

CADTH Health Technology Review: Evidence Update

# Direct Oral Anticoagulants for Atrial Fibrillation

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## Abbreviations

<b>ACC</b>	American College of Cardiology
<b>AF</b>	atrial fibrillation
<b>AHA</b>	American Heart Association
<b>aHR</b>	adjusted hazard ratio
<b>CCS</b>	Canadian Cardiovascular Society
<b>CHRS</b>	Canadian Heart Rhythm Society
<b>CI</b>	confidence interval
<b>DOAC</b>	direct oral anticoagulant
<b>EACTS</b>	European Association for Cardio-Thoracic Surgery
<b>ESC</b>	European Society of Cardiology
<b>HR</b>	hazard ratio
<b>HRS</b>	Heart Rhythm Society
<b>HTA</b>	health technology assessment
<b>ICH</b>	intracerebral hemorrhage
<b>INR</b>	international normalized ratio
<b>NVAF</b>	non-valvular atrial fibrillation
<b>OAC</b>	oral anticoagulation
<b>OR</b>	odds ratio
<b>RCT</b>	randomized controlled trial
<b>RR</b>	relative risk
<b>VHD</b>	valvular heart disease
<b>VKA</b>	vitamin K antagonist

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## Key Messages

- Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. Oral anticoagulation is an important intervention to prevent thromboembolic complications of AF. Drug options include vitamin K antagonists (VKAs), such as warfarin, and direct oral anticoagulants (DOACs), such as apixaban, dabigatran, edoxaban, and rivaroxaban.
- Updated American (2019), Canadian (2020), and European (2020) guidelines on the management of patients with AF all recommend the use of DOACs over VKAs to prevent stroke and other thromboembolic complications in patients with non-valvular AF. These recommendations are based on evidence of similar or improved efficacy of DOACs in preventing stroke, lowering the risk of intracerebral hemorrhage, and reducing mortality, compared with VKAs.
- A focused literature search was conducted to retrieve new evidence (systematic reviews, meta-analyses, health technology assessments) published since the North American and European guidelines on AF were updated. No new evidence was retrieved. As such, evidence reviewed by the American, Canadian, and European guidelines is still current.

## Background and Policy Issues

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and affects up to 1 million Canadians. Untreated AF is associated with a 1.5- to 4-fold increase in mortality mainly due to higher risk of thromboembolic events and heart failure. Without oral anticoagulation, patients with AF have a 3- to 5-fold increased risk of stroke, and these strokes are generally more severe and recur more often than strokes unrelated to AF.<sup>1</sup>

Recent North American and European guidelines on the management of patients with AF now recommend use of direct oral anticoagulants (DOACs) over the use of vitamin K antagonists (VKAs), such as warfarin.<sup>1-3</sup> There are 4 DOACs approved in Canada for the prevention of stroke and thromboembolism in patients with non-valvular AF (NVAFA): apixaban (Eliquis),<sup>4</sup> dabigatran (Pradaxa),<sup>5</sup> edoxaban (Lixiana),<sup>6</sup> and rivaroxaban (Xarelto).<sup>7</sup> These drug products were reviewed between 2011 and 2017 by the CADTH Common Drug Review for their Health Canada–approved indication for the prevention of stroke and systemic embolism in patients with AF. Listing recommendations were also developed for this indication by the CADTH Canadian Drug Expert Committee to inform reimbursement policies of publicly funded drug programs in Canada.<sup>8-11</sup>

In response to recently updated national and international guidelines on AF, some publicly funded drug programs in Canada wanted to determine whether their reimbursement criteria for DOACs needed to be updated for this indication. To assist Canadian drug programs in their decision-making process, this Health Technology Review provides a brief overview of the most current Canadian, American, and European guideline recommendations on the use of oral anticoagulants in patients with AF. The evidence supporting these recommendations is also discussed.

## Methods

### Literature Search Methods

A previous CADTH report on DOACs considered AF guidelines from the Canadian Cardiovascular Society (CCS), the American Heart Association (AHA) in conjunction with the American College of Cardiology (ACC), and the European Society of Cardiology

(ESC).<sup>12</sup> Therefore, a manual search was conducted by the lead reviewer to determine whether these professional societies had recently updated their guidelines on the management of AF.

