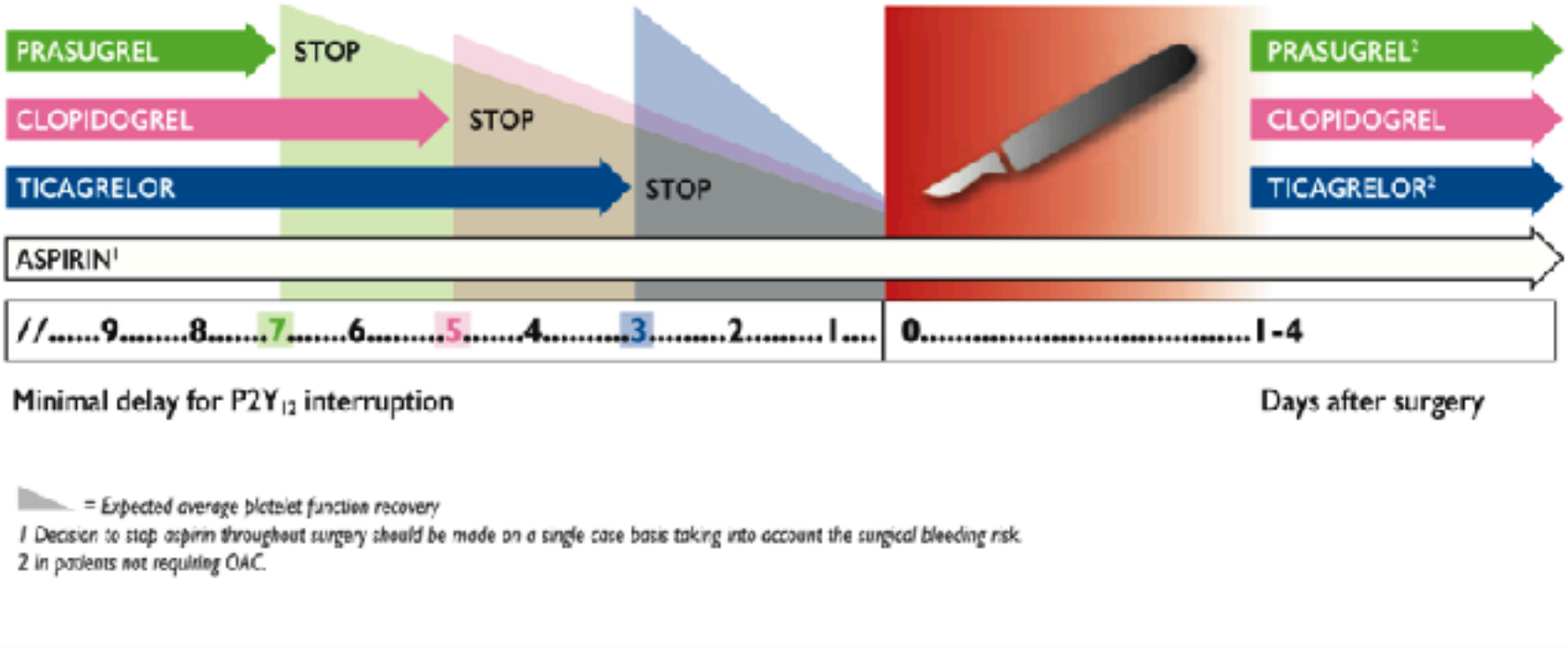

Figure 9 Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery
OAC = oral anticoagulant.

Figure 10. Essential perioperative time frames fro discontinuation and reinstitution of DAPT (52)

