Perioperative antithrombotic (antiplatelet and anticoagulant) therapy in urological practice- A critical assessment and summary of the Clinical Practice Guidelines

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Abstract

Purpose: The perioperative management of patients who are receiving antithrombotic (antiplatelet or anticoagulant) therapy and require urologic surgery is challenging due to the inherent risk for surgical bleeding and the need to minimize thromboembolic risk. The aim of this review is to assess the quality and consistency of clinical practice guidelines (CPGs) and clinical practice recommendations (CPRs) on this topic, and to summarize the evidence and associated strength of recommendations relating to perioperative antithrombotic management.

Methods: A pragmatic search of electronic databases and guidelines websites was performed to identify relevant CPGs/CPRs. The AGREE II (Appraisal of Guidelines for REsearch and Evaluation) instrument was used to assess the methodological quality and integrity of the CPGs.

Results: The CPGs provided by the European Association of Urology (EAU), the American College of Chest Physicians (ACCP) and the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA), and the CPRs provided by the International Consultation on Urological Disease (ICUD)/American Urologic Association (AUA) were retrieved and reviewed. The 3 CPGs were critically assessed using the AGREE II instrument. Inconsistent recommendations were provided based on the indication for antithrombotic medication, the antiplatelet/anticoagulant agent and the type of urological procedure. Based on the AGREE II tool for CPG assessment, the EAU CPGs scored higher (83.3 points) compared to the ESC/ESA (75 points) and ACCP CPG (66.7 points).

Conclusion: The perioperative management of antithrombotic therapy in urological patients is potentially challenging but inconsistent CPG of varying quality may create uncertainty as to best practices to minimize thromboembolic and bleeding risk.

Introduction

Acute or elective management of patients on antithrombotic (antiplatelet or anticoagulant) therapy presents a challenge for surgeons because of the intrinsic risk for intra- and post-operative bleeding associated with most urologic surgery and the need to minimize thromboembolic risk. With an aging population, an increasing number of patients are receiving anticoagulant therapy for stroke prevention in atrial fibrillation (AF) or the management of venous thromboembolism (VTE) and antiplatelet therapy for coronary or peripheral vascular disease. Such patients, typically, have multiple comorbidities that increase thromboembolic risk. The rationale for withholding antithrombotic therapy during the perioperative period is to minimize blood loss during and after surgery; however, this approach needs to be balanced against the risk of perioperative thromboembolism that may arise after stopping treatment, especially in high-risk patients.

Among antiplatelet drugs, aspirin irreversibly binds to cycloxygenase (COX)-1, effectively inhibiting thromboxane A_2 production and platelet aggregation, whereas $P2Y_{12}$ receptor inhibitors, comprising clopidogrel, prasugrel and ticagrelor, reduce platelet aggregation by inhibiting the activation of the glycoprotein IIb/IIIa receptor complex.[1–5] Dipyridamole, which is typically combined therapeutically with aspirin, inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase, increases platelet cAMP levels and reduces thromboxane A_2 activity and platelet aggregation.[6][7] Less commonly used agents are abciximab, eptifibatide and tirofiban, which act on platelet glycoprotein IIb/IIIa receptors to inhibit platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules.[8–10]

Anticoagulant medications, on the other hand, suppress thrombus formation and propagation by targeting different clotting factors involved in the coagulation cascade that culminates with the production of fibrin. As venous thrombi contain high levels of fibrin, anticoagulants mainly reduce the incidence of venous thromboembolic events, but anticoagulants are also effective to prevent

intracardiac thrombus formation in patients with AF, thereby reducing the risk for cardioembolic stroke.