Once it was confirmed that AHA/ACC, CCS, and ESC had updated their respective guidelines in 2019 or 2020, a focused literature search was conducted by an information specialist. This search aimed to identify any new evidence published since the North American and European guidelines were updated. This search was run in MEDLINE All (1946-present) via Ovid and in Embase (1974-present) via Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were DOACs and AF. Search filters were applied to limit retrieval to systematic reviews, health technology assessments (HTAs), and meta-analyses. Conference abstracts, comments, newspaper articles, editorials, and letters were excluded from the search results. The search was limited to English-language documents published between January 1, 2020, and April 26, 2021. This search period was selected to complement the literature searches conducted by members of the CCS, AHA/ACC, and ESC who updated their respective guidelines on the management of AF. The rationale for selecting January 1, 2020, as the start date of our focused literature search was because it was assumed that AHA/ACC, CCS, and ESC had collectively reviewed the literature up to the end of 2019. While we could only retrieve one literature search cut-off date stated in these documents (August 2018 in the 2019 American guideline),<sup>2</sup> the other 2 guidelines were updated in 2020.<sup>1,3</sup> In particular, the CCS guideline was accepted for publication in September 2020;<sup>1</sup> therefore, it was deemed reasonable to search for new publications published since January 2020 to update evidence reviewed by the recent North American and European guidelines.

## Summary of Evidence

### Literature Search Results

#### Manual Search of Clinical Practice Guidelines

AHA and ACC updated their joint guideline in 2019 whereas CCS and ESC updated their respective guidelines in 2020. Each of these updated guidelines is described in the Clinical Practice Guidelines section of this report.

#### Electronic Search of Systematic Reviews, Meta-Analyses, and HTAs

The electronic search retrieved 246 citations. Screening of these citations identified 5 potential new systematic reviews, meta-analyses, or HTAs. Full-text publications were ordered for each of these citations. However, the review of these publications led to the exclusion of all 5 articles (Figure 1 in Appendix 1).

### Clinical Practice Guidelines

#### North American Clinical Practice Guidelines

- CCS Guideline
  - CCS updated their clinical practice guideline on AF in 2020 jointly with the Canadian Heart Rhythm Society (CHRS);<sup>1</sup> the previous version of the CCS guideline was released in the form of a focused update in 2018.<sup>13</sup> With respect to oral anticoagulants, the 2020 CCS/CHRS guideline continues to recommend the use of

DOACs over VKAs, such as warfarin, to prevent stroke and thromboembolic events in patients with NVAf. This recommendation is based on 4 original phase III randomized clinical trials (RCTs) of DOACs in patients with AF:

