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Use of direct oral anticoagulants and warfarin in the context of atrial fibrillation and venous thromboembolism

English summary

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This is the English summary of the guidance entitled Usage des anticoagulants oraux directs et de la warfarine dans le contexte de la fibrillation auriculaire et de la thromboembolie veineuse - Rapport en soutien aux guides d'usage optimal - published in April 2019.

The complete version of this guidance (in French) is available on the website of INESSS in the Publications section.

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SUMMARY – GUIDES AND STANDARDS

Introduction

Atrial fibrillation (AF) and venous thromboembolism (VTE) are very common in Canada, and since their prevalence increases with age, one can expect an increase in the number of cases in the coming years because of the aging of the population. Anticoagulants constitute the basic treatment for preventing stroke and systemic embolism (SE) in patients with AF and for treating VTE and preventing recurrences. This class of drugs includes vitamin K antagonists (VKAs, or synthetic coumarin derivatives, such as warfarin), which have been used for many years in these patient populations. These drugs have a narrow therapeutic window, and there is wide variability in the intra-individual and inter-individual dose response. Consequently, frequent monitoring of the anticoagulant effect, expressed as the international normalized ratio (INR), is necessary. In the past few years, apixaban, dabigatran, edoxaban and rivaroxaban, direct oral anticoagulants (DOACs) that do not require such monitoring, have appeared on the Canadian market. Furthermore, CoaguChek XS PT TEST® test strips, which are used for INR monitoring in patients treated with a VKA, are now covered by the public prescription drug insurance plan (PPDIP). Lastly, in 2016, Health Canada approved idarucizumab, a specific antidote that neutralizes the effect of dabigatran.

Given this substantial increase in DOAC use in Québec in the past few years and the priority the Ministère de la Santé et des Services sociaux (MSSS) accords to the optimal use of these drugs in the "clinical relevance project - optimal use of drugs", INESSS undertook work to create optimal use guides (OUGs) on DOACs and warfarin in patients with AF or VTE.

Methods

These OUGs are based on the best available scientific evidence from systematic reviews (SRs) of primary studies, on pharmacoeconomic analyses and on recommendations in clinical practice guidelines (CPGs). They were enriched with legislative and organizational information specific to Québec and with the experiential knowledge of several Québec experts and clinicians who collaborated in this work. A systematic review was conducted in collaboration with a scientific data specialist in the MEDLINE, EBM Reviews and Embase databases to find CPGs and guidelines, consensus conference reports, pharmacoeconomic analyses, and scientific data on the patient perspective. The literature search was limited to items published in or after January 2016 (in the case of CPGs on the use of DOACs) or January 2012 (in the case of the other publications) in French or English. A grey literature search was conducted as well by consulting, among others, the websites of the Guidelines International Network (G-I-N), the National Guideline Clearinghouse (NGC), the National Institute for Health and Care Excellence (NICE), France’s Haute Autorité de Santé (HAS), the Scottish Intercollegiate Guidelines Network (SIGN), the Canadian Cardiovascular Society and Thrombosis Canada. The bibliographies of the selected publications were examined for other relevant items. In addition, the search engine Google was used to find publications from North American

regulatory agencies, including the Food and Drug Administration (FDA) and Health Canada. The official product monographs for the DOACs and warfarin were consulted as well.

Results

The risk of stroke or of VTE recurrence is higher in patients with AF or VTE, respectively. However, using an anticoagulant, which constitutes the basic treatment for these problems, significantly increases the bleeding risk. One of the main challenges in managing AF and VTE is, therefore, to identify patients in whom the benefits of anticoagulation therapy outweigh its risks. This could explain, at least in part, why anticoagulants are underprescribed and why DOACs are underdosed in the context of AF. A few years ago, the Canadian Cardiovascular Society developed the tool called CHADS-65, a simplified decision algorithm based on clinically validated criteria that enables clinicians to better identify most of the medical problems for which the benefits of oral anticoagulant therapy outweigh its risks in patients with AF. Used together with the tool called CHA_2DS_2-VASc, which permits a more accurate assessment of patients' thromboembolic risk, it makes the clinician's decision-making as to whether or not to prescribe oral anticoagulation therapy to a patient with AF clearer. The situation with VTE is somewhat different because the benefits of anticoagulation therapy outweigh its risks in all VTE patients. However, the clinician should carefully assess the recurrence risk after an initial treatment of 3 months' duration to decide whether the treatment should be continued. Since the recurrence risk depends overall on the initial cause of the VTE and on the persistence of this cause, it would seem important to clearly identify the recurrence risk associated with the different causes of VTE and the different situations in which prolonged treatment should be considered.