Among anticoagulant drugs, warfarin decreases blood clotting by blocking reactivation of vitamin K1; without sufficiently active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability.[11] Unfractionated heparin binds reversibly to antithrombin III and greatly accelerates the rate at which it inactivates thrombin (factor IIa) and factor Xa. Low-molecular-weight heparins (LMWHs) bind and activate antithrombin, with a stronger affinity to factor Xa than unfractionated heparin and affect only the intrinsic coagulation cascade. Fondaparinux is a selective factor Xa inhibitor that prevents the conversion of prothrombin to thrombin. [12] Direct oral anticoagulants (DOACs) include dabigatran and factor Xa inhibitors. Dabigatran etexilate is an oral prodrug that disrupts the coagulation cascade and inhibits the formation of clots by offering reversible and direct inhibition of direct thrombin.[13] Rivaroxaban, apixaban and edoxaban are factor Xa inhibitors. All DOACs inhibit the formation of circulating and clot-bound thrombin and have no effects on platelet function.[14–18] With respect to reversibility of action, dabigatran can be reversed selectively with idarucizumab, a humanized monoclonal antibody fragment, while further reversal agents for DOACs are on the horizon.**Table 1** summarizes the characteristics and pharmacological properties of the currently available main antithrombotic agents. For perioperative, it is important to note that their elimination half-lives are 10-14 hours (longer for patients taking dabigatran and have impaired renal function) and have a rapid (1-3 hour) peak anticoagulant effect after oral intake.

In the urological setting, surgeons will frequently need to decide on the perioperative management of patients on anticoagulants or antiplatelets undergoing open or endoscopic, acute or elective urological procedures. The number of patients taking antithrombotic agents has increased in the past decade, especially as DOAC have become widely used in patients with AF and VTE. Thus, it is critical for the surgeon to be aware of the characteristics of antithrombotic agent and their mechanism

of action to facilitate decision-making such as optimal timing of discontinuation and restarting as well as antithrombotic reversal, if feasible.

In addition and separate to pure clinical knowledge and practice, the methodological quality of the available guidelines and recommendations becomes a critical component of evidence-based patient care in the era of evidence-based medicine. To the best of our knowledge, the available recommendations on the perioperative management of antithrombotic treatment in the urological setting has not been systematically reviewed and methodologically assessed.

The current review will identify the clinical practice guidelines (CPGs) and clinical practice recommendations (CPRs) on the management of antiplatelets and anticoagulants in the acute and elective urological surgical setting, as provided by four main medical and surgical organizations. In addition, the methodological quality of the CPGs will be objectively assessed with a validated instrument.

Methods

A pragmatic search of the available electronic databases and guidelines websites, including PubMed, EMBASE and the National Guideline Clearinghouse (www.guideline.gov) was performed. Databases were searched from their inception date to March 2019; only English-written guidelines were searched and retrieved. Following identification of guidelines authors reached consensus on internationally endorsed CPGs or CPRs with direct clinical relevance to the urological surgical practice.

CPGs/CPRs were reviewed and main recommendations were summarized into tables. Two independent trained appraisers (KD and MO) used the AGREE II (Appraisal of Guidelines for REsearch and Evaluation) instrument to evaluate the three CPGs. AGREE II is an international, validated instrument that assesses the methodological quality and integrity of the Guidelines and is globally endorsed by several health care organizations.[19] It consists of 23 separate items evaluating six

different domains: 1) scope and purpose (items 1–3); 2) stakeholder involvement (items 4–6); 3) rigor of development (items 7–14); 4) clarity of presentation (items 15–17); 5) applicability (items 18–21); and 6) editorial independence (items 22–23). The AGREE II instrument uses a 7-point scoring system for each one of these 23 individual items, with a score of 1 indicating no/poor information provided for the appraised item while a score of 7 indicates exceptional quality of reporting. There is also a final domain assessing the overall quality of the Guideline (score 1-7) and a separate item pertaining to whether the reviewer would recommend the appraised guideline for clinical use (Yes, Yes with modifications, No).

Scores for each domain are calculated by summing up all appraisers' scores of all individual domain items and by scaling the total as a percentage of the maximum possible score for that domain using the formula (Obtained score – Minimum possible score) x 100/(Maximum possible score – Minimum possible score). According to the AGREE II Consortium, there are no set scores used to differentiate between high- and poor-quality guidelines; instead, this decision should be made by the AGREE II user. However, domain scores can certainly be used for comparisons among different CPGs.