- RE-LY trial comparing dabigatran versus warfarin (published in 2009)<sup>14</sup>
  - ROCKET AF trial comparing rivaroxaban versus warfarin (published in 2011)<sup>15</sup>
  - ARISTOTLE trial comparing apixaban versus warfarin (published in 2011)<sup>16</sup>
  - ENGAGE AF-TIMI 48 trial comparing edoxaban versus warfarin (published in 2013).<sup>17</sup>
- The 2020 CCS/CHRS guideline also based their recommendations supporting the use of DOACs over VKAs on the results of a meta-analysis published by Ruff et al. in *The Lancet* in 2014.<sup>18</sup> This meta-analysis combined data from the 4 previously mentioned pivotal phase III RCTs (i.e., RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI-48). The authors assumed a class effect when comparing the DOACs to warfarin. In addition to pooling data from the whole population of these RCTs, the authors of this meta-analysis evaluated the efficacy and safety of DOACs in different key clinically meaningful subgroups of these trials. For example, some of these subgroups were based on age (e.g., younger or older than 75 years) or sex. Other subgroups included the severity of AF, defined through the baseline CHADS<sub>2</sub> score, a widely used tool to predict thromboembolic risk in patients with AF;<sup>1,3</sup> the presence of pre-existing conditions such as diabetes or reduced renal function; and the different doses used for certain DOACs in the RCTs.<sup>18</sup> Overall, these authors found the following:
- When used at the dosage regimens approved in Canada for AF (i.e., dabigatran 150 mg twice daily, edoxaban 60 mg once daily, rivaroxaban 20 mg once daily, and edoxaban 5 mg twice daily), DOACs reduced stroke or systemic embolic events by 19% compared with warfarin (relative risk [RR] = 0.81; 95% confidence interval [CI], 0.73 to 0.91; P < 0.0001). This effect was mainly driven by a reduction by half in hemorrhagic stroke (RR = 0.49; 95% CI, 0.38 to 0.64; P < 0.0001). Compared with warfarin, DOACs also reduced all-cause mortality by 10% (RR = 0.90; 95% CI, 0.85 to 0.95; P = 0.0003). No differences were found between DOACs and warfarin with respect to the risk of ischemic stroke (RR = 0.92; 95% CI, 0.83 to 1.02; P = 0.10) or myocardial infarction (RR = 0.97; 95% CI, 0.78 to 1.20; P = 0.77).<sup>18</sup>
  - With respect to bleeding events, use of DOACs at dosages approved in Canada for AF reduced intracranial hemorrhage, including hemorrhagic stroke and subdural, epidural, and subarachnoid bleeding, by slightly more than 50% (RR = 0.48; 95% CI, 0.39 to 0.59; P < 0.0001) compared with warfarin. For major bleeding events, a similar risk was observed between DOACs and warfarin (RR = 0.86; 95% CI, 0.73 to 1.00; P = 0.06). Compared with warfarin, the use of DOACs also was found to increase the risk of gastrointestinal bleeding (RR = 1.25; 95% CI, 1.01 to 1.55; P = 0.043).<sup>18</sup>
  - The use of DOACs may present an advantage when comparing the risk of major bleeding events based on the quality of anticoagulation achieved with warfarin, defined as the time during which the international normalized ratio (INR) is within the target range. Ruff et al. found that, compared with warfarin, there was a greater relative reduction in major bleeding with DOACs when the centre-based time in the therapeutic range was less than 66% (i.e., lower-quality anticoagulation with warfarin; RR = 0.69; 95% CI, 0.59 to 0.81) compared with when it was 66% or more (i.e., higher-quality anticoagulation with warfarin; RR = 0.93; 95% CI, 0.76 to 1.13).<sup>18</sup>
  - The relative efficacy and safety of DOACs, compared with warfarin, were consistent for the various subgroups of patients included in the 4 RCTs, although statistical significance was not reached for all comparisons. The authors of the

meta-analysis commented that this is an important finding because both the risk of stroke and bleeding vary significantly across the range of patients with AF. For example, older patients and patients with a previous stroke have an increased risk of these events. These higher-risk groups were under-represented in individual RCTs; therefore, the pooling of subgroup data from the 4 RCTs augmented the confidence that the relative efficacy and safety of DOACs is consistent across a broad range of higher-risk AF patients.<sup>18</sup>