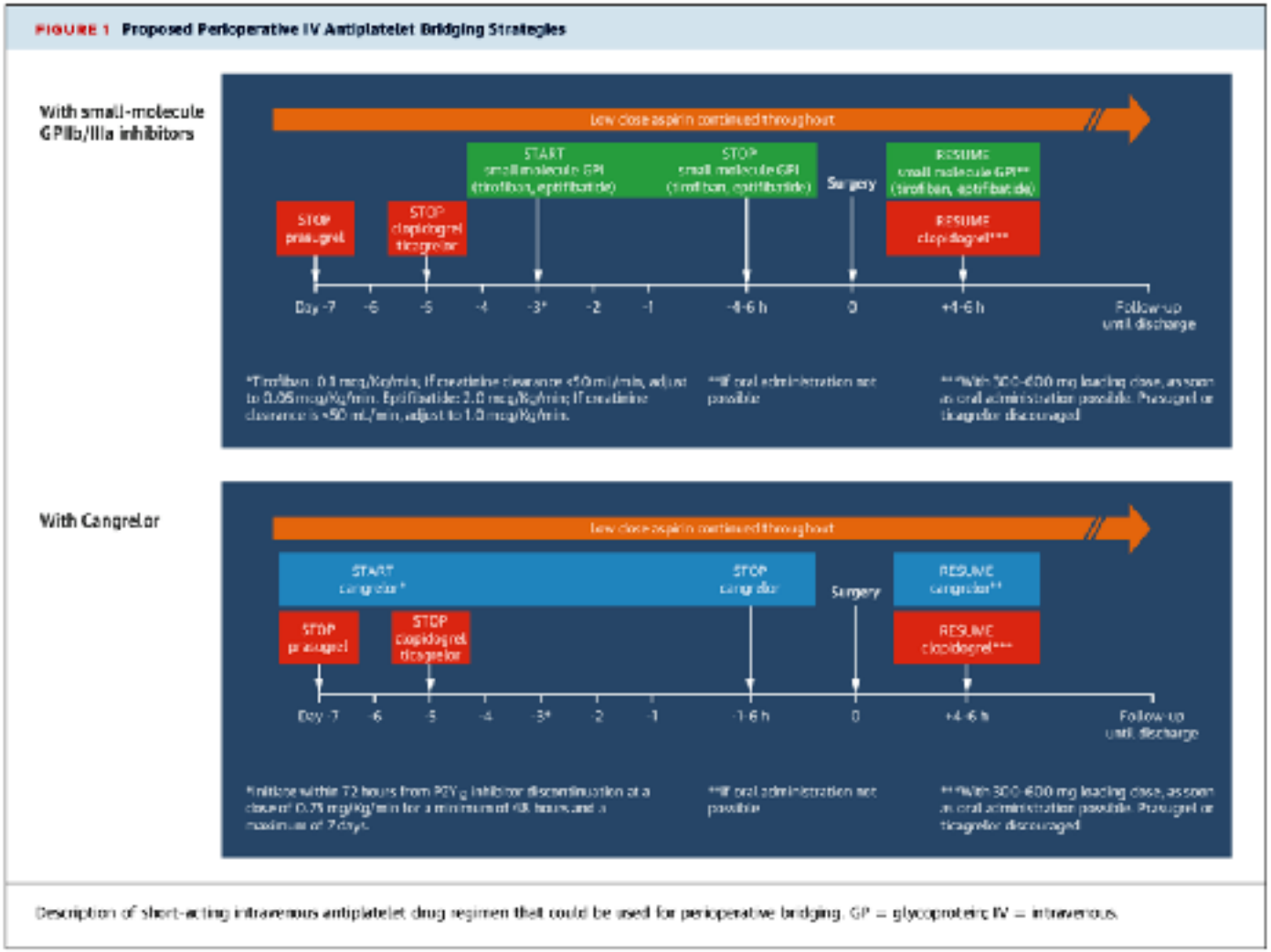

Figure 11. Proposed perioperative intravenous bridging algorithm (48)

Table 12. Basic platelet function tests for the evaluation of the effect of antiplatelets in the laboratory(53)	
Conventional photometric aggregation	Multiplate
Serum thromboxane B_2	ROTEM platelet
VASP test	PFA
VerifyNow	TEG
Aggregation is mainly detected by changes in impedance	PlateletMappring™

Table 13. Basic Anticoagulant Agents (47)								
	Oral					**Parental**		
	Warfarin	**Dabigatran**	**Apixaban**	**Edoxaban**	**Rivaroxaban**	**UFH (s.c./i.v)**	**LMWH (s.c.)**	**Fondaparinux (s.c.)**
Biovailability	80%	6%	66%	62%	80%	30%	90%	100 hours
Half - life	20-60 hours	12-14 hours	8-15 hours	10-14 hours	7-10 hours	1 hour	4 hours	17 hours
Duration of action from last dose	48-96 hours	48 hours	24 hours	24 hours	24 hours	Dose dependent (s.c.)	Dose dependent	48-96 hours
Peak plasma concentration	Variable	2 hours	2.5-4 hours	1-2 hours	1-3 hours	4 hours (s.c.)	3 hours	2 hours
Elimination	Metabolism	80% renal	25% renal	50% renal	50% renal, 50% hepatic	Reticulo-endothelial system	Hepatic metabolism, renal excretion 10%	Renal
Drug interaction	CYP2CP, CYP3A4, CYP1A2	P-GP inh	CYP3Y4, P-GP inh	P-GP inh	CYP3Y4, P-GP inh ή P-GP ind			

Minimal bleeding risk procedures	Low bleeding risk procedures (2-day risk of major bleed <2%)	High bleeding risk procedures (2-day risk of major bleed ≥2%)
• Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) • Cataract procedures • Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings • Pacemaker or cardioverter-defibrillator device implantation[a]	• Arthroscopy • Cutaneous/lymph node biopsies • Shoulder/foot/hand surgery • Coronary angiography • Gastrointestinal endoscopy +/- biopsy • Abdominal hysterectomy • Laparoscopic cholecystectomy • Abdominal hernia repair • Haemorrhoidal surgery • Bronchoscopy +/- biopsy • Epidural injections with INR <1.2	• Major surgery with extensive tissue injury • Cancer surgery • Major orthopaedic surgery • Reconstructive plastic surgery • Urologic or gastrointestinal surgery • Transurethral prostate resection, bladder resection, or tumour ablation • Nephrectomy, kidney biopsy • Colonic polyp resection[b] • Bowel resection • Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography • Surgery in highly vascular organs (kidneys, liver, spleen) • Cardiac, intracranial or spinal surgery • Any major operation (procedure duration of >45 min)

[a]For oral direct thrombin inhibitor or factor Xa inhibitor therapy: Interruption of therapy is currently recommended[P. 4].
For warfarin: Associated with pocket haematoma, but randomized controlled trial Level 1 evidence reveals that procedure can be performed without oral anticoagulation interruption.
[b]The size of the polyp influences the risk of bleeding. It may be appropriate to categorise polyps less than 1 cm in size as low-risk for bleeding.