Results

Four different internationally endorsed CPGs and CPRs were identified following the initial search. These included the CPGs of the European Association of Urology (EAU) published in 2018,[20, 21] the American College of Chest Physicians (ACCP) CPG published in 2012[22] and the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) CPGs published in 2014.[23] Finally, the CPRs provided by the International Consultation on Urological Disease (ICUD)/American Urologic Association (AUA) were included in this pragmatic review.[24]The overall results of the appraisal of the three CPGs with the use of the AGREE-II instrument are presented in **Table 2**.

The applicability of the AGREE II instrument to assess the ICUD/AUA publication was also assessed by the reviewers. The AUA/ICUD white paper reported consensus-based recommendations and as the authors reported in their publication, they focused on constructing a review based on a systematic literature search, instead of developing a full CPG. Thus, to ensure methodological consistency, it was decided that AGREE II would not be used to appraise the AUA/ICUD recommendations which should be regarded as CPRs instead of CPGs.

With respect to overall guideline assessment, the EAU and ESC/ESA CPGs had scores of 83.3, and 75, respectively, while the ACCP CPGs scored lower (66.7) mainly because they were considered to require revision to ensure updated recommendations. As regards scope and purpose, the ACCP Guidelines had the highest score (88.9) compared to the EAU (63.9) and ESC/ESA (52.8) CPGs. The ESC/ESA Guidelines scored higher in terms of stakeholder involvement (55.6 versus 52.8 for both EAU and ACCP CPGs), and for applicability (70.8 versus 33.3 for ACCP and 8.3 for EAU). The EAU Guidelines had the highest score as regards rigor of development (56.3 versus 55.2 for ESC/ESA and 43.8 for ACCP Guidelines), clarity of presentation (94.4 compared to 83.3 for ACCP and 75.0 for ESC/ESA CPGs), while the EAU and ACCP CPGs scored 100 for editorial independence compared to 91.7 for those of the ESC/ESA.

For all CPGs, modifications were deemed necessary to further improve the quality of their recommendations and methods. Whereas a similar pattern of scoring was identified across almost all the examined CPG domains, discrepancies were identified in applicability, with a range of 62.5 points (8.3–70.8).

Table 3 provides a detailed summary of the CPGs and CPRs relating to the perioperative management of antithrombotic agents. For brevity, all recommendations will be presented and discussed below, separate for antiplatelet and antithrombotic agents.

Discussion

Antiplatelet agents

With respect to the management of patients who are using antiplatelet agents, most CPGs/CPRs focused on aspirin and clopidogrel, although additional recommendations regarding the management of patients on ticagrelor or prasugrel also were provided. It is noteworthy that all CPGs/CPRs discuss the need for the clinician to weigh the risks of perioperative bleeding against the risk of thromboembolic complications.

In general, the main clinical settings discussed in the CPGs/CPRs represent the perioperative management of monotherapy (with aspirin or other antiplatelets) and dual antiplatelet treatment (with aspirin and one P2Y12 inhibitor). While a variety of recommendations is noted in regards to the perioperative management of aspirin monotherapy (EAU advises stopping prior to operation based on recent evidence, AUA and ACCP recommend in general continuing with aspirin through the time of surgery and ESC/ESA advise individualized approach), it is clear that all CPGs/CPRs agree on stopping all remaining antiplatelets (such as clopidogrel or ticagrelor) preoperatively.

The challenging management of DAPT in the elective/urgent/emergency surgical setting is highlighted across all four CPGs/CPRs. Deferring any elective procedures until the completion of the DAPT course is clearly the consensus recommendation with the clinicians advised to explore simpler and less invasive management alternatives for a minimum time period that depends on the original clinical indication for DAPT (e.g. insertion of bare metal or drug eluting stent). If this is not possible (for example in the case of a clinical emergency), then multidisciplinary approach is encouraged by all organizations and different recommendations are provided such as continuing with the DAPT perioperatively (EAU and ACCP), or continuing with single antiplatelet treatment with aspirin around the time of surgery with or without bridging based on indications and with a 24/7 catheterization laboratory available to treat patients in case of perioperative TEs (ESC/ESA).