- In addition to the previously mentioned RCTs and meta-analysis, CCS also considered patient values and preferences in developing their recommendations (Appendix 2).
- AHA/ACC/HRS Guideline
  - The joint AHA/ACC/Heart Rhythm Society (HRS) guideline on the management of AF was updated in 2019,<sup>2</sup> which was a focused update of the AHA/ACC/HRS guideline for the management of patients with AF that was published in 2014.<sup>19</sup> The 2014 joint AHA/ACC/HRS guideline did not include edoxaban because this DOAC was not yet available in the US and it also did not recommend DOACs over VKAs,<sup>19</sup> which is a recommendation that now prevails for patients with AF.<sup>2</sup> The 2019 American guideline does make an exception for patients with moderate-to-severe mitral stenosis or a mechanical heart valve for whom warfarin is still preferred.<sup>2</sup>
  - The same evidence used in the 2020 CCS/CHRS guideline on the management of AF<sup>1</sup> was also considered by the authors of the 2019 joint AHA/ACC/HRS guideline to support their new recommendation.<sup>2</sup> This evidence mainly comprised the ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF trials.<sup>2</sup> The joint 2019 AHA/ACC/HRS guideline on the management of AF also cited the 2014 Ruff et al. meta-analysis of these pivotal phase III RCTs.<sup>2</sup> Another meta-analysis was cited in the American guideline,<sup>2</sup> which was an article published by Pan et al. in 2017 that aimed to assess the effects of DOACs versus warfarin in patients with AF and valvular heart disease (VHD).<sup>20</sup> This article was cited primarily to support the use of DOACs in patients with AF and mild valvular lesions (as previously noted, warfarin is still preferred in AF patients with moderate-to-severe mitral stenosis or a mechanical heart valve).<sup>2</sup> The 2017 systemic review and meta-analysis by Pan et al. included the same 4 phase III pivotal RCTs previously mentioned (i.e., ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF). However, the article focused on the subgroups of patients enrolled in these 4 RCTs who had native VHD in addition to AF. The authors reported that, compared with warfarin, DOACs reduced the risk of stroke or systemic embolism (hazard ratio [HR] = 0.70; 95% CI, 0.60 to 0.82) and intracranial hemorrhage (HR = 0.47; 95% CI, 0.24 to 0.92) in this particular population. Compared with warfarin, no reduction in major bleeding was observed in AF patients with VHD using DOACs (HR = 0.93; 95% CI, 0.67 to 1.28). The authors indicated that 3 of the 4 DOACs (apixaban, edoxaban, and dabigatran) were mainly responsible for the reduction in bleeding events in these studies (major bleeding: HR = 0.79; 95% CI, 0.69 to 0.91; intracranial hemorrhage: HR = 0.33; 95% CI, 0.25 to 0.45) but not rivaroxaban (major bleeding: HR = 1.56; 95% CI, 1.20 to 2.04; intracranial hemorrhage: HR = 1.27; 95% CI, 0.77 to 2.10). Also, DOACs did not reduce the overall mortality rate in AF patients with VHD compared with warfarin (HR = 1.01; 95% CI, 0.91 to 1.12).<sup>20</sup>

## European Clinical Practice Guidelines

- ESC Guideline
  - The ESC, in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), published a new guideline on the management of patients with AF in 2020<sup>3</sup> as an update to their 2016 guideline. Similar to the most recent Canadian and American guidelines, the 2020 European guideline also recommended the use of DOACs over VKAs in patients with AF, with the exception of patients with mechanical



heart valves or moderate-to-severe mitral stenosis. Also similar to the 2 North American guidelines, the ESC/EACTS recommendation was based on evidence of similar or improved efficacy of DOACs in preventing stroke, lower risk of intracerebral hemorrhage, and reduced mortality compared with VKAs.

- Similar to the authors of the 2020 CCS/CHRS and the joint 2019 AHA/ACC/HRS guidelines, authors of the 2020 ESC/EACTS guideline supported their recommendation with the 4 phase III pivotal RCTs of DOACs (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF) as well as the 2014 Ruff et al. meta-analysis of these trials.<sup>3</sup> However, they also considered the results of a meta-analysis published by Wang et al. in 2015.<sup>21</sup> Authors of this article extracted data of patients from Asian and non-Asian countries who were enrolled in the phase III RCTs of DOACs to determine the relative effect of DOACs in these populations. Wang et al. did not have access to patient-level data and therefore used the country of residence reported in these RCTs as a surrogate for ethnicity; this limitation was acknowledged in their publication.<sup>21</sup> In addition to including data from the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI-48 trials, they also used data from the Japanese version of the ROCKET AF trial (i.e., J-ROCKET AF).<sup>22</sup> They found that, compared with warfarin, use of standard-dose DOACs (doses used in Canada) reduced the risk of stroke or systemic embolism in people from both Asian (odds ratio [OR] = 0.65; 95% CI, 0.52 to 0.83) and non-Asian (OR = 0.85; 95% CI, 0.77 to 0.93) countries. Compared with warfarin, DOACs also reduced all-cause mortality in people from both Asian (OR = 0.80; 95% CI, 0.65–0.98) and non-Asian (OR = 0.91; 95% CI, 0.86 to 0.97) countries. With respect to major bleeding events, DOACs were safer in people living in Asian countries (OR = 0.57; 95% CI, 0.44 to 0.74) than those living in non-Asian countries (OR = 0.89; 95% CI, 0.76 to 1.04). Hemorrhagic stroke was reduced in both groups (Asian countries: OR = 0.32; 95% CI, 0.19 to 0.52; non-Asian countries: OR = 0.56; 95% CI, 0.44 to 0.70). The risk of gastrointestinal bleeding was less elevated in people living in Asian countries (OR = 0.79; 95% CI, 0.48 to 1.32) than those living in non-Asian countries (OR = 1.44; 95% CI, 1.12 to 1.85).<sup>22</sup>

