# CPAMS COSTING STUDY ADDENDUM

## Including Non-Vitamin K Oral Anticoagulants

Final Report submitted to
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**Study Brief:**

This CPAMS Costing Study Addendum follows the Original Costing study methodologies and data to extend the analysis to include new oral anticoagulants. The original study comparing CPAMS to usual care (UC), from the NSDHW's perspective, found the following points.

- The literature generally supported that CPAMS type programs were at least as effective as UC (typically primary-care physicians providing anticoagulation management).
- CPAMS type programs were generally accepted by physicians (MDs) and preferred to UC by patients.
- NS CPAMS was at least as effective as UC except when MDs were paid their full anticoagulation management (unlikely in reality).
- If CPAMS analyses were limited to later months in the study, TTRs were more consistent with the literature and NS CPAMS was a cost-effective alternative to UC except when MDs maintain their full anticoagulant fees.
- If CPAMS analyses were limited to later months in the study, the cost savings was generally enough to allow NSDHW to provide a small referral payment to MDs.

The CPAMS original costing study showed CPAMS to be a cost-effective alternative to UC. This Addendum to the original CPAMS Costing study examines whether non-vitamin K antagonist anticoagulants (known as NOACs) are cost-effective alternatives to NS CPAMS as they are becoming more readily prescribed by physicians. The literature points to a settling of an ongoing debate surrounding anticoagulation treatment with NOACs versus warfarin but no comparisons with CPAMS type programs was identified. The following points came out of the literature review.

- NOACs are comparable to warfarin for treatment of VTEs and stroke and perhaps with fewer adverse events.
- In many of the clinical trials and studies comparing NOACs to warfarin, warfarin patients experienced poor anticoagulation maintenance (low TTRs).

• A closer examination of a studies presenting disaggregation by TTR indicated that NOACs were significantly better, on average, when compared to poorly-managed warfarin patients but not so when compared to well-managed warfarin patients.

• Cost-effectiveness analyses have provided heterogenous results.

• Evidence on compliance to NOACs and warfarin was heterogenous, but it was suggested that the closer monitoring needed for warfarin may guard against non-compliance.

• NOACs are contraindicated for patients with mechanical heart valves and cautioned in patients with issues with renal functions.

This addendum includes a costing study performed using data from the NS CPAMS demonstration project, cost results from the original costing study, and data from the updated literature review. As the literature points to warfarin providing better anticoagulation control for well-managed patients (higher TTRs), updated scenarios are examined.

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*Scenario A: All anticoagulation patients are referred to CPAMS. Patients achieving a TTR>64% after 3 months in CPAMS remain in the program. Those who cannot achieve a TTR>64% are transitioned onto NOACs. NSDHW pays $50/patient/month for CAPMS.*

*Scenario B: All anticoagulation patients are prescribed NOACs by their physicians (except where contraindicated).*

*CPAMS full-year sample☆ intent-to-treat data for patients enrolled in CPAMS for one year; Mean TTR was 68.75%.*

*CPAMS last five-months sample☆ intent-to-treat data for patients enrolled in CPAMS for the last five-months of the study (March to July 2019). Mean TTR was 75.35%.*

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Both scenarios were compared to the original CPAMS full-year sample and last five-months sample.

Results of the updated costing analyses are summarized.

• Slightly less than 2/3 of CPAMS patients (64.1% of the full-year sample and 65.6% of last five-months sample were able to achieve a TTR>64 after 3 months (table 3).

- Scenario A with dabigatran was a cost-effective alternative to CPAMS (both samples) (Table 10). Scenario A with dabigatran was more costly than CPAMS but the event savings (effectiveness) outweighed the added program costs.

- Scenario B was only as cost-effective as CPAMS if considering dabigatran in the full-year sample. Treating all patients with dabigatran is more expensive than CPAMS but the lower event costs more than offset the higher treatment costs in the full-year sample.

- No Scenario B/NOAC combination was shown to be a cost-effective alternative to NS CPAMS last five-months sample.

Given dabigatran was a cost-effective alternative to CPAMS in three of the four scenarios, scenario A (hybrid CPAMS/NOACs) was compared to Scenario B (NOACs alone) (Table 11) to explore whether Scenario B was a cost-effective alternative for Scenario A.

- Scenario B (dabigatran) was as effective as Scenario A (dabigatran) in the full-year sample but the high cost of dabigatran, outweighed the potential savings, so it was not a cost-effective alternative to Scenario A (dabigatran).

- Scenario B was not as effective as Scenario A for other NOACs in the full-year sample or any NOAC in the five-month sample, as a result, it was not as cost effective as Scenario A (Scenario B had higher event costs than Scenario A).

Sensitivity analyses examined the consequences of generics being available for NOACs (table 12 and 13).

- In both samples, the introduction of 75% generic prices for NOACs (table 12) push Scenario A to be a cost-effective alternative to CPAMS for all NOACs except rivaroxaban. Scenario A costs more than CPAMS but the added costs are less than the lower adverse event costs of the NOACs except for rivaroxaban.

- In both samples, the introduction of 25% generic prices for NOACs leads Scenario A to be dominant over CPAMS except for rivaroxaban. Scenario A is more effective and less costly than CPAMS, so it is dominant (for all but rivaroxaban).

- 75% generic pricing does not lead to more cost-effective instances for Scenario B.

- When 25% generics are available, Scenario B with dabigatran or apixaban are dominant (more effective and less costly than) over CPAMS in the full-year data and Scenario B with dabigatran is dominant in the 5-month data.

- The effectiveness of the scenarios does not change with price changes, so comparing Scenario B to Scenario A dabigatran was the only effective NOAC and it is currently a 75% generic.

- If multiple generics become available for dabigatran and the price falls further, it becomes dominant (more effective and less costly) over scenario A given full-year sample TTRs.

- No NOAC alone (Scenario B) is as effective as the CPAMS hybrid/NOAC (Scenario A) given last five-month sample TTRs. So, Scenario B is not a cost-effective alternative to Scenario A.