AUA is the only association that provides with procedure-specific recommendations. Patients on low-dose aspirin can have prostatic biopsies while remaining on the antiplatelet drug with a risk of minor bleeding approximately a third higher than the controls. Laser operations such as ureteroscopy or laser prostatectomy can can be safely performed without stopping the AP agent. For more complicated procedures such as PCNL, TURP, or even more invasive operations (e.g. radical prostatectomy or partial nephrectomy) this is not the case and therefore AP should be stopped and bridging should be offered prior to the procedure. For ESWL, AP drugs should be discontinued or reversed prior to the ESWL session, although no specific timings of cessation/reinstitution of antiplatelet drugs were provided, as they warrant multidisciplinary and case-specific discussions.

Anticoagulant agents

Two main categories of anticoagulants are discussed by the CPGs/CPRs discussed in this review: warfarin and the newer DOACs. It should be noted that the ACCP Guidelines do not address perioperative DOAC management. With respect to procedure-specific guidance, the recommendations provided by the AUA remain the same with the ones provided in the case of APs.

In regards to perioperative management of warfarin, all four CPGs/CPRs use a risk stratification approach to provide with recommendations. For patients on warfarin at low risk for TEs, warfarin should be stopped 3-5 days prior to procedure; warfarin can be restarted after 1-4 days depending on the CPG/CPR. All CPGs/CPRs agree that patients at high risk for TEs will need to stop warfarin 5 days before the procedure and start bridging with LMWH 4 days before the operation or once INR <2.0. ACCP Guidelines encourage a patient/surgery-based approach in patients at moderate risk for TEs where the clinician can decide on whether bridging should or should not be offered. ESC/ESA CPGs and AUA CPRs tend to favour the use of UFH as bridging agent in patients with metallic heart valves, ACCP CPGs discuss both LMWH and UFH while EAU CPGs only recommend LMWH.

For the management of DOACs, some variation in recommendations is noted reflecting the new practice and constantly evolving evidence. EAU CPGs follow the same approach with warfarin: stop

preoperatively with no bridging; if the TE is recent, defer operation if possible – if not, continue with the anticoagulants around the procedure or offer bridging. AUA also advise consultation with cardiology/haematology for urgent/emergency procedures. While AUA approaches standard and high risk procedures in the same way (stop DOAC 2-5 days prior to operation, bridging might be required) ESC/ESA offer different recommendations based on the risk of bleeding (stop DOACs preoperatively for 2-3/4-5 times their biological half-lives for low and high risk procedures, respectively) and in general recommends against bridging except in case surgical intervention is delayed for several days.

Of note, ACCP Guidelines do not provide with recommendations on the management of DOACs as their use was not common when ACCP CPGs were released. Recently however, Douketis et al. published the results of the PAUSE (Perioperative Anticoagulation Use for Surgery Evaluation) study, assessing a simple proposed discontinuation/resumption strategy for patients with AF on DOACs who were to be offered various types of elective surgery (not urological, necessarily).[25] DOACs were stopped 1 or 2 days before a low- or high-risk procedure respectively, and were resumed 1 day after a low risk procedure or 2-3 days after a high-risk one. In more than 3000 patients included, the rates of major bleeding and arterial thromboembolism were low, regardless of the DOAC agent.

Methodological aspects

With respect to the methodological quality of the CPGs assessed in this review, some critical points need to be discussed and clarified. First, the methodological framework of the CPGs discussed in this review is not the same and therefore, the processes linking the available evidence to the provided recommendations can vary significantly. In addition, the levels of evidence and strengths of recommendations as presented in the CPGs might not be exactly the same as the Guidelines organisations can be using different grading systems and therefore, interpreting the statements and comparing the recommendations directly based on their strength should be approached with extreme caution.