Figure 12. Two - day risk of major procedural bleeding (54)

HAS-BLED parameters (52)*
Hypertension†
Abnormal renal function‡
Abnormal liver function§
Prior stroke
History of or predisposition to (anemia) major bleeding
Labile INR (VKA)‖
Elderly (>65 years)
Concomitant use of an antiplatelet agent or nonsteroidal anti-inflammatory drug
Alcohol or drug usage history (≥8 drinks/week)¶
Additional items included in the periprocedural management algorithm
Prior bleed event within 3 months (including intracranial hemorrhagic)
Quantitative or qualitative platelet abnormality
INR above the therapeutic range at the time of the procedure (VKA)
Bleed history from previous bridging
Bleed history with similar procedure

*Each bullet is counted as 1 point. A HAS-BLED score ≥3 was shown to be highly predictive of bleeding events, with 1 point being given for the presence of each individual parameter (54). †Defined in HAS-BLED as systolic blood pressure >160 mm Hg. ‡Defined in HAS-BLED as presence of chronic dialysis, renal transplantation, or serum creatinine >200 micromol/L. §Defined in HAS-BLED as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× ULN, AST or ALT >3× ULN). ‖Defined in HAS-BLED as time in the therapeutic range <60%. ¶Defined in HAS-BLED as >8 U/week.

ALT = alanine transaminase; AST = aspartate transaminase; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol; INR = international normalized ratio; ULN = upper limit of normal; and VKA = vitamin K antagonist.

Figure 13. Patient related bleed risk factors (55)

Table 14. Risk of thromboembolism (9)			
Mechanical heart valve	Bileaflet aortic valve prosthesis (no AF or other risk factors for stroke)	Bileaflet aortic valve prosthesis plus one or more of the following: • AF, prior stroke or TIA • Arterial hypertension • Diabetes mellitus • Congestive heart failure • >75 years old	• Mitral valve prosthesis • Caged - ball or tilting disc aortic valve prosthesis • Stroke or TIA within 6 months
Atrial Fibrillation (AF)	$CHADS_2$ 0 - 2 (no prior stroke or TIA)	$CHADS_2$ 3 - 4	• $CHADS_2$ 5 - 6 • Stroke or TIA within 3 months • Rheumatic valvular heart disease
Venous Thromboembolism (VTE)*	VTE beyond 12 months with no other risk factors	• VTE within the previous 3 - 12 months • Non-severe thrombophilia (e.g. prothrombin gene mutation) • Recurrent VTE • Active cancer	• VTE within the previous 3 months • Severe thrombophilia (e.g. antiphospholipid antibodies)
TIA: transient ischemic attack *Patients who require surgery within the first three months following an episode of VTE are likely to benefit from delaying elective surgery, even if the delay is only for a few weeks			

Table 15: $CHADS_2$ score (55)	
	Score
Congestive heart failure	+1
Hypertension	+1
Age >/=75 ἐτη	+1
Diabetes Meliitus	+1
Previous stroke/transient ischemic attack	+2
Table 16: CHA_2DS_2-VASc score (5)	
	Score
Age	<65: 0, 65-74: +1, >/=75: +2
Gender	Female: +1, Male: 0
Congestive heart failure	+1
Previous stroke/transient ischemic attack	+1
Vascular disease	+1
Diabetes Meliitus	+1

