

# Therapeutics Initiative

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## Apixaban is safer and more effective than rivaroxaban for non-valvular atrial fibrillation

### Abstract

**Background:** Non-valvular atrial fibrillation (NVAf) poses risks of mortality and thromboembolic events, necessitating anticoagulant therapy. Direct oral anticoagulants (DOACs) such as apixaban and dabigatran have emerged as alternatives to warfarin due to their convenience. Choosing the appropriate DOAC involves weighing benefits against risks, considering patient factors and preferences.

**Methods:** A systematic review of observational studies directly comparing the effectiveness and safety of apixaban with other DOACs for NVAf was conducted. Cohort studies totaling 2,936,126 participants were analyzed, with meta-analysis conducted on 27 studies (N=2,135,415) reporting total event numbers. Primary outcomes including total mortality, major bleeding and thromboembolic events, were analyzed and compared across DOACs.

**Results:** Apixaban had lower risks of major bleeding compared to dabigatran and rivaroxaban, while demonstrating similar efficacy in preventing stroke and systemic embolism. Apixaban was associated with a reduced risk of total mortality, ischemic stroke, and intracranial hemorrhage compared to rivaroxaban. Apixaban and dabigatran exhibited similar risks of death and intracranial hemorrhage, but apixaban showed superiority in preventing systemic embolism or stroke when compared to dabigatran.

**Conclusions:** Observational evidence consistently favours apixaban over rivaroxaban, dabigatran, and edoxaban as the preferred first choice DOAC for NVAf patients accepting twice-daily dosing. Given its efficacy and safety profile, particularly in reducing major bleeding, apixaban is a suitable option for long-term anticoagulation in NVAf patients, supported by the recent availability of cost saving generic formulations.

**Keywords:** Anticoagulants, Apixaban, Atrial Fibrillation, Comparative Effectiveness Research, Drug Costs, Patient Safety, Rivaroxaban, Stroke, Thromboembolism.

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.



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**Vignette:** Your 78-year-old patient developed persistent atrial fibrillation in hospital after elective total hip replacement. After surgery, she was treated with rivaroxaban 20mg/d, partly for initial prophylaxis of thromboembolism. Now recovered, her rivaroxaban prescription is about to expire. If she agrees to ongoing anticoagulation to prevent arterial embolic events, **how do you decide what to prescribe?**

### Summary and Conclusions

- **Observational studies of comparative effectiveness provide consistent scientific evidence to inform the choice of a direct oral anticoagulant (DOAC) for non-valvular atrial fibrillation (NVAf).**
- **For patients with NVAf, apixaban is associated with a lower risk of major bleeds than rivaroxaban or dabigatran, and is similar to rivaroxaban but more effective than dabigatran for prevention of stroke and systemic embolism.**
- **Compared with rivaroxaban, apixaban use is associated with a lower risk of premature death or intracerebral bleeds.**
- **Generic formulations have lowered the price of apixaban and rivaroxaban by 75%.**

**Vignette resolution:** Your patient agrees to long-term anticoagulation, to be reviewed from time to time. Given the evidence that apixaban is at least as effective and safer than alternative DOACs, you prescribe a trial of generic apixaban with renewals if tolerated, and your patient accepts the twice daily dosing. You counsel her about precautions to reduce her chance of dangerous bleeds.

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For groups of people with chronic NVAf, the potential benefits of anticoagulant drug therapy are expected to outweigh potential harms. As both the embolic outcomes of atrial fibrillation and the hemorrhagic outcomes of anticoagulation can be devastating, informed and shared decision making with patients is desirable. But which of several alternative anticoagulants should one choose? This Letter examines evidence accumulated since 2010 when we expressed initial scepticism about evidence used to license dabigatran, the first direct oral anticoagulant (DOAC). Consistent scientific evidence now favours apixaban over rivaroxaban, dabigatran, and edoxaban, as a first choice direct oral anticoagulant for patients who accept twice daily dosing.