Although AGREE II is a validated instrument that assesses the methodological quality of health system guidelines, there are no pre-defined thresholds to define high, moderate and low quality guidelines due to the lack of empirical basis to define them. An arbitrary threshold of <30% to define low quality and >70% to define high quality can be used for the subdomains as users should be encouraged to avoid using the overall score as the sole indicator of methodological quality. Moreover, depending on the primary research aim solitary domains could have a higher weight (e.g. stakeholder involvement and applicability) and therefore their scores will require different interpretation. Thus, we discourage the readers from preferring a specific guideline over another one based on the AGREE II results only.

The 3 CPGs assessed in the current SR had high scores in Editorial Independence (best domain for all 3) and Clarity of Presentation and moderate scores in Stakeholder Development and Rigor of Development. In Scope and Purpose, EAU and ESC/ESA CPGs had moderate scores while ACCP CPGs scored fairly high. The most impressive score range was detected in Applicability, with EAU CPGs scoring very low, ACCP CPGs having low score and ESC/ESA scoring rather moderate-to-high.

It is clear that the CPGs panel need to work more on identifying the facilitators and barriers to their Guidelines application and on how their recommendations can be applied. In addition, auditing criteria and processes need to be clearly provided to further improve the Applicability domain score. With respect to the Rigour of Development domain, main weak points were clear descriptions of the methodology and in specific the link between recommendations and supporting evidence, the external review and the update procedures. In Stakeholder Development, clear description of the target users of the CPGs was not frequently provided and it was unclear how the views and preferences of patients were sought and taken into consideration. The lack of clear descriptions of the health questions, objectives and target population covered in the CPGs can explain the rather moderate scores in Scope and Purpose. For all 3 CPGs, reviewers felt that additional modifications were necessary to further improve the quality of recommendations and methods.

Limitations and Strengths

A possible limitation of this review is the fact that only 4 CPGs/CPRs were included, presented, assessed and discussed. Indeed, a more inclusive approach could have been followed in this review with a more exhaustive literature search to give the reader a more holistic overview of the available literature and mainly the evidence-derived recommendations. There is a big number of international, national and departmental guidelines available currently but the aim of this review was to discuss the perioperative management of the antithrombotic agents in the urological setting in specific. As a result, it was decided that the recommendations provided by the two main international urological associations (EAU and AUA) should be discussed. The ESC/ESA and ACCP CPGs do not exclusively refer to urological operations but provide with evidence based recommendations on the general perioperative management of antithrombotic medications and are endorsed by multiple medical and surgical societies globally. In addition, their clinical recommendations represent the main basis for guidelines provided by other associations.

To the best of our knowledge, this is the first pragmatic review to summarise the evidence on the perioperative management of antiplatelet/anticoagulant agents in the urological setting with a critical assessment of the included CPGs. We feel that from a clinical perspective this will represent a helpful tool, will facilitate the decision-making process, simplify clinical practice and improve patient care. From the methodological view, the current review review will also highlight to the reader the methodological limitations, challenges and strengths behind the available evidence-based recommendations.

Conclusions

The perioperative management of antithrombotic therapy in urological patients is potentially challenging but inconsistent CPG of varying quality may create uncertainty as to best practices to minimize thromboembolic and bleeding risk. Various recommendations have been provided by several surgical and medical organisations on the perioperative management of antiplatelet and antithrombotic agents in the urological field and are presented in the current review. Clinicians are

encouraged to critically endorse them to develop patient-specific evidence-based management plans tailored to meet individual needs. On the other hand, this review also reveals weaknesses and gaps in the quality of the available guidelines, highlighting the need for further improvement to the guidelines panels and organisations.

Authors' contribution

K. Dimitropoulos: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

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K. Dimitropoulos is a Senior Associate of the EAU Guidelines Office and a member of the EAU Guidelines Office Urethral Strictures panel, M.I. Omar is the EAU Guidelines Office Methodology Supervisor, S. Gravas is the Chair of the EAU Guidelines Office Male LUTS panel and J. Douketis is the first author of the ACCP Guidelines publication

Research involving Human Participants and/or Animals: Not applicable

Informed consent: Not applicable

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