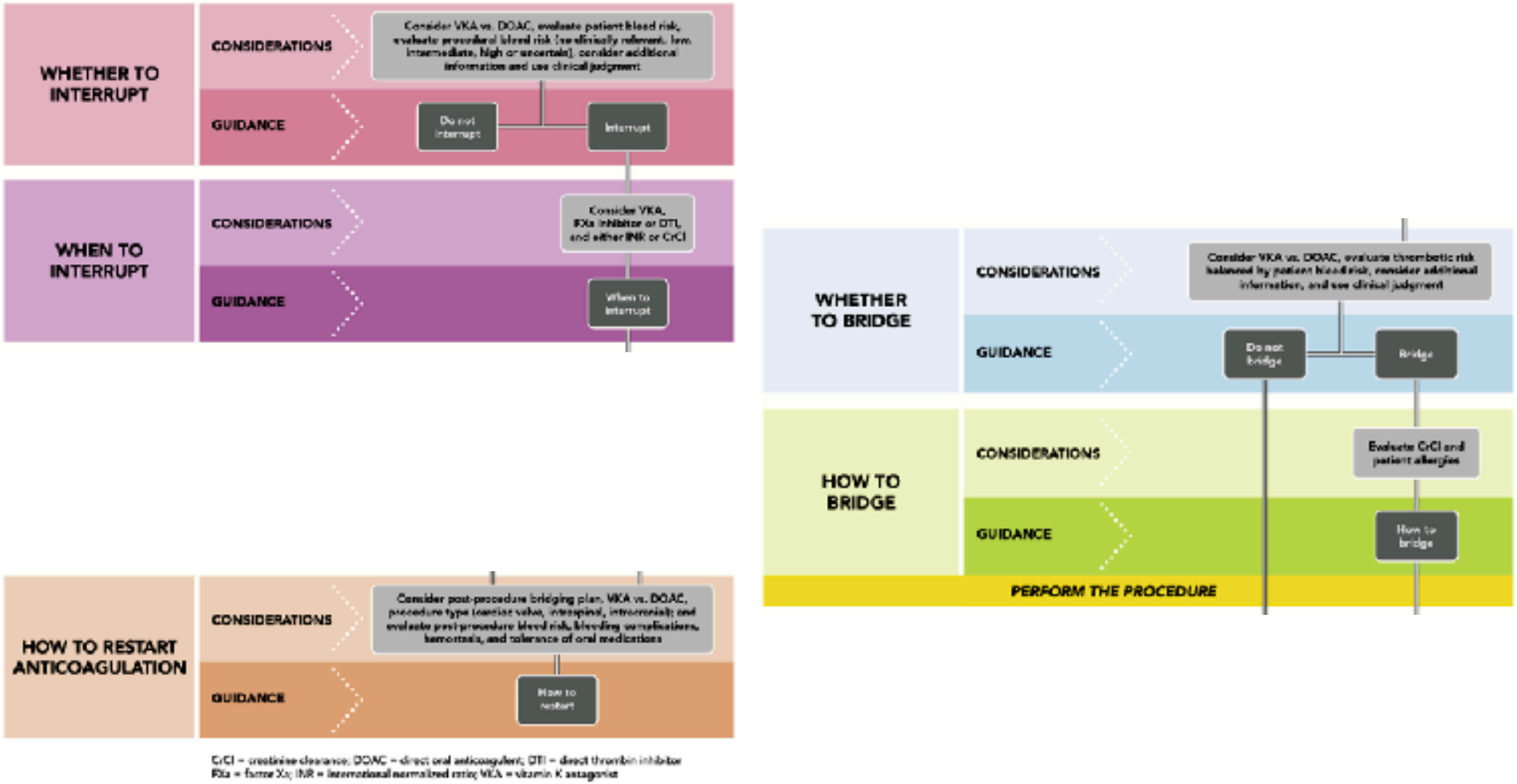

Figure 14. Perioperative management of anticoagulant therapy - Pathway decision algorithm (55)

Table 17. Plan for the discontinuation of warfarin pre-operatively (no bridging therapy is required) (9)							
Days preoperatively	6	5	4	3	2	1	0
Warfarin	Take last dose of warfarin	No warfarin	No warfarin	No warfarin	No warfarin	No warfarin	No warfarin
INR						Check if INR < 1.5	

Table 18. Plan for the discontinuation of warfarin pre-operatively and institution of enoxaparin (no bridging therapy is required) (9)							
Days preoperatively	6	5	4	3	2	1	0
Warfarin	Take last dose of warfarin	No warfarin	No warfarin	No warfarin	No warfarin	No warfarin	No warfarin
INR			Check INR			Either 1 day prior, or morning of surgery: Check if INR < 1.5	
Enoxaparin	No enoxaparin	No enoxaparin	Start enoxaparin when INR is </=2			Stop enoxaparin 24 hours before procedure	

Table 19. Enoxaparin plan (9)	
Creatinine clearance (CrCl)	**Dose***
If CrCl <30 mL/min	Hematologist or renal physician help
If CrCl >/=30 mL/min	1 mg/kg subcutaneous injection twice daily OR 1,5 mg/kg once daily
*Adjus doses for extremes of body weight	

Table 20. Effect of DOACs on coagulation assays (9)			
	Dabigatran	**Rivaroxaban**	**Apixaban**
Unlikely	aPTT and thrombin time (TT) normal	PT normal	Normal PT **DOES NOT** exclude presence of therapeutic apixaban
Likely	aPTT and thrombin time (TT) prolonged	PT prolonged	PT prolonged or normal
Specific assays	Dilute thrombin clotting time (Hemoclot assay)	Modified anti-Xa, specific for rivaroxaban	Modified anti-Xa, specific for Apixaban

Table 21. Perioperative plan for Dabigatran (9)		
Dabigatran (110 or 150 mg twice a day)	**Low bleeding risk surgery**	**High bleeding risk surgery**
CrCl >/=80 mL/min	Last dose 1 day preoperatively	Last dose 2 days preoperatively
CrCl 50-80 mL/min	Last dose 1 - 2 days preoperatively	Last dose 2 - 3 days preoperatively
CrCl 30-49 mL/min	Last dose 48 - 72 hours preoperatively	Last dose 4 days preoperatively
CrCl <30 mL/min		

Table 22. Perioperative plan for Apixaban (9)		
Apixaban (2.5 or 5 mg twice a day)	**Low bleeding risk surgery**	**High bleeding risk surgery**
CrCl >/=50 mL/min	Last dose 1 day preoperatively	Last dose 2 - 3 days preoperatively
CrCl 30-50 mL/min	Last dose 2 days preoperatively	Last dose 3 days preoperatively
CrCl <30 mL/min		

Table 23. Perioperative plan for Rivaroxaban (9)		
Rivaroxaban (15 or 20 mg once a day)	**Low bleeding risk surgery**	**High bleeding risk surgery**
CrCl >/=50 mL/min	Last dose 1 day preoperatively	Last dose 2 - 3 days preoperatively
CrCl 30-50 mL/min	Last dose 2 days preoperatively	Last dose 3 days preoperatively
CrCl <30 mL/min		