- 'Back-of-the-envelope' calculations for a hypothetical five-year cost to the NSDHW of Scenario B compared to Scenario A for dabigatran showed the NSDHW would pay $436.10/patient more over five years if all patients were prescribed dabigatran (Scenario B) as opposed to keeping those whom can maintain an adequate TTR in CPAMS and prescribing dabigatran to those whom cannot (Scenario A).

- If dabigatran prices drop substantially (by about 2/3), Scenario B becomes the less costly alternative for the NSDHW saving just over $1,400/patient over 5 years.

In summary, using the NS CPAMS data, current prices, and assumptions drawn in this costing study from the NSDHW's perspective, of anticoagulation choices studied herein, the most cost-effective alternative is a hybrid program (Scenario A) where all anticoagulation patients are referred to CPAMS. Those whom cannot achieve a TTR>64 after 3 months, and do not have contraindications, are removed from CPAMS and prescribed dabigatran. However, if the price of dabigatran falls substantially (by about 67%), prescribing dabigatran to all patients who do not have contraindications becomes the most cost-effective alternative.

CPAMS Costing Study Addendum

## Introduction

This addendum adds evidence on new oral anticoagulants to the CPAMS Costing Report (submitted by Dr. LJ Curtis, August, 2019). The original study found that: the literature generally found that CPAMS type programs were at least as effective as usual care (UC – typically primary-care physicians providing anticoagulation management); CPAMS type programs were shown to be generally accepted by physicians and preferred to UC by patients; NS CPAMS was at least as effective as UC, from the NSDHW's perspective, except when physicians (MDs) were paid full anticoagulation management alongside of CPAMS[1]. When CPAMS data were limited to the later months in the study[2], the mean times in therapeutic range (TTR) were more consistent with the literature, resulting in NS CPAMS being more cost effective than UC except when MDs maintained their full anticoagulant fees. The cost savings were generally enough to allow a small one-time referral payment to MDs without changing the cost-effectiveness[3].

Warfarin (a vitamin-K antagonist (VKA)) has been in use for decades and is effective at reducing the risk of stroke in patients with atrial fibrillation. Maintaining a tight therapeutic range (high TTR) is important in limiting untoward risks such as hemorrhage or embolism, thus close monitoring is necessary. Interactions have been noted with foods and other drugs which can affect anticoagulation.

New anticoagulants, non vitamin-K antagonist oral anticoagulants (NOACs or NVKA), also known as direct oral anticoagulants (DOACs) have been developed[4]. NOACs (dabigatran (a direct thrombin inhibitor), and rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors)) have been promoted as overcoming some of warfarin's limitations while maintaining efficacy in stroke prevention (see for example Fanaroff & Ohman, 2019). Their direct anticoagulation effect is obtained by inhibiting the action of a specific coagulation factors. The drugs are reported as having more predictable dose-dependent effects on anticoagulation and wider therapeutic

[1] It is assumed that MDs would not be paid current anticoagulation management fees alongside CAPMS.
[2] Faulty test strips were identified to be an issue in the study. The issue was corrected for the last seven months of data (see original Costing Study and Research Power Inc., 2019)
[3] It is likely that a one-time referral fee would be paid to MDs but the fee would be inconsequential over long-term treatment with CAPMS, so it is not included in the current analysis.
[4] The term NOAC will be used in this study.

window than warfarin so, NOACs do not require routine frequent monitoring (see for example Fanaroff & Ohman, 2019). However, some hesitation was noted on the part of physicians and patients over reversibility concerns (Baumann, Keenan, Morton, et al., 2014) when NOACs were introduced but not more recently (Enriquez, Lip, Baranchuk, 2015; Pollack Jr, Reilly, Eikelboom, et al., 2015). NOACs are contraindicated for patients with mechanical heart valves and must be used with caution in patients with reduced renal function (see for example Chen, Stecker, Warden, 2020).

Early clinical trials indicated that NOACs were at least as effective as warfarin, however there is concern that those studies did not examine NOACs effectiveness relative to patients who were well-managed with warfarin therapy[5] or for long-term therapy[6]. In addition, NOACs are substantially more expensive than warfarin (see for example CADTH, 2012, Nova Scotia, 2020). Thus, this addendum examines current evidence comparing the effectiveness and cost-effectiveness of NOACs compared to warfarin and to each other for non-valvular atrial fibrillation. No studies were identified that compared NOAC use to warfarin anticoagulation managed in CPAMS type programs. So, evidence from the NS CPAMS project and the literature are used to develop 'scenarios' comparing effectiveness and cost-effectiveness of possible NOAC use to CPAMS for anticoagulation management with warfarin.

Summary of Evidence comparing NOACs to Warfarin[7]

Several well-designed clinical trials comparing warfarin to NOACs in patients with atrial fibrillation were completed starting about a decade ago. Given the effectiveness of warfarin, NOACs could not be ethically compared to placebos in randomized trials. Instead, the original effectiveness trials for these drugs were non-inferiority studies comparing them to warfarin (e.g., RE-LY (Connolly, Ezekowitz, Yusuf, et al., 2009), RE-COVER (Schulman, Kearon, Kakkar, et al., 2009), ARISTOTLE (Granger, Alexander, McMurray, 2011), AMPLIFY-EXT (Agnelli, Buller, Cohen, et al., 2013), ENGAGE AF–TIMI (Giugliano, Ruff, Braunwald, et al., 2013), ROCKET AF (Patel MR, Mahaffey KW, Garg J, et al., 2011; Piccini, Hellkamp, Lokhnygina, et

[5] The debate suggests that many of the clinical trials compared patients who were poorly managed on warfarin (low mean TTRs) to those who received NOACs (see Trussler, 2015 & 2015 for example).
[6] Most clinical trials were for short-term treatment. AMPLIFY-EXT was an exception.
[7] No studies were found comparing NOAC use to CAPMS type management of warfarin anticoagulation.

al., 2014) and RE-COVERII (Schulman, Kakkar, Goldhaber et al., 2014)[8]. A noninferiority study tests the hypothesis that a new treatment is not worse than an existing effective treatment (D'Agostino Sr, 2017). In general, the non-inferiority studies indicated that the NOACs were noninferior to warfarin with respect to the prevention of stroke or systemic embolism (SE) and were associated with equal or lower rates of untoward effects (i.e., hemorrhage or death). However, as noted in the following summaries, on average, the anticoagulation control was poor for warfarin patients in the studies.