### Background

NVAf affects about 1-2% of all Canadians, but prevalence increases dramatically with age (<10% up to 50 years of age, 4% at 65 years, and 12% above age 80).<sup>1</sup> NVAf is independently associated with a 1.5- to 4-fold increased risk of mortality, predominantly due to thromboembolic events and ventricular dysfunction. Compared with people who are anticoagulated, non-anticoagulated AF patients have a 3- to 5-fold increased risk of stroke, although absolute risks depend on many other factors.<sup>2</sup>

However, anticoagulated patients risk serious morbidity and mortality from hemorrhage. In the United States from 2007 through 2009, bleeding attributed to warfarin caused one-third of the nearly 100,000 emergency hospitalizations for an adverse drug event in people age 65 or older.<sup>3</sup> A similar analysis in older people in Ontario from 2006 through 2008 found anticoagulants (unspecified, but prior to approval of DOACs) responsible for 15% of adverse drug events assessed in emergency departments.<sup>4</sup>

The decision to provide anti-coagulant therapy depends on multiple clinical factors, including the anticipated risk of stroke, bleeding history, kidney and liver function, prior drug experience, and patient goals and preferences.

### Warfarin

Warfarin is a low-cost and effective therapy used since the 1950s to reduce the risk of stroke in NVAf patients. But it requires regular blood tests to maintain the international normalized ratio (INR) within the target therapeutic range. Numerous drug and food interactions affect warfarin's efficacy and safety.

### Direct oral anticoagulants (DOACs)

In 2010 Health Canada approved the thrombin (Factor IIa) inhibitor dabigatran (Pradaxa) as the first direct oral anticoagulant (DOAC) for stroke prevention in patients with NVAf. Approval was based mainly on one large



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randomized controlled trial (RCT). The RE-LY trial compared dabigatran with warfarin, but it was not double blinded. Therapeutics Letter 80 analysed the RE-LY trial and concluded that licensing of dabigatran at 150mg BID was “premature, pharmacologically irrational and unsafe for many patients.”<sup>5</sup> However, dabigatran quickly became a popular alternative to warfarin because of the major convenience advantage that blood tests to adjust dose are neither required nor practical.

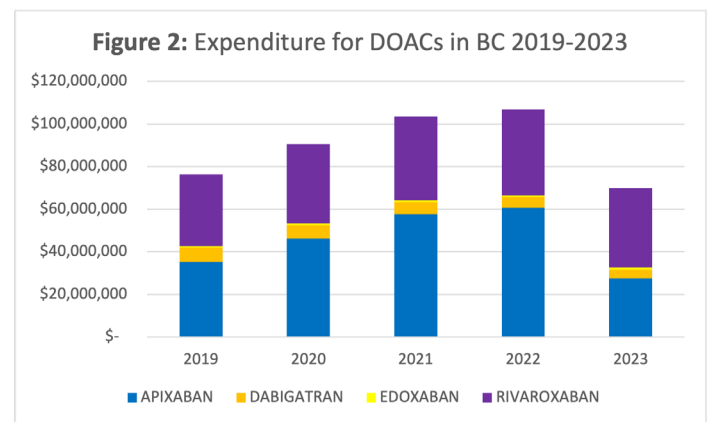
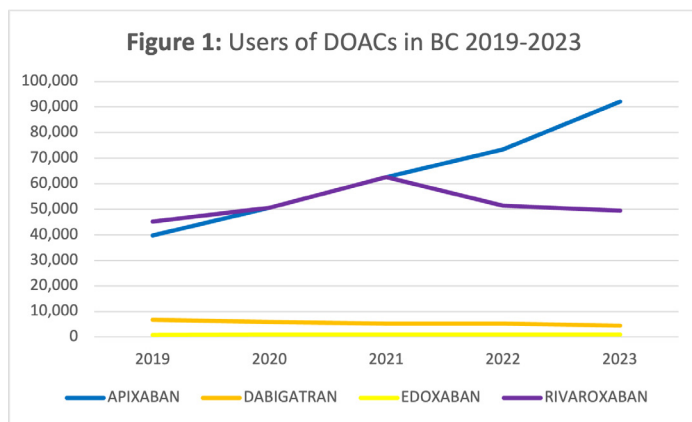
Between 2012 and 2016 Health Canada approved 3 Factor Xa (prothrombinase) inhibitor DOACs for treatment of NVAF: apixaban, rivaroxaban and edoxaban (Table 1).