Table 24. Recommencing DOACs after a procedure (9)	
Risk of major procedural bleeding (48 hours)	**When to recommence DOACs**
Low risk (0% - 2%)	Reinstitute 1 day postoperatively
High risk (2% - 4%)	Do not start therapeutic dosing until 2 to 3 days postoperatively Think about VTE prophylaxis when required

Procedure Name	Bleed Risk Level			
	Low	Intermediate	High	Uncertain
Craniotomy	☐	☐	☒	☐
Laminectomy	☐	☐	☒	☐
Discectomy	☐	☐	☒	☐
Fusion, spinal	☐	☐	☒	☐
Endarterectomy, carotid	☐	☐	☒	☐
Angiogram, cerebral	☐	☒	☐	☐
Stent, carotid	☐	☒	☐	☐
Embolization, intracranial	☐	☐	☒	☐
Embolization, spinal	☐	☒	☐	☐
Embolectomy, stroke	☐	☐	☒	☐
Decompression, peripheral nerve	☐	☒	☐	☐
Stimulation, deep brain	☐	☐	☒	☐
Stimulation, spinal cord	☐	☐	☒	☐
Craniectomy	☐	☐	☒	☐
VP (ventriculoperitioneal) shunt	☐	☐	☒	☐
Lumbar puncture	☐	☐	☒	☐
Pituitary surgery	☐	☐	☒	☐

We are grateful for this contribution by Dr. Bernard Bendok and the American Association of Neurological Surgeons.

Figure 15. Common Neurosurgical procedures and associated procedural bleeding risk (55)

Table 25. Search strategy

Frame	P (patients, participants, population)	I (intervention)	C (comparator / reference test)	O (outcome)	Time	
Mesh terms	#1. Adults #2. "Anticoagulants" OR "venous thromboembolism, prevention" OR "venous thromboembolism, control" #3. "Guidelines" OR "Recommendations" # 4. English language	#5."Cranial surgery" OR "Spine surgery"	#6. Any	#7."Risk of bleeding", OR "Risk of coagulation" OR "other"	The search period: 1964 until March, 2020	Last search: (-)
Search	#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7					
Exclusion Criteria	Irrelevant title or abstract, Irrelevant full-text, Editorial, reviews, case-reports, meta-analysis, pediatric/neonatal studies, experimental/nonhuman studies, non –English studies, observational studies, experimental studies, editorials, letter to the editor					
Sources	Databases (PubMed and Scopus) Reference list					