## New Clinical Evidence

As indicated in Figure 1 (Appendix 1), the focused literature search did not retrieve any new evidence in the form of systematic reviews, meta-analyses, or HTAs. Also, all 3 updated guidelines based their respective recommendations supporting the use of DOACs over VKAs on the original 4 phase III pivotal RCTs (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF) and the meta-analysis conducted in 2014 by Ruff et al. that combined the results of these 4 trials.<sup>1-3</sup> This suggests that no new key study comparing any of the DOACs of interest to warfarin was recently published.

Although we did not retrieve new citations that met the eligibility criteria, some of the publications that were excluded reached conclusions that aligned with the guidelines and evidence described previously in this report. For example, in a meta-analysis by Diener et al. that compared DOACs with warfarin for the secondary prevention of stroke in patients with AF, the authors combined the results of the subgroups of patients with AF and a history of prior stroke or transient ischemic attack enrolled in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials.<sup>23</sup> They found:

- A reduction in stroke or systemic embolism with DOACs compared with warfarin (RR = 0.86; 95% CI, 0.77 to 0.97; P = 0.01)
- No difference in ischemic stroke between DOACs and warfarin (RR = 1.01; 95% CI, 0.88 to 1.16; P = 0.87)
- A more than 50% reduction in hemorrhagic stroke with DOACs compared with warfarin (RR = 0.45; 95% CI, 0.33 to 0.61; P < 0.00001)

- A non-significant reduction in major bleeding with DOACs, compared with warfarin (RR = 0.86; 95% CI, 0.77 to 0.96; P = 0.007)
- A reduction in death from any cause with DOACs compared with warfarin (RR = 0.89; 95% CI, 0.82 to 0.97; P = 0.01).<sup>23</sup>

## Discussion

Ruff et al. indicated that their meta-analysis was the first to include the 4 pivotal phase III RCTs for the DOACs (i.e., RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48).<sup>18</sup> This may explain why this analysis was used by all 3 updated sets of guidelines (i.e., CCS, AHA/ACC, and ESC).<sup>1-3</sup> Two other meta-analyses were cited in the recent guidelines: 1 published by Pan et al. in 2017<sup>20</sup> that was included in the 2019 American guideline and 1 published in 2015 by Wang et al.<sup>21</sup> that was included in the 2020 European guideline. The 2017 meta-analysis included the 4 phase III pivotal RCTs used by the updated guidelines (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48), and the analysis was focused on the subgroups of patients with AF and VHD.<sup>20</sup> This analysis may have some relevance for clinicians to guide their treatment decisions in particular clinical situations encountered with patients with AF and a mild valvular lesion. However, from a Canadian perspective, CCS formally recommends use of warfarin in patients with a mechanical prosthetic valve and those with AF and moderate-to-severe mitral stenosis.<sup>1</sup> This recommendation is based on the increased risk of thrombosis and bleeding complications observed with dabigatran in the RE-ALIGN trial, a phase II RCT comparing different doses of dabigatran, versus warfarin, in a population with recent aortic or mitral valve replacement.<sup>24</sup> Furthermore, the use of DOACs in patients with valvular AF is not approved or recommended by Health Canada.<sup>4-7</sup> As for the 2015 meta-analysis by Wang et al.<sup>21</sup> included in the 2020 European guideline, it may have application to the Canadian context given that some areas of Canada have significant populations of individuals originating from Asian countries. However, although we did not present results from this meta-analysis that considered DOACs used at lower doses, the Japanese version of the ROCKET AF trial (J-ROCKET-AF) did use a lower dose of rivaroxaban (15 mg daily)<sup>22</sup> than the rivaroxaban dose approved in Canada for AF (20 mg daily).<sup>7</sup>

To determine whether new evidence was published since the release of the updated guidelines, a focused literature search was conducted to identify systematic reviews, meta-analyses, or HTAs published between January 2020 and April 2021. We found no new evidence. Meta-analyses published during this period focused on subgroups comprised of patients with pre-existing stroke enrolled in the same 4 original phase III pivotal RCTs of DOACs as the ones considered in the updated guidelines. This further suggests that no new key RCTs comparing apixaban, dabigatran, edoxaban, or rivaroxaban to a VKA in patients with NVAF were published recently.