**Table 1: DOACs approved in Canada for NVAF**

| Chemical name | Brand name | Approved | Usual dose | Daily ingredient cost (generic) | Daily ingredient cost (brand) |
|---------------|------------|----------|------------|---------------------------------|-------------------------------|
| Dabigatran    | Pradaxa    | 2010     | 150 mg BID | \$2.71                          | \$3.61                        |
| Apixaban      | Eliquis    | 2012     | 5 mg BID   | \$0.88                          | \$3.53                        |
| Rivaroxaban   | Xarelto    | 2012     | 20 mg OD   | \$0.77                          | \$3.07                        |
| Edoxaban      | Lixiana    | 2016     | 60 mg OD   | not available                   | \$3.17                        |

Randomized controlled trials found DOACs to be at least as safe and effective as warfarin,<sup>6</sup> and they are now recommended as first-line therapy in NVAF patients for whom anticoagulation is indicated! Apixaban and rivaroxaban are the most commonly prescribed DOACs for NVAF. This is true in BC where the total costs in 2023 for apixaban and rivaroxaban were \$27,600,000 and \$37,400,000, respectively.<sup>7</sup> Since generic formulations of apixaban, dabigatran, and rivaroxaban became available in Canada during 2023, annualized ingredient costs have dropped by 75% for both apixaban and rivaroxaban, versus 25% for dabigatran.

Figures 1 and 2 show changes in utilization of DOACs in BC and total drug ingredient costs (public and private, not including dispensing fees) since 2019.



### Choosing a DOAC for NVAF

Randomized clinical trials directly comparing the DOACs for atrial fibrillation were never conducted, making it impossible to choose a superior DOAC based on direct evidence.<sup>8</sup> This differs from some conditions such as hypertension, diabetes, or depression.<sup>9-11</sup> Indirect evidence is available from network meta-analyses of the large pre-approval RCTs that compared different DOACs with warfarin. But it is compromised by marked differences between these RCTs in the populations studied, in blinding strategies, and in the quality of warfarin management.<sup>8</sup> However, comparative effectiveness research using large administrative databases, and increasingly sophisticated study methodology, provide a growing body of scientific evidence from which to compare the observed benefits and harms of the four DOACs licensed in Canada.

### Clarifying comparative effectiveness and safety: TI systematic review

We conducted a systematic review of observational studies that compare directly the effectiveness and safety of apixaban with other DOACs for treatment of NVAF patients (Table 2).

**Table 2: PICOS and study inclusion criteria**

|                            |   |
|----------------------------|---|
| <b>Population:</b>         | Patients with NVAF aged ≥18 years, treated for stroke prevention  |
| <b>Intervention:</b>       | Apixaban  |
| <b>Comparators:</b>        | Dabigatran, edoxaban, rivaroxaban   |
| <b>Outcomes:</b>           | <ul style="list-style-type: none"> <li>Total mortality</li> <li>Stroke/systemic embolism</li> <li>Ischemic stroke</li> <li>Intracranial hemorrhage</li> <li>Major bleeding</li> </ul> |
| <b>Eligible studies:</b>   | Prospective and retrospective cohort studies  |
| <b>Databases searched:</b> | Medline, Embase and Cochrane CENTRAL up to September 5, 2023  |

We identified 42 cohort studies (N=2,936,126). Of these, we could meta-analyze 27 studies (N=2,135,415) that reported the total number of events during the study periods.<sup>12</sup> The remaining 15 studies (N=800,711) reported

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only hazard ratios (HRs) for clinical outcomes, precluding meta-analysis. We tabulated clinical outcomes as defined in the 27 observational studies suitable for meta-analysis. While these studies define some outcomes differently, the events are obviously clinically important. Major bleeding was typically - but not always - defined as requiring hospitalization, an emergency room visit, transfusion, or in a critical anatomical site (as opposed to a drop in hemoglobin >20g/L alone).<sup>13, 14</sup>