APAXIBAN

The ARISTOTLE study comparing apixaban to warfarin found apixaban to be at least as good as warfarin for stroke or embolism (a hazard ratio (HR) of 0.79 (95% confidence interval (CI) 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority), major bleeds (HR 0.69 (95% CI, 0.60 to 0.80; P<0.001 for noninferiority), hemorrhagic stroke (HR 0.51 (95% CI, 0.35 to 0.75; P<0.001), and all-cause mortality (HR 0.89 (95% CI, 0.80 to 0.99; P=0.047). There were no significant differences in other types of strokes. The mean TTR for warfarin patients was 62.2% indicating anticoagulation management of warfarin patients was not optimum.

The AMPLIFY-EXT study compared apixaban to placebo for extended treatment (up to a year) of anticoagulant patients. Warfarin was not a comparator. The trial concluded that compared to placebo (ethical as extended prophylaxis had not been studied previously), extended anticoagulation with apixaban either 5 mg or 2.5 mg reduced the risk of recurrent venous thromboembolism (VTE) without increasing the rate of major bleeding. No conclusions could be made about its effectiveness compared to warfarin as it was not a comparator.

[8]RE-LY=Randomized Evaluation of Long-Term Anticoagulation Therapy Study; The ROCKET AF=Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial; ARISTOTLE=Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation study; AMPLIFY-EXT=Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First Line Therapy–Extended Treatment; ENGAGE AF-TIMI 48=Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction; RE-Cover= Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism; RE-CoverII= Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis.

DABIGATRAN

The RE-LY study indicated that low-dose dabigatran (110mg) was not significantly different than warfarin at reducing SE or stroke but significantly better at reducing adverse effects (major bleeding rate was 3.36%/year vs 2.71%/year (P=0.003) and the rate of hemorrhagic stroke was 0.38%/year vs 0.12%/ (P<0.001) for warfarin and low-dose dabigatran, respectively. Higher dose dabigatran (150mg) was significantly better at stroke and SE reduction (HR 0.66 (95% CI, 0.53 to 0.82); P<0.001 for superiority) but was not significantly different at reducing adverse events than warfarin. Mean TTR in the warfarin group was 64% showing marginally acceptable anticoagulation management of warfarin patients.

RE-COVER showed insignificant differences for recurrent VTE or major bleeding between warfarin and dabigatran. Dabigatran had lower rates of any bleeding (HR 0.71 (95% CI=0.59 to 0.85)). However, more patients had events that lead to treatment discontinuation with dabigatran than with warfarin (9.0% vs 6.8%; P=0.05, respectively). Other outcomes were similar between warfarin and dabigatran patients. Mean TTR for warfarin patients was 60%, showing poor anticoagulation.

RE-COVER II showed insignificant differences between dabigatran and warfarin on recurrent VTEs, death, major bleeding and most adverse events. There was a significant difference for any bleeds (HR 0.67 (95% CI=0.56–0.81)). Pooled analysis of RE-COVER and RE-COVER II provided similar results. Mean TTR in the RE-COVER II study was low at 57% indicating poor anticoagulation management for warfarin patients.

EDOXABAN

In the ENGAGE AF–TIMI trial (Giugliano, Ruff, Braunwald, et al., 2013), the authors claimed that high-dose edoxaban showed a ‘favourable trend’ and low-dose an ‘unfavorable trend’ when compared to warfarin (the intent-to-treat results were not significant at the 5% level but were at 10% level). In the treated sample, the annualized rate of major bleeding was significantly lower in edoxaban (HR 0.80 (95% CI=0.71 to 0.91; P<0.001) and 0.47 (95% CI=0.41 to 0.55; P<0.001) for high- and low-dose edoxaban, respectively). The median TTR for warfarin users was respectable at 68.4%.

RIVAROXABAN

The ROCKET AF trial showed no significant difference in the prevention of stroke, embolism, and major or nonmajor clinically relevant bleeding. Rivaroxaban showed significant reductions in intracranial hemorrhage, 0.5% vs. 0.7% (P=0.02) and fatal bleeding, 0.2% vs. 0.5% (P=0.003) relative to warfarin patients, respectively. Mean TTR (55%) indicated poor anticoagulation management for warfarin patients.

Piccini, Hellkamp, Lokhnygina, et al., (2014) re-examined the ROCKET AF data to assess whether the anticoagulation level (TTR) of warfarin patients effected the outcomes of the original study. Data on individual level TTRs were not available so TTRs were aggregated at the centre level (cTTR). They found that the treatment effect of rivaroxaban was not significantly different across a range of cTTRs. The authors concluded that the results showed that the original results held regardless of cTTR. However, when examined more closely, significant effects were only observed at very low (rivaroxaban more effective) and high (warfarin more effective) mean cTTRs (discussed further in the following presentation). Mean cTTRs differed substantially by geographic area with cTTRs ranging from 65% in North American centres to 52% in Eastern European centres.

These early randomized clinical trials (RCT) indicated, on average, that NOACs were at least as effective as warfarin at reducing strokes, VTEs, and death but had, on average, less likelihood of major and particularly minor bleeds. However, as noted herein, anticoagulation control with warfarin tended to be poor in the trials. The Canadian Agency for Drugs and Technologies in Health (CADTH) (CADTH, 2012), reported that NOACs[9] had demonstrated efficacy within clinical trials in preventing stroke and SE in patients with AF but effectiveness had not been demonstrated in clinical practice or with subpopulations. And the cost differential between NOACs and warfarin had not been considered. On the one hand, NOAC costs could put them out of reach for some patients, on the other hand, the frequent monitoring necessary for warfarin was costly and inconvenient. Hence, cost-effectiveness studies of the alternatives were undertaken.