The guidelines also considered observational studies to support their statements and recommendations. These were not discussed in this report because inclusion of such studies was beyond the scope of this brief update. Of interest, our focused literature search retrieved 2 recent Canadian observational studies comparing DOACs to warfarin in patients with AF. We did not conduct a systematic review of observational studies; therefore, interpretation of these results needs to be done cautiously because they do not reflect the entirety of the observational evidence on DOACs. Their results may be of interest from a Canadian perspective with respect to the comparative efficacy and safety of DOACs and warfarin when used to treat patients with AF in the real-world setting. Although the larger cohort study by Durand et al.<sup>25</sup> reported results aligned with those of the phase III pivotal

RCTs of DOACs, the smaller cohort study by Holbrook et al.<sup>26</sup> found no differences between DOACs and warfarin when used to prevent stroke in patients with AF (Appendix 3).

In addition to clinical evidence, patient values and preferences were considered in some guidelines, in particular the 2020 CCS guidelines.<sup>1</sup> Such preferences may go beyond the strictly defined clinical benefits and consider aspects such as the convenience of use of DOACs. For example, contrary to VKAs that require regular INR monitoring, routine laboratory monitoring is not required with DOACs to ensure patients are adequately anticoagulated.<sup>18,23</sup>

## Conclusions and Implications for Decision- or Policy-Making

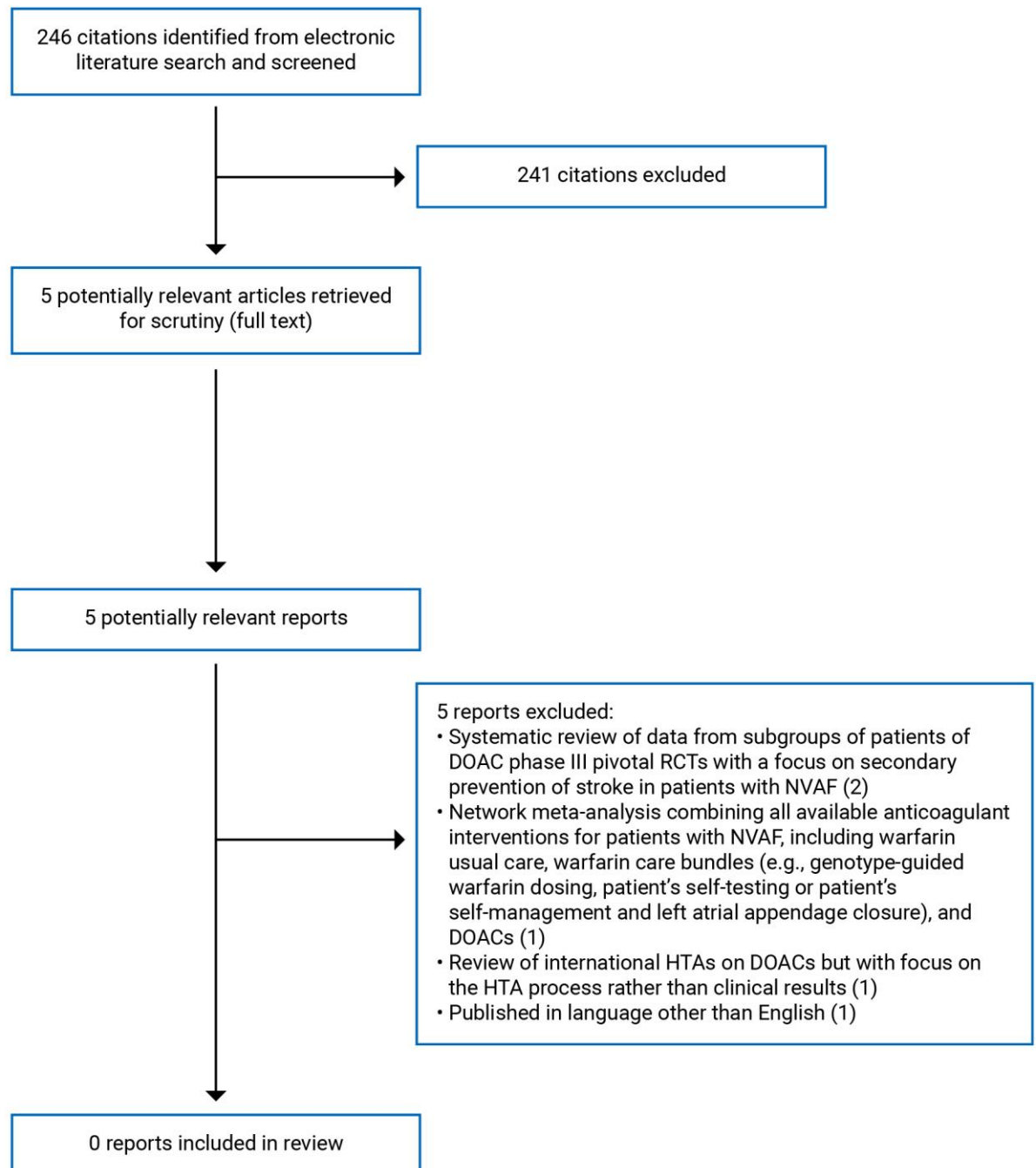
The current brief review of the available evidence suggests that the use of DOACs for NVAf is associated with improved clinical benefits. These include similar or improved efficacy of DOACs in preventing stroke, lower risk of intracerebral hemorrhage (a serious complication of anticoagulation), and reduced mortality compared with VKAs. Some clinical practice related-factors may influence the extent to which the clinical benefits measured in DOAC phase III pivotal RCTs materialize in the real-world setting. Evidence-based reimbursement policies may assist with optimizing anticoagulation therapy to prevent stroke and other systemic embolisms in patients with NVAf.