Figure 16. Prisma flowchart

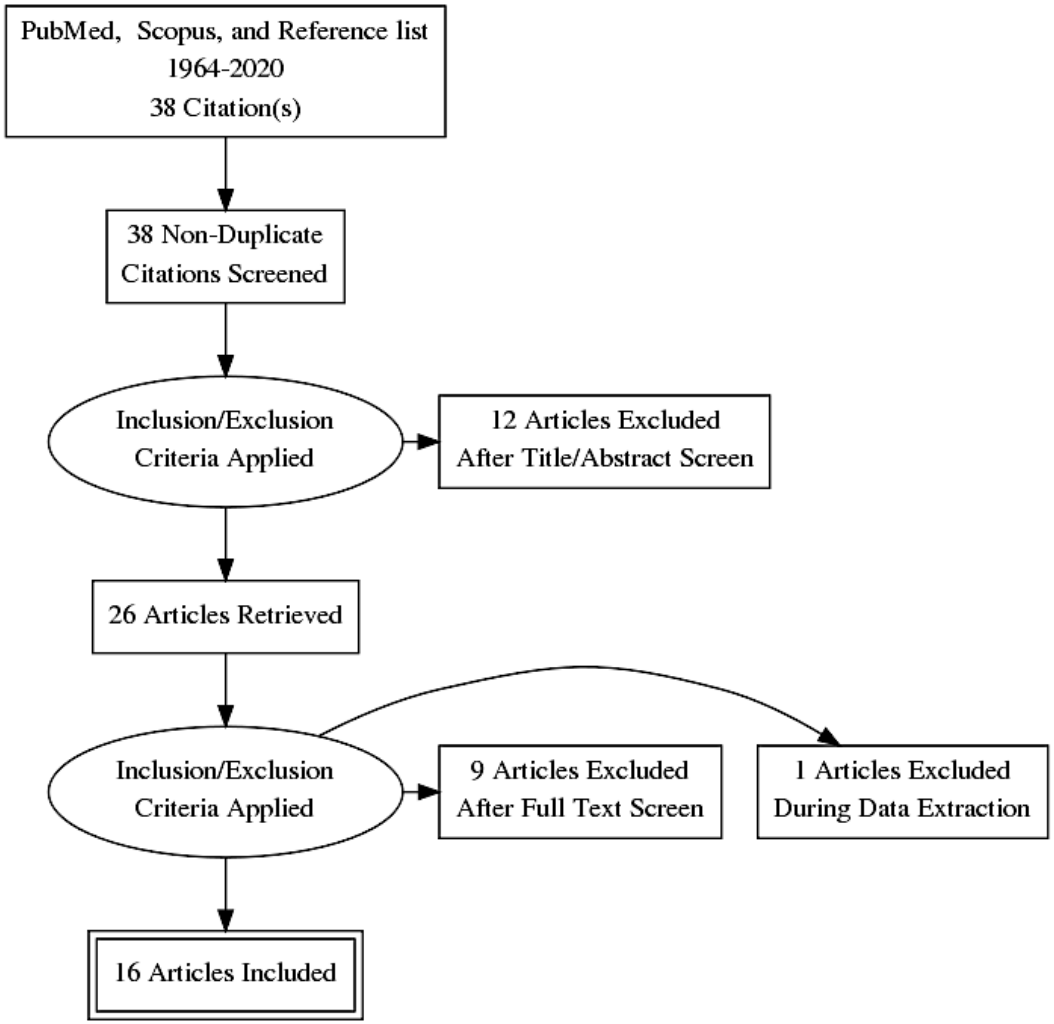

Table 26. Individual score of guidelines

Recommendations	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Overall	Average
Albaladejo (2018)	0,83	0,56	0,17	0,81	0,44	0,46	0,50	0,54
Goldier (2018)	0,83	0,28	0,42	0,92	0,50	0,50	0,63	0,58
Madhugiri (2018)	1,00	0,00	0,23	1,00	0,17	1,00	0,81	0,60
Rossini (2018)	0,94	0,50	0,56	0,81	0,56	0,54	0,63	0,65
Armstrong (2013)	1,00	0,00	0,56	0,89	0,33	1,00	0,81	0,66
Kozek (2016)	0,94	0,22	0,80	1,00	0,38	0,50	0,88	0,67
Steffel (2018)	0,97	0,17	0,50	0,97	0,81	0,79	0,63	0,69
Cec (2018)	1,00	0,53	0,31	1,00	0,73	0,50	0,81	0,70
Bono (2009)	1,00	0,44	0,98	1,00	0,27	0,63	0,75	0,72
Douketis (2012)	1,00	0,00	0,58	1,00	0,92	1,00	0,75	0,75
Doherty (2017)	1,00	0,47	0,65	1,00	0,60	0,83	0,75	0,76
Kristensen (2014)	1,00	0,75	0,55	1,00	0,65	0,67	0,75	0,77
Narouze (2018)	0,94	0,58	0,78	0,97	0,56	0,83	0,81	0,78
Fleisher (2014)	1,00	0,67	0,88	1,00	0,65	0,67	0,75	0,80
Valgimigli (2018)	1,00	0,78	0,86	1,00	0,92	0,92	0,75	0,89
Hert (2018)	1,00	0,75	0,93	1,00	0,83	1,00	0,75	0,89