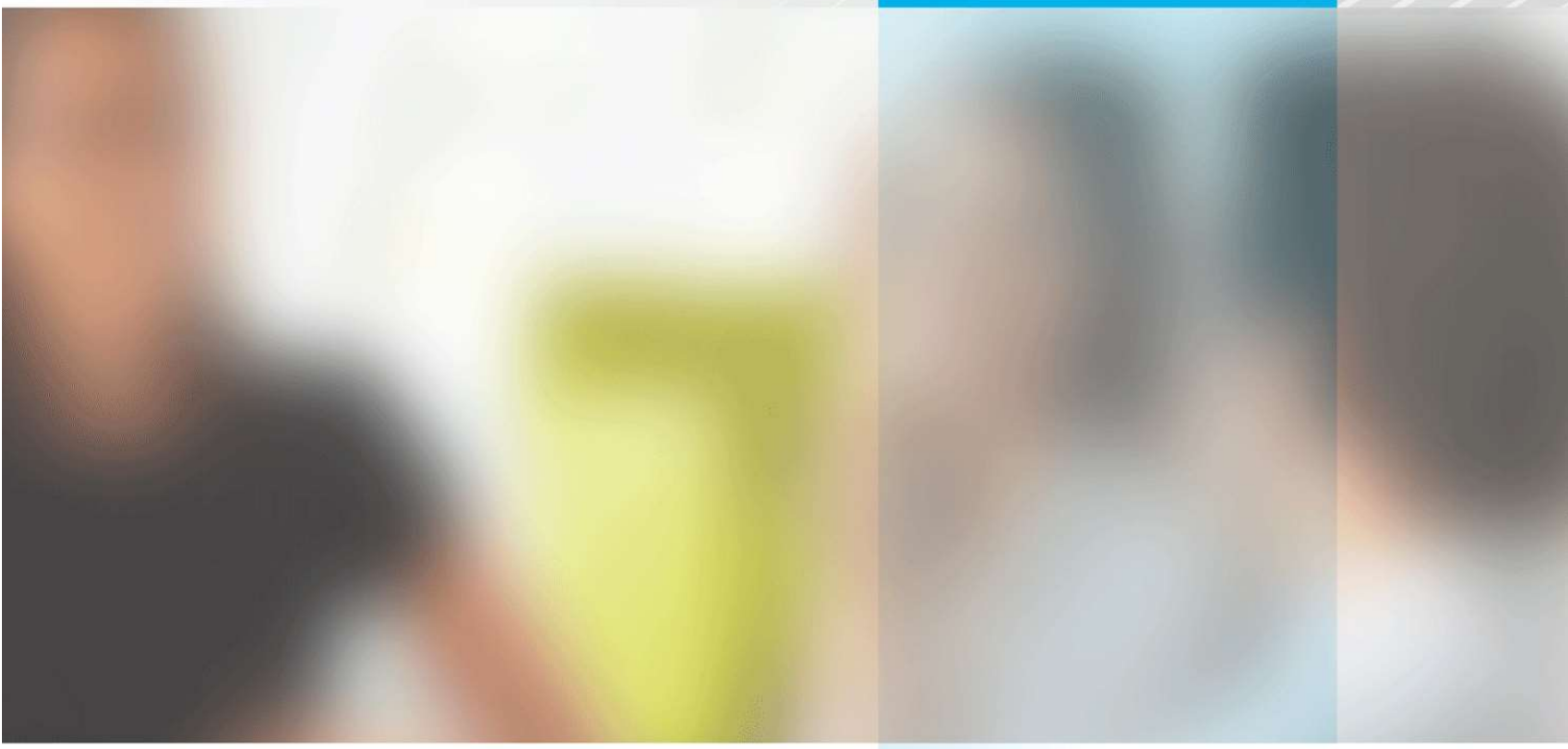
Although VKAs previously constituted the standard of care for most health problems requiring oral anticoagulation therapy, increasingly, they are being replaced with DOACs. In this regard, this report supports the preferential use of DOACs over VKAs in patients in whom their use is not contraindicated, this both for preventing stroke and systemic embolism in patients with AF and for treating VTE and preventing recurrences. This also applies to elderly patients and those with renal failure whose creatinine clearance (Clcr) is greater than 30 ml/min. Furthermore, although subcutaneously administered LMWHs constituted the standard of care for cancer patients who developed VTE, this report also supports the use ─ with caution ─ of apixaban, edoxaban and rivaroxaban in these patients. Caution is, indeed, essential, especially in the presence of gastrointestinal or urogenital cancer because of the potentially higher risk of bleeding. However, there are still certain medical problems for which the use of DOACs is contraindicated or for which there is insufficient data for supporting their use, notably, a Clcr of less than 15 ml/min and antiphospholipid syndrome. It is important to note that well-controlled VKA therapy is an effective and entirely valid option for treating many patients, and the decision to switch patients on a VKA to a DOAC should be discussed with them, taking into account their values and preferences. Also, the inconvenience of the standard follow-up, provided by a health professional, of patients on VKA anticoagulation therapy can limit its acceptability. In this regard, this report supports the option of anticoagulation therapy self-monitoring

and self-management. Although they are at least as effective and safe as a standard follow-up provided by a health professional, there is some uncertainty regarding the exact population that would derive the greatest benefit. Furthermore, this type of follow-up requires greater patient commitment and a solid understanding of anticoagulation therapy. The decision as to the type of follow-up to be provided should therefore be shared between the clinician and the patient, with the latter's abilities, values and preferences taken into account.

Lastly, another major challenge is to lower the risk of bleeding complications in patients on anticoagulation therapy. Since this risk can be difficult to assess, certain patients with AF are prescribed a reduced DOAC dose to lower the bleeding risk, even though they could benefit from a full dose in terms of efficacy. It is therefore important to better equip clinicians so that they can identify situations where a patent's bleeding risk requires special measures. In this regard, a decision was made to use an approach integrating several aspects of anticoagulation therapy: first, a reminder of the main bleeding risk factors and emphasizing, in the context of AF, the modifiable risk factors; second, a reminder of the DOAC dose reduction criteria as defined in the product monographs; and third, a detailed list of the main documented or suspected drug interactions with DOACs and clarifying the clinical situations where withdrawing antiplatelet therapy or adding a proton pump inhibitor (PPI) should be considered.

Conclusions

The recommendations developed in this report reflect the latest changes that could impact the practice regarding DOAC use in Québec. In emphasizing that oral anticoagulation therapy should be chosen according to different patient populations with AF or VTE, and indicating the primary means of limiting the risk of bleeding complications due to the use of an anticoagulant, the tools developed should make it possible to better guide and support health professionals’ practice and thereby optimize the use of oral anticoagulants.



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