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## Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



DOAC = direct oral anticoagulant; HTA = health technology assessment; NVAF = non-vascular atrial fibrillation; RCT = randomized controlled trial.

## Appendix 2: Values and Preferences Considered in the 2020 CCS Guidelines<sup>1</sup>

**Recommendation 21: We recommend most patients should receive a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) in preference to warfarin when OAC therapy is indicated for patients with NVAF (strong recommendation; high-quality evidence).<sup>1</sup>**

- **Values and preferences.** This recommendation places a relatively high value on the results of several large RCTs showing that the DOACs are either noninferior or superior to warfarin in preventing AF-related stroke, that they have no more or less major bleeding compared with warfarin, that they are associated with less ICH compared with warfarin, and on the greater ease of use of DOACs compared with dose-adjusted warfarin.
- **Practical tip.** Baseline renal function and complete blood counts should be measured before initiation of anticoagulation and at regular intervals thereafter.
- **Practical tip.** The dose of DOAC prescribed should follow the doses used in the RCTs and Health Canada–approved prescribing information. Receipt of a higher than recommended dose is associated with increased bleeding events and overall mortality. Receipt of a lower than recommended dose is associated with increased rates of stroke and/or systemic embolism.
- **Practical tip.** Consideration should be given to switching eligible patients from warfarin to a DOAC, particularly if they are unable to maintain a therapeutic INR.<sup>1</sup>

**Recommendation 22: We recommend that warfarin be used for patients with a mechanical prosthetic valve and those with AF and moderate-to-severe mitral stenosis (strong recommendation; moderate-quality evidence).<sup>1</sup>**

- **Values and preferences.** This recommendation places high value on the evidence from 1 RCT about the inferiority of dabigatran compared with warfarin for the prevention of thromboembolism in patients with a mechanical prosthetic valve.
- **Values and preferences.** This recommendation places a relatively high value on the long experience and clinical reports on the use of warfarin in patients with rheumatic mitral stenosis.<sup>1</sup>

## Appendix 3: Recent Canadian Observational Studies of DOACs in AF – Overview

Two Canadian observational studies were identified through the focused literature search conducted for this project. Given this report is intended to inform decision-making on the funding on DOACs in a Canadian publicly funded drug program, a short description of these studies is provided below.