Following a comprehensive review of NOACs efficacy and/or effectiveness and cost-effectiveness (CADTH, 2012), the Canadian Drug Expert Committee (CDEC) provided

[9] only dabigatran and rivaroxaban were approved in Canada when the study was undertaken.

recommendations for the use of NOACs for prevention of stroke and SE in patients with non-valvular atrial fibrillation. They recommended that, NOACs were only an alternative to warfarin for patients where adequate anticoagulation was not achievable and there was a high risk of stroke. They recommended that, if NOACs were necessary, the should be guided by clinical factors due to the dearth of comparisons across NOACs, long-term data, and strong cost-effectiveness analyses. A CADTH brief put out in 2013 that included apixaban (see www.cadth.ca/clots) repeated the recommendation that warfarin should be used as the 'first-line therapy' for preventing stroke in patients with atrial fibrillation; that new oral anticoagulants should be used as a 'second-line option' for some patients with non-valvular atrial fibrillation who were not doing well on warfarin.

As NOACs became prevalent in physician prescribing in Canada, some MDs argued that NOAC evidence may be over-rated (e.g., Burn & Pirmohamed, 2018; Trussler, 2014, 2015). They pointed to RCT evidence being relevant when warfarin anticoagulation was relatively poor (i.e., for patients with TTRs in the mid 60s or lower) and that CPAMS type models which lead to higher TTRs (usually in the low to mid 70s) being available. As discussed previously, a study comparing rivaroxaban vs warfarin effects over different cTTRs (Piccini, Hellkamp, Lokhnygina, et al., 2014) showed that only centres with very low and very high mean cTTRs had significant effects. Rivaroxaban was more effective than poorly controlled warfarin but well-controlled warfarin (cTTR>65.71) showed better outcomes than rivaroxaban. Notably, it has been difficult to predict, apriori, patient TTR scores even in models using up to 85 patient characteristics (see for example, Williams, Evans, Honushefsky, et al., 2017; Apostolakis, Sullivan, Olshansky, 2013).

Data were pooled from several clinical trials in order to perform sub-group analyses comparing NOACs to Warfarin (see figure 1) (Ruff, Giugliano, Braunwald, et al., 2014). The study found that the relative risk of stroke or SE events (Panel A) and major bleeding (Panel B) for subgroups showed that NOACs performed similarly to warfarin and in some cases better (controlling hemorrhage). Of note, for patients in centres with mean TTR< 66% NOACs perform substantially better than warfarin, but for centres with mean TTR ≥66% no significant differences were observed.

Compliance issues were also raised regarding NOACs compared to warfarin. However, the evidence in the literature is mixed. A large study of Ontario patients (Jackevicius, Tsadok, Essebag, et al, 2017) found approximately one third of patients with prescriptions for dabigatran or rivaroxaban discontinued their use (had a gap in prescription refills of 14 days or more) within about 6 months (warfarin compliance was not examined). Almost half of all anticoagulation patients discontinued medications in follow up in another large study (Kachroo, Hamilton, Liu, et al., 2016) but it found that patients taking NOACs were less likely than those taking warfarin to independently discontinue use. Compliance rates were shown to be high for a small group of patients on NOACs in yet another study (Gulpen, ten Cate, Henskens, 2019). Garkina, Vavilova, Lebedev & Mikhaylov (2016) argued that while studies may show higher compliance rates for NOACs, the monitoring necessary with warfarin provided more information regarding compliance and, possibly, quicker reaction to noncompliance in clinical practice.

A recent environmental scan (Ndegwa, Boucher, Farrah, 2017) found that many international publicly funded pharmaceutical plans reimbursed all four NOACs for the prevention of stroke and SE in patients with AF but reimbursement tended to be related to specific clinical criteria; specifically risk factors associated with high CHADS2 scores. Publicly funded plans in the United States (US) considered NOACs as non-preferred and required additional criteria for some NOACs to be reimbursed. However, very recent recommendations from the US and the UK support NOACs as primary treatment because of its lack of frequent monitoring particularly in the current pandemic (January, Wann, Calkins et al., 2019; UK NHS, 2020).

As concerns over the representativeness of the warfarin populations in RCTs (see for example, Lee, Monz, Clemens, et al. 2012; Camm, Amarenco, Haas, et al. 2014 Camm, Amarenco, Haas, et al. 2016), and the effectiveness of NOACs rather than their efficacy, including compliance issues, (see for example, CADTH, 2012) evolved, observational studies including larger population-based samples were undertaken. A particularly large Swedish study (Sjogren, Bjorn, Renlund, et al., 2017) matched all AF patients, in a large administrative data base, started on NOACs to patients started on warfarin. The data covered 2.5 years beginning mid-2011, leading to a sample of 12,694 NOACs patients (dabigatran (40.3%), rivaroxaban (31.2%), and apixaban (28.5%)) matched with 36,317 warfarin patients. Given matching, the groups were similar with respect to previous experience with warfarin, mean age (just over 72), sex, and mean follow-up

time. Mean TTR was reasonable at 70% for the warfarin group. Like many studies, no significant differences were found in the rates of thromboembolic or thrombotic events or gastrointestinal bleeding. However, NOAC patients had lower rates of major bleeding (HR 0.78 (95% CI=0.67–0.92)), intracranial bleeding (HR 0.59 (CI=0.40–0.87)), hemorrhagic stroke (HR 0.49 (CI=0.28–0.86)), and other major bleeding (HR 0.71 (CI=0.57–0.89)). The authors concluded that, for patients with AF, NOACs as a group (dabigatran, rivaroxaban and apixaban) were as effective for stroke prevention as well-managed warfarin and caused fewer major bleeds.

Figure 2 provides an overview of comparisons of clinical trials and observational studies (Fanaroff & Ohman, 2019). The hazard ratios (compared to warfarin) of NOACs (dabigatran, rivaroxaban, and apixaban) for stroke or SE (Chart A) and major bleeds (Chart B) are displayed. Clinical trials are demarcated by a square and retrospective studies by a circle with lines representing confidence intervals. The retrospective results indicate that warfarin and the three NOACs are similar in their effectiveness (Panel A), but NOACs seemed to be favoured, more so in the retrospective studies than clinical trials, over warfarin when major bleeds were considered (Panel B).

In sum, the literature points to NOACs being comparable to warfarin at reducing the likelihood of stroke or embolism and perhaps slightly better at limiting adverse events. However, studies did not typically control for warfarin patients' anticoagulation management (TTRs). As well, NOACs cost substantially more than warfarin but, warfarin monitoring costs must also be considered. Thus, economic evaluations including the possible additional benefits of NOACs and their additional costs were needed to the costs of warfarin treatment were completed.