Figure 17. AGREE II, elective spine procedures

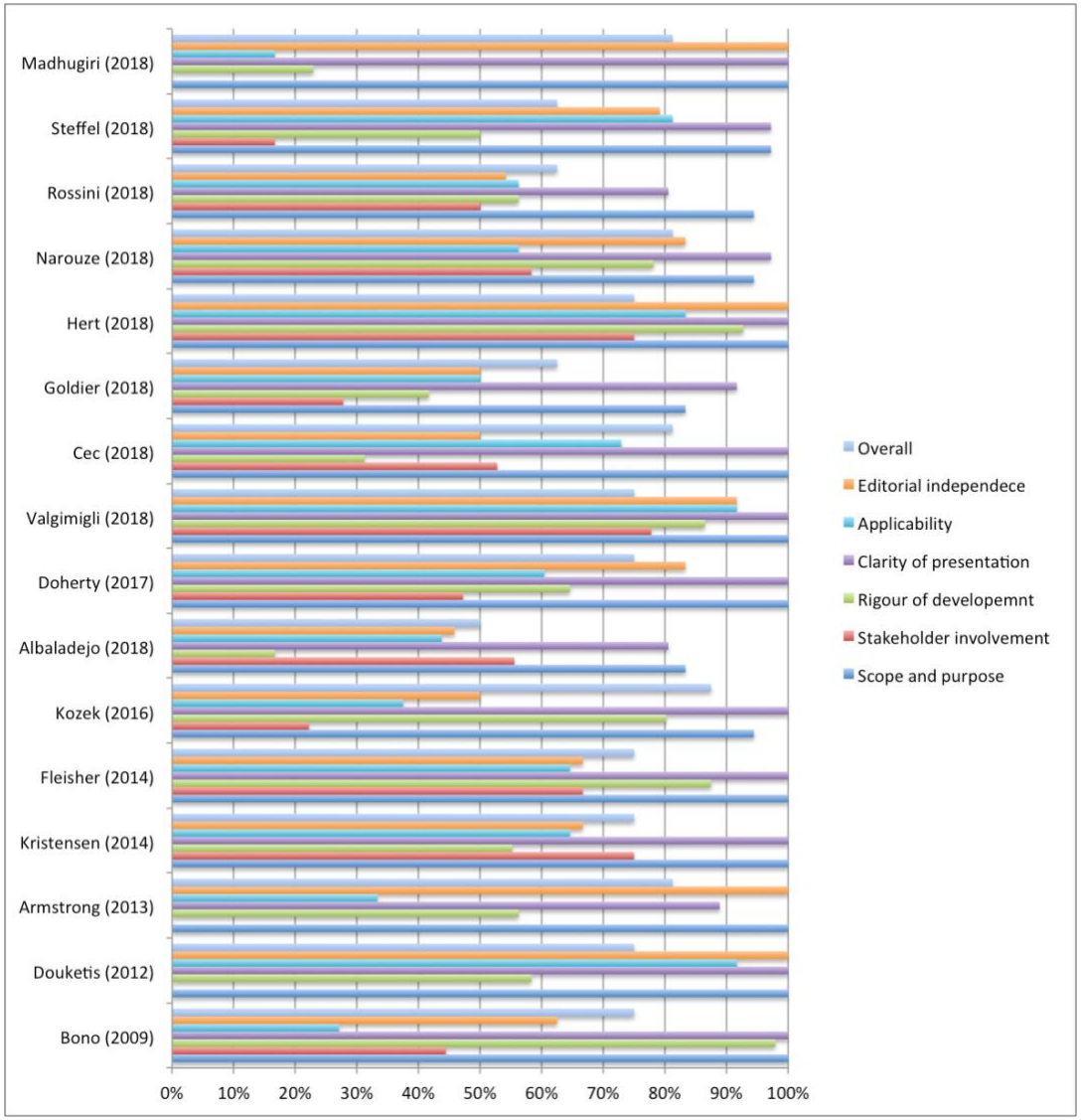

Table 27. Summary scores on the topic

	Value						
	Applicability	**Clarity of presentation**	**Editorial independence**	**Overall**	**Rigor of development**	**Scope and purpose**	**Stakeholder involvement**
Valid	16	16	16	16	16	16	16
Missing	0	0	0	0	0	0	0
Median	0.5800	1.000	0.7300	0.7500	0.5700	1.000	0.4850
Std. Deviation	0.2270	0.06718	0.2057	0.09430	0.2486	0.05808	0.2742
Minimum	0.1700	0.8100	0.4600	0.5000	0.1700	0.8300	0.000
Maximum	0.9200	1.000	1.000	0.8800	0.9800	1.000	0.7800
25th percentile	0.4250	0.9575	0.5300	0.7200	0.4800	0.9400	0.2075
50th percentile	0.5800	1.000	0.7300	0.7500	0.5700	1.000	0.4850
75th percentile	0.7500	1.000	0.9400	0.8100	0.8150	1.000	0.6025

Figure 18. Boxplots

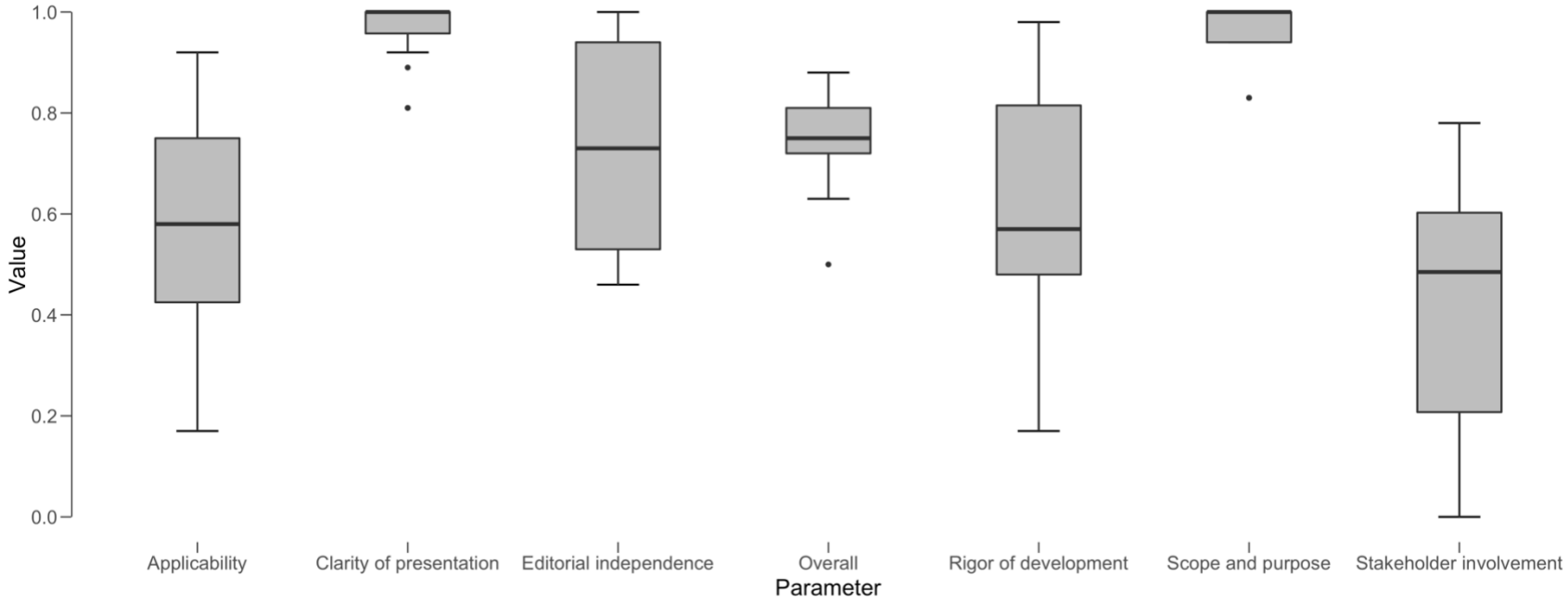

Figure 19.