- Durand et al. conducted a population-based observational multi-centre cohort study and performed a meta-analysis of collected data.<sup>25</sup> The authors obtained the administrative data from 7 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia). Patients with NVAF who initiated therapy with either apixaban, dabigatran, or rivaroxaban between 2009 and 2017 were matched to an equal number of patients who initiated warfarin during the same time frame.<sup>25</sup> They found:
  - Lower risks of major bleeding (adjusted hazard ratio (aHR) = 0.81; 95% CI, 0.69 to 0.97) and intracranial bleeding (aHR = 0.55, 95% CI, 0.45 to 0.66) with DOACs than with warfarin
  - Lower risks of the composite outcome of ischemic stroke or systemic embolization, major bleeding, and all-cause mortality with DOACs compared with warfarin (aHR = 0.81; 95% CI, 0.74 to 0.89)
  - Lower all-cause mortality with DOACs compared with warfarin (aHR = 0.81; 95% CI, 0.78 to 0.85)
  - No difference between DOACs and warfarin in ischemic stroke or systemic embolization between DOACs and warfarin (aHR = 1.02; 95% CI, 0.87 to 1.20)
  - No difference between DOACs and warfarin in myocardial infarction (aHR 0.96, 95% CI, 0.84 to 1.09) or gastrointestinal bleeding (aHR = 1.00; 95% CI, 0.88 to 1.15).<sup>25</sup>
- In contrast, Holbrook et al. conducted a retrospective cohort study of all adults living in British Columbia with a diagnosis of AF and a first prescription for an oral anticoagulant (apixaban, dabigatran, rivaroxaban, or warfarin) dispensed between October 1, 2010, and June 30, 2013. Treatment effects were estimated using time-to-event models with high-dimensional propensity score adjustment to control confounding. Several covariates were selected; some examples include, but are not limited to, neighbourhood income quintile, rural residence, visit to cardiologist or internist within 7 days prior to cohort entry, and the number of medications used in the year prior to cohort entry.<sup>26</sup> They found:
  - No difference between DOACs and warfarin in the co-primary outcomes of ischemic stroke or systemic embolism (adjusted rate ratio = 1.15; 95% CI, 0.91 to 1.46)
  - No difference between DOACs and warfarin in major bleeding (adjusted rate ratio = 0.94; 95% CI, 0.82 to 1.08)
  - No difference between DOACs and warfarin in the net clinical outcome composite rate (ischemic stroke, systemic embolism, myocardial infarction, pulmonary embolism, major bleeds, or death) (adjusted rate ratio = 0.98; 95% CI, 0.90 to 1.06)
  - Increased risk of adverse outcomes for those switching oral anticoagulant class (i.e., from warfarin to a DOAC or vice versa):
    - stroke and systemic embolism: adjusted rate ratio = 2.24; 95% CI, 1.46 to 3.45
    - major bleeding: adjusted rate ratio = 1.41; 95% CI, 1.04 to 1.91
    - net clinical harm: adjusted rate ratio = 1.54; 95% CI, 1.29 to 1.85.<sup>26</sup>

In the study by Holbrook et al., they also measured a number of determinants of care (expressed as unadjusted RR):

- Patients starting a DOAC instead of warfarin were less likely to:
  - be of lower income (RR = 0.81; 95% CI, 0.78 to 0.84)
  - have been hospitalized previously for AF (RR = 0.70; 95% CI, 0.67 to 0.73).
- Patients starting a DOAC were more likely to:
  - live in an urban location (RR = 1.06; 95% CI, 1.05 to 1.07)
  - have a low comorbidity score (RR = 1.21; 95% CI, 1.18 to 1.24)
  - have been seen immediately beforehand by a cardiologist (used as a surrogate for initial prescriber) (RR = 2.41; 95% CI, 2.24 to 2.59).<sup>26</sup>