Cost Effectiveness of NOACs compared to warfarin

A Markov-model, using data from the clinical trials discussed earlier (Harrington, Armstrong, Nolan, et al., 2013) demonstrated that warfarin had the lowest cost of $77,813 (SD, $2,223) and the lowest Quality Adjusted Life Years (QALYs) of 7.97(±0.04). Rivaroxaban 20 mg had the second lowest cost and QALYs at $78,738(±$1,852) and 8.26(±0.06), respectively. Dabigatran 150 mg cost $82,719(±$1,959) with 8.41(±0.07) QALYs and apixaban 5 mg had the highest costs and QALYS at $85,326(±$1512) and 8.47 (SD, 0.06), respectively. Compared to warfarin, rivaroxaban had an incremental cost-effectiveness ration (ICER) of $3,266/QALY, dabigatran's ICER was $11,211/QALY while apixaban's was $15,130/QALY. Given the low cost/QALY, the

NOACs were considered cost-effective alternatives to warfarin at usual willingness to pay levels. A Multi-Criteria Decision Analysis performed a considering benefit-risk and drug costs (Mendoza-Sanchez, Silva, Rangel, et al., 2018) using data from the previously noted study (Harrington, Armstrong, Nolan, et al., 2013). It concluded that apixaban, had the best results followed by dabigatran, warfarin, and rivaroxaban.

Using administrative data from the US, Gilligan, Franchino-Elder, Xue Song et al., (2018) examined all-cause costs among newly diagnosed non-valvular AF patients beginning oral anticoagulation therapy with dabigatran to those starting on apixaban, rivaroxaban, and warfarin. They included health-care resource utilization and all-cause 30-day readmission rates for differently treated patients. The matched samples showed that dabigatran patients had lower adjusted total healthcare, inpatient, and outpatient costs compared to rivaroxaban ($4,093 vs $4,636, $1,476 vs $1,862, and $2,016 vs $2,121, respectively, all $p < 0.001$) and warfarin ($4,199 vs $4,872, $1,505 vs $1,851, and $2,049 vs $2,514, respectively, all $p < 0.001$)[10]. Adjusted costs were similar for dabigatran and apixaban. The study concluded that dabigatran lead to lower all-cause costs than rivaroxaban and warfarin and comparable to apixaban.

A Markov model was used to complete a cost-utility analysis of available anticoagulant options for the prevention of recurrent VTE in patients with unprovoked events in outpatient settings in Halifax, NS for three-, six- and 12-month and life-time treatment regimes (Al Saleh, Berrigan, Anderson, et al., 2017). The costs of pharmaceuticals, laboratory testing, hematologist fees, and treatment of recurrent VTE and major bleeding events were considered. Apixaban represented the most cost-effective NOAC relative VKA (e.g., warfarin) in the three- and six-month treatment scenario, with an ICER of $7,380/QALY and $84.08/QALY gained, respectively, and dominated all strategies at 12 months. For lifetime treatment, NOACs were not found to be cost-effective alternatives at usual willingness to pay levels as they were twice as costly as warfarin and only increased QALYs marginally leading to ICERs of close to $150,000/QALY for apixaban and over $275,000/QALY for rivaroxaban. Dabigatran was dominated by apixaban.

In an extensive cost-utility analysis for the CADTH, Klarenbach, Boucher, So, et al., (2016) compared apixaban 5mg and 2.5mg, edoxaban, dabigatran, and rivaroxaban to VKA in three-

[10] Dabigatran values are different in the comparisons as each comparison uses a different matched sample.

and six-month, and life-long anticoagulation. The findings were similar in dominance to the Al Saleh, Berrigan, Anderson, et al., (2017) study but the ICERs were much larger; indicating that NOACs were not cost effective at usual willingness to pay. The three-month scenario found that apixaban 5 mg dominated the other NOACS but had an ICER of $170,481/QALY relative to VKA. The six-month scenario showed ICERs of $184,380/QALY for apixaban 5 mg and $221,922/QALY for apixaban 2.5 mg relative to VKA, respectively. The other NOACs were dominated. Finally, for the life-long treatment scenario, apixaban 5 mg had an ICER of $296,113/QALY compared to VKA. The other NOACs were dominated. While the general results of the report held to sensitivity analyses, the authors did caution that large changes in the costs of NOACs (e.g., generics) or the monitoring costs for VKAs (e.g., INR home testing) could change the outcomes substantially.

A recent systemic review of cost-effectiveness evaluations among NOACs, included seven studies [11] (Al Mukdad, Al-Badriyeh, & Elewa, 2019). Two of the studies were completed in a Canadian setting (Al Saleh, Berrigan, Anderson, et al., 2017; Quon, Raymond, Mtibaa, et a., 2016 (compared extended treatments)). The authors of the review began by concluding that NOACs were more effective than warfarin, so they asked which NOAC was the most cost effective. They concluded that the seven studies were of fair quality, none being of poor quality, and the two Canadian studies of good quality. Apixaban dominated (had better outcomes and was less costly) the other NOACs for prevention and treatment of VTE, including extended treatment, due to lower recurrence rates of VTE and lower major bleed rates. Rivaroxaban, edoxaban, and dabigatran were ranked second, third and fourth, respectively for cost-effectiveness.