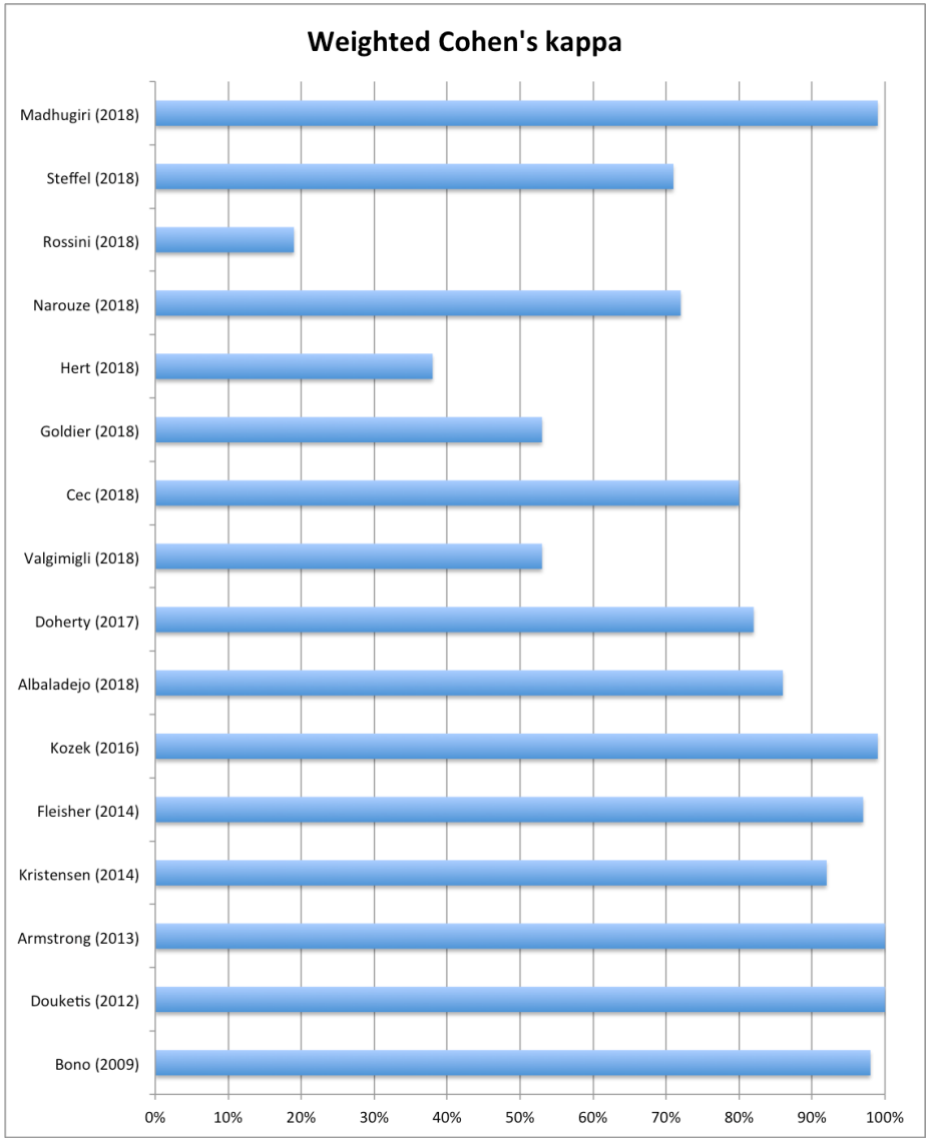

Table 28. Non – parametric ANOVA for comparison

One-Way ANOVA (Non-parametric)

Kruskal-Wallis

	χ^2	df	p	ε^2
Value	64.3	6	< .001	0.579

Dwass-Steel-Critchlow-Fligner pairwise comparisons between the AGREE-II domains

		W	p
Applicability	Clarity of presentation	6.393	< .001
Applicability	Editorial independence	2.592	0.526
Applicability	Overall	2.820	0.419
Applicability	Rigor of development	0.374	1.000
Applicability	Scope and purpose	6.664	< .001
Applicability	Stakeholder involvement	-2.215	0.704
Clarity of presentation	Editorial independence	-4.263	0.041
Clarity of presentation	Overall	-6.664	< .001
Clarity of presentation	Rigor of development	-6.172	< .001
Clarity of presentation	Scope and purpose	0.184	1.000
Clarity of presentation	Stakeholder involvement	-6.933	< .001
Editorial independence	Overall	-0.323	1.000
Editorial independence	Rigor of development	-1.950	0.814
Editorial independence	Scope and purpose	4.462	0.027
Editorial independence	Stakeholder involvement	-4.249	0.042
Overall	Rigor of development	-1.878	0.839
Overall	Scope and purpose	6.869	< .001
Overall	Stakeholder involvement	-5.102	0.006
Rigor of development	Scope and purpose	6.282	< .001
Rigor of development	Stakeholder involvement	-2.722	0.464
Scope and purpose	Stakeholder involvement	-6.935	< .001

Table 29. Interobserver agreement

	Weighted Cohen's kappa
N	16
Missing	0
Median	0.840
Minimum	0.190
Maximum	1.00
25th percentile	0.665
50th percentile	0.840
75th percentile	0.982

Interpretation:

0-.20: No agreement

0.21-0.39: Minimal agreement

0.40-0.59: Weak agreement

0.69-0.79: Moderate agreement

0.80-0.90: Strong agreement

Above 0.90: Almost perfect agreement

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