### Findings

**Table 3 shows that apixaban was associated with lower risks of major bleeds, compared with dabigatran and rivaroxaban.** Despite similar stroke or systemic embolism risks, **apixaban was associated with a lower risk of total mortality, ischemic stroke and intracranial hemorrhage compared with rivaroxaban.** Apixaban and dabigatran were associated with similar risks of death and intracranial hemorrhage; but apixaban was associated with a lower risk of stroke or systemic embolism and of ischemic stroke, compared with dabigatran. Because edoxaban was licensed later, observational data are insufficient for us to compare effectiveness and safety with equivalent confidence as for the 3 previously licensed DOACs. Findings of 3 published observational studies of edoxaban are mostly compatible with those shown in Table 3.

**Table 3: TI Meta-analysis of DOAC observational studies**

| Outcome                  | Comparison               | Number of studies (N) | Pooled Relative Risk (95% CI) |
|--------------------------|--------------------------|-----------------------|-------------------------------|
| Total mortality          | apixaban vs. dabigatran  | 11 (515,706)          | 1.03 (0.93, 1.15)             |
|                          | apixaban vs. rivaroxaban | 13 (1,267,040)        | <b>0.86 (0.79, 0.95)</b>      |
| Stroke/systemic embolism | apixaban vs. dabigatran  | 12 (828,396)          | <b>0.89 (0.81, 0.98)</b>      |
|                          | apixaban vs. rivaroxaban | 14 (1,826,473)        | 0.92 (0.85, 1.00)             |
| Ischemic stroke          | apixaban vs. dabigatran  | 18 (394,554)          | <b>0.85 (0.73, 0.99)</b>      |
|                          | apixaban vs. rivaroxaban | 19 (1,087,791)        | <b>0.75 (0.58, 0.98)</b>      |
| Intracranial hemorrhage  | apixaban vs. dabigatran  | 15 (922,271)          | 0.96 (0.85, 1.10)             |
|                          | apixaban vs. rivaroxaban | 18 (1,973,314)        | <b>0.76 (0.68, 0.85)</b>      |
| Major bleeds             | apixaban vs. dabigatran  | 16 (375,591)          | <b>0.80 (0.72, 0.89)</b>      |
|                          | apixaban vs. rivaroxaban | 15 (592,394)          | <b>0.62 (0.53, 0.74)</b>      |

Pooled relative risk estimates shown in **bold** denote statistically significant differences where the 95% CI excludes 1.00.

### Discussion

The retrospective design of administrative database studies has inherent limitations that preclude establishing causal relationships as confidently as one can assert from randomized clinical trials. Due to the non-randomized nature of the evidence, we cannot exclude the possibility of residual confounding and other biases, even with the use of innovative statistical methods.<sup>8</sup>

In this instance the research studies on comparative effectiveness are large, methodologically sound, and remarkably consistent. This provides useful guidance for physicians to choose the most appropriate DOAC for their patients. In support of this position, previous systematic re-

views found that the results of many large, well-designed observational studies of DOACs versus warfarin were consistent with the findings from RCTs.<sup>15, 16</sup>

Despite its twice daily dosing, use of apixaban has increased much faster than other DOACs, such that it is now the most frequently prescribed DOAC in BC, the USA and UK.<sup>17</sup> Health Canada's 2022 approval of generic formulations has made apixaban yet more appealing as a first-choice DOAC.

**Vignette resolution:** *Your patient agrees to long-term anticoagulation, to be reviewed from time to time. Given the evidence that apixaban is at least as effective and safer than alternative DOACs, you prescribe a trial of generic apixaban with renewals if tolerated, and your patient accepts the twice daily dosing. You counsel her about precautions to reduce her chance of dangerous bleeds.*

### Data Sources

We used the following data sources: BC Ministry of Health [creator] (2023); PharmaNet. BC Ministry of Health [publisher]. Data Stewardship Committee (2022).

### Disclaimer

All inferences, opinions and conclusions from BC prescription data are those of the UBC Therapeutics Initiative and do not reflect the opinions or policies of the data stewards.

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