To summarize, the new non-vitamin K antagonist anticoagulants (NOACs) have been shown to be comparable to warfarin for treatment of VTEs and stroke (usually in patients with AF) and perhaps with less risk of adverse events. However, discussion in the literature regarding whether the comparisons of NOAC patients with poorly controlled warfarin patients (i.e., lower TTRs) and lack of controlling for TTRs in the studies bias conclusions. Would the conclusions differ if comparator populations (warfarin patients) were better anticoagulated? In addition, on the one

[11] Quon, Raymond, Mtibaa, et a., 2016; Amin, Bruno, Trocio, et al., 2016; Al Saleh, Berrigan, Anderson, et al., 2017; Jugrin, Hosel, Ustyugova, et al., 2016; Amin, Jing, Trocio, et al., 2015; Amin, Jing, Trocio, et al., 2014; Lanitis, Leipold, Hamilton, et al., 2016.

hand, there was less clinical experience with NOACs than with warfarin, particularly for long-term treatment, and NOACs are more costly than warfarin to purchase. On the other, warfarin use necessitates close monitoring which is costly but may be useful in identifying noncompliance. Cost-effectiveness analyses provided heterogenous results with some studies showing NOACs to be more cost effective than warfarin and others showing the opposite particularly in long-term use. NOACs are contraindicated for patients with mechanical heart valves and cautioned in patients with renal function issues. Recent introduction of CPAMS programs have shown to increase anticoagulation management in warfarin patients and lower costs. Given the interest in NOACs and the heterogenous results in the literature, the NS CPAMS project analyses were extended to include NOACs.

The Extension to original CPAMS Study includes:

1) Outcomes and costs calculated for the sample of patients remaining in CPAM for the final five months of the study (last five-months sample) (March to July 2019)[12].

2) Costs calculated assuming the NSDHW reimburses $50/month for each patient in CPAMS and pharmaceutical costs as per the Nova Scotia Formulary (2020).

3) Outcomes and costs calculated for a scenario where all patients are referred to CPAMS for anticoagulation management. Patients remain in the program for three months. TTRs are then calculated. Patients whom do not achieve a TTR > 64 after the three months are taken off warfarin[13], therefore removed from the CPAMS, and started on NOACs[14] (scenario A). The analysis is completed for two samples: 1) the original CPAMS full-year sample, and 2) CPAMS last five-months sample.

[12] Study organizers felt that this was the most representative data available in the study due to issues with test strips earlier in the study (see Research Power Inc., 2019).
[13] Williams et al., (2020) suggests 12 weeks to regulate INR>64
[14] The anticoagulation reason for most patients in the CAPMS data was atrial fibrillation or thrombosis, many reported the reason as 'other'. There were 49 patients who identified mechanical heart valve as the reason (contraindication for all NOACs (see January, Wann, Calkins et al., 2019)). Half those patients maintained a TTR>64 for the study. The outcomes for patients with mechanical heart valves were similar to others in the sample. Due to similar outcomes and the small proportion of the sample identified as having mechanical heart valve, the results did not differ significantly with inclusion/exclusion of mechanical heart valve patients. For these reasons and lack of information on the presence or not and/or type of valve for most patients and to maintain sample size, those

4) Outcomes and costs calculated for a second scenario where all patients in need of anticoagulation are prescribed NOACs and warfarin is no longer used[12] (thus CPAMS is not necessary) (Scenario B) for two samples: 1) CPAMS full-year, and 2) CPAMS last five-months.

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*Scenario A: All anticoagulation patients are referred to CPAMS. Patients achieving a TTR>64% after 3 months in CPAMS remain in the program. Those who do not maintain a TTR>64% are moved onto NOACs. NSDHW pays $50/patient/month for CPAMS.*

*Scenario B: All anticoagulation patients are prescribed NOACs by their physicians (except where contraindicated).*

*CPAMS full-year sample☆ intent-to-treat data for patients enrolled in CPAMS for one year; Mean TTR was 68.75%.*

*CPAMS last five-months sample☆ intent-to-treat data for patients enrolled in CPAMS for the last five-months of the study (March to July 2019). Mean TTR was 75.35%.*

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For detailed discussion of CPAMS methods and data refer to methods and data sections in original CPAMS study.

Results

Table One presents the clinical data for the original CPAMS study for the full-year and last five-months samples. It is clear, those remaining in the study longer had better anticoagulation control with a mean TTR of just over 75% and fewer than 2% of patients having very low (<1.5) or very high (>4.0) INRs. The mean number of INR tests was substantially reduced over time to just over seven from almost 20, on average, earlier in the study. The intent-to-treat (IIT) sample was reduced from 928 to 783 (16%).

with mechanical valves were not excluded. However, contraindications regarding mechanical heart valves and NOACs are important considerations in prescribing.

Table 2 presents the clinical outcomes for CPAMS patients in Scenario A. All patients begin in CPAMS, those achieving mean TTRs>64 after three months remain in CPAMS, those with mean TTRs ≤ 64 are transitioned to NOACs. The mean TTR in CPAMS patients for the two samples is, as expected, higher than the original study; both ITT TTRs signal, by design, very well-managed anticoagulation; the TTR is just over 74% for the full-year sample and almost 84% for the last five-months sample. CPAMS sample sizes fall by about 1/3 in both samples as patients who cannot achieve a TTR of at least 64% are transitioned to NOACs.

Table 3 provides comparisons of the study sample sizes for CPAMS and Scenario A. The proportions are used to calculate expected costs and outcomes for the different samples for Scenario A. Relative to the CPAMS full-year sample (928 patients), the last five-month sample is 16% smaller as previously discussed. Sixty-four percent of the full-year sample was able to achieve a TTR >64 after 3 months in CPAMS (Scenario A) and 66% of the last five-months sample (just over half of the original sample) was able to do the same. The remainder of the patients (about 1/3) were transitioned to NOACs.

Pharmaceutical and CPAMS monitoring costs are presented in Table 4[15]. Pharmaceutical costs range from $6.11/month for patients on warfarin to $99.38 for a one-month prescription of Apixaban. Prices in the first column of data are as reported in the Nova Scotia Formulary (2020).[16] The second column of data estimates prices for the pharmaceuticals when a single generic is available (assumed to be 75% of the formulary cost except for dabigatran and warfarin which are already available in generic form). The final column presents estimated prices when multiple generics are available (assumed to be 25% of the formulary except for dabigatran which is at 1/3 the formulary price and warfarin which currently has multiple generics available). All NOACs remain substantially more expensive than warfarin even when generic prices are assumed. However, when multiple generics come onto the market, the NOAC prices are about half the $50.00 management fee the NSDHW is assumed to pay for CPAMS.

Table 5 presents the expected treatment costs for Scenario A across the NOACs and the two samples. Considering the full-year sample, the estimated treatment costs per patient per month

[15] Dosages were taken from Canadian studies and the CAPMS data (see table 4 notes). Similar dispensing fees are assumed across the different drugs and thus not included.
[16] The drug prices were not adjusted by the price index back to 2018 as the 2020 listed prices were almost identical to the prices used in the CADTH study (Klarenbach, Boucher, So, et al., 2016)

range from 61.56/patient/month when dabigatran is the NOAC prescribed to patients who cannot achieve an adequate TTR to 67.72/patient/month if apixaban is prescribed with the other two NOACs at just under $65/patient/month. As the proportion of CPAMS and NOAC patients differ only slightly in the two samples, treatment costs/patient/month are similar (within about 50 cents per month).

Table 6 presents adverse events per patient year for Ischemic stroke (IS), hemorrhagic stroke (HS), systemic embolism (SE), major bleed except HS (MBEHS), clinically relevant non-major bleed (CRNB), and minor bleed (MBld) for different TTRs[17]. As eluded to in the literature review, the occurrence of adverse events with warfarin anticoagulation is dependent on TTRs. The TTRs in the range of those found in most clinical trials (TTR<65) are associated with substantially higher adverse events than those associated with TTRs>65. Table 7 presents the adverse event occurrences for NOACs. The per patient year occurrences for the NOACs are much closer to those in table 6 for higher TTRs than for lower ones. Estimated costs for each of the adverse events are presented in table 8[18].

Table 9 uses the data in tables 6, 7, and 8 to estimate yearly event costs for Scenarios A and B given the two samples. CPAMS' event costs are the comparator. As can be seen for Scenario A (both samples), all NOACs except rivaroxaban have lower event costs than original CPAMS sample. Comparing Scenario B to the original CPAMS using the full-year sample, apixaban and dabigatran have lower event costs while rivaroxaban and edoxaban have higher ones. If the CPAMS last five-month sample is used as the comparator, Scenario B is associated with higher event costs for all NOACs prescribed except dabigatran.

The study results comparing Scenarios A and B to CPAMS are presented in table 10. The first column stipulates the scenario, NOAC, and sample being considered. Scenario A, full-year sample is presented first, then Scenario A five-month sample. Scenario B is presented in the same manner. The first column of data is the difference between the original CPAMS (the comparator) and the Scenarios' event costs (from table 9). A negative value indicates the

[17] data taken from the CAPMS report (table 11) adding adverse events for higher TTR scores (Source: Amin et al., 2014).

[18] From original CAPMS study (table 11). Canadian Costs Table 11 in original CAPMS costing study IS and HS (Goere et al., 2005); SE (Regier et al., 2006); MBEHS (Brown et al., 2007; CADTH, 2009); CRNB (Nova Scotia Health Authority, 2019); MBld (Amin et al., 2014).

Scenario's expected adverse events costs are less than CPAMS' expected adverse events costs (the scenario is more effective than CPAMS) and a positive value indicates the scenario is not as effective as CPAMS[19]. The next column of data presents the same for treatment costs (from tables 4 and 5). A negative value in this column indicates that the scenario's treatment costs are less than CPAM's treatment costs and a positive value indicates the scenario's treatments are more costly than CPAMS. A scenario dominates CPAMS if it has lower adverse event costs and lower treatment costs (a negative in the two columns). An alternative is not effective if its adverse event costs are higher than CPAMS (a positive value) and thus, the difference in treatment costs is of no consequence. There were no instances of the adverse event costs being identical for scenarios and CPAMS. If the scenario/NOAC has lower adverse event costs (a negative in that column) and the treatment costs are higher than CPAMS' (a positive in the treatment difference column), the question is, do the adverse event cost savings outweigh the added treatment costs?

To answer the question, the last column presents the cost-benefit results (the sum of the first two columns). It shows whether any lower event costs for scenarios with different NOACs are outweighed by higher treatment costs for alternative scenarios compared to CPAMS. The colour coding indicates that compared to CPAMS the alternate scenario/NOAC has: lower event costs, lower treatment costs (dominates); lower event costs and higher treatment costs (benefits>costs, so alternative scenario is a cost-effective option); lower event costs and higher treatment costs (benefits<costs, so alternative scenario is not a cost-effective option); higher event costs but lower treatment costs (is not as effective, so cannot be cost effective); higher event costs and higher treatment costs (is not as effective, so cannot be cost effective). So, green and purple indicate a cost-effective alternative.

Table 10 shows that Scenario A is cost-effective when dabigatran is the prescribed NOAC in both the full-year and last five-month samples. While apixaban, and edoxaban were shown to be effective (negative difference in event costs), the higher treatment costs outweighed the lower event costs, so they were not shown to be cost-effective alternatives. Scenario B (full-year sample) is only effective when apixaban and dabigatran are the prescribed NOACs but apixaban treatment costs far outweigh the lower event costs when compared to CPAMS. Dabigatran is

[19] If a scenario is not effective, it cannot be cost-effective.

shown to be cost-effective as the higher treatment costs are slightly lower than the benefits of fewer adverse events. When the last five months sample is considered, Scenario B is not a cost-effective alternative to CPAMS in conjunction with any NOAC. The only NOAC that is more effective when Scenario B is compared to CPAMS is dabigatran and the high treatment costs outweigh the cost savings from lower adverse events.

As Scenarios A (both samples) and B (full-year sample) with dabigatran are demonstrated as cost-effective alternatives to the original CPAMS, the question becomes, which is the better alternative Scenario A or B? The data presented in table 11 compares Scenario B to Scenario A (comparator) for the two samples. Although only some scenarios with dabigatran were shown to be cost-effective with dabigatran in table 10, all NOACs are compared in table 11 for completeness. As the results clearly indicate, Scenario B (NOACs alone) is never shown to be effective compared to Scenario A (CPAMS/NOACs hybrid) in the last five-month sample, so it cannot be cost-effective. Scenario B with dabigatran is as effective as Scenario A with dabigatran in the full-year sample. But the high costs of the drug outweigh the adverse event costs savings, so it is not a cost-effective alternative to Scenario A.

Sensitivity results assuming NOAC prices at 75% of current formulary prices (Table 12) show that compared to the original CPAMS samples, Scenario A becomes a cost-effective alternative with all prescribed NOACs except rivaroxaban for samples. The original results are not affected by a move to generics for dabigatran as it is already in generic form. When multiple generic forms come to market, Scenario B becomes cost-effective when compared to the original CPAMS full-year sample for the NOAC apixaban. Dabigatran, which was cost effective (higher treatment costs outweighed by lower adverse event costs) becomes dominant over CPAMS (lower event costs and lower treatment costs). In fact, all the NOACs which were shown to be effective in table 10 are now not only cost-effective at the lower generic prices (25%) but are dominant over CPAMS (colored green in the table = more effective and less costly).

As previously discussed, having shown that three out of the four dabigatran scenarios/samples show cost-effectiveness when compared to CPAMS, the more interesting comparison is Scenario B to Scenario A. The generic price sensitivity analyses for this comparison appears in table 13. The cost-effectiveness results do not change for the 75% generic price as dabigatran is already at that price and the other NOACs were not effective. In the full-year sample, 25% generic price,

dabigatran becomes a cost-effective alternative as its price drops substantially. Given the other Scenario B/NOACs combinations were not as effective as Scenario A, price changes will not affect the cost-effectiveness of the alternative (an alternative must be effective, to be cost effective).

Finally, table 14 provides results from a 'back-of-the-envelope' calculation of a hypothetical[20] five-year cost to the NSDHW of Scenario B as compared to Scenario A for dabigatran. Dabigatran is the only NOAC that showed cost-effectiveness when compared to Scenario A. Scenario B cost results change over time due to discounting[21]. Scenario A results change from the first year to the second year as patients who cannot achieve a TTR are removed from CPAMS in the first year and are not present in the second and subsequent years and the mean TTR for year two (and beyond) increases[22]. It is assumed that Scenario A's mean TTR increases to 78.21% in the full-year sample and 85.38% in the last five-month sample[23] after the first year. For the last 5-months sample, Scenario B (prescribing dabigatran for all patients) is not an effective alternative to Scenario A (hybrid CPAMS/dabigatran). Thus, Scenario B cannot be a cost-effective alternative to Scenario A. If the full-year sample is examined, the NSDHW would pay $436.10 more per patient over 5 years if all patients were prescribed dabigatran (Scenario B) as opposed to keeping those whom can maintain an adequate TTR in CPAMS and prescribing dabigatran to those whom cannot at current NS formulary prices (Scenario A). If dabigatran prices drop substantially (by about 2/3), Scenario B becomes the less costly alternative for the NSDHW saving just over $1,400 over 5 years.

## Summary and Conclusions

The results included in this addendum add to the results in the original CPAMS Costing study. The addendum calculated the costs and effects of CPAMS as if the last five months of data were

[20] Calculates results for a hypothetical scenario as populations are assumed to be identical from year to year. This would never be the case as patients are added, therapies change or stop, patients age, and patients die. A Markov model following a cohort over time would be needed to examine a more realistic long-run cost of the scenarios.
[21] A typical five percent discount rate is used.
[22] In the first year, the mean TTRs include those who are poorly controlled in first three months of CAPMS before they transitioned to NOACs. In the second and subsequent years the poorly controlled patients do not participate in CAPMS and thus CAPMS mean TTRs increase.
[23] These values are obtained by calculating the TTRs for all patients in the sample after dropping those who did not achieve a TTR of at least 64% (about 2/3 of the sample) after three months.

considered representative of the program results. The cost and effects were also calculated for two new scenarios using CPAMS results and data from the literature. The first included CPAMS being available to patients whom could achieve adequate anticoagulation control in CPAMS (on warfarin) after three months and transitioning those whom could not to NOACs (apixaban, rivaroxaban, dabigatran, or edoxaban) (Scenario A). The second scenario included prescribing all anticoagulation patients NOACs (Scenario B). CPAMS was the comparator in the first instance. Given the high costs for NOACs and the possibility of generics coming to market, sensitivity analyses were performed using generic prices assumed to be 75% and 25% of the current NS formulary price.

The initial results showed that Scenario A was a cost-effective alternative to CPAMS if the NOAC prescribed to those who transitioned out of CPAMS was dabigatran for both full-year and last five-months samples. Scenario B with dabigatran was the only cost-effective alternative to CPAMS and only in the full-year sample. As Scenarios A and B with dabigatran lead to some cost-effectiveness compared to CPAMS, they were compared to each other to see which was the 'better option'. Comparing Scenario B to Scenario A illustrated that Scenario B was not a cost-effective alternative. In fact, Scenario B was only an effective alternative in the full-year sample if dabigatran was prescribed, but the high drug costs outweighed the lower adverse-effect costs, so it was not cost effective.

Scenario A became a more attractive alternative to CPAMS once generic prices were considered. Scenario B results did not improve with 75% generic prices. If multiple generics come onto the market for NOACs and their prices fall substantially as a result, Scenario A becomes dominant except with rivaroxaban (in both samples) and Scenario B with dabigatran becomes dominant in both samples and with apixaban in the full-year sample. In the sensitivity analyses comparing Scenario B to Scenario A, there is only one instance when Scenario B becomes a more cost-effective alternative to Scenario A; in the full-year sample when dabigatran is the prescribed NOAC and dabigatran prices fall substantially (to about 1/3 of its current level).

In sum, if the assumptions of the CPAMS costing studies, and current prices hold, the most cost-effective alternative of the three examined (CPAMS, a hybrid CPAMS/NOAC, and NOACs alone) is the hybrid CPAMS/NOAC (Scenario A) when dabigatran is the NOAC prescribed. This result holds unless the price of dabigatran falls considerably which is assumed to occur only if

multiple generics come onto the market. The results of the study demonstrate that the extent of anticoagulation control (mean TTRs) should be considered when comparing NOACs to treatments based on warfarin. It should be noted that the current results did not take patient preferences or longer-term results into consideration, a more complex cost-utility analysis would be needed to consider preferences for different treatment regimes and long-term consequences of the different alternatives. As well, NOACs are contraindicated for patients with mechanical heart valves and cautioned in patients with renal issues, so an alternative treatment must always be available for these patients.

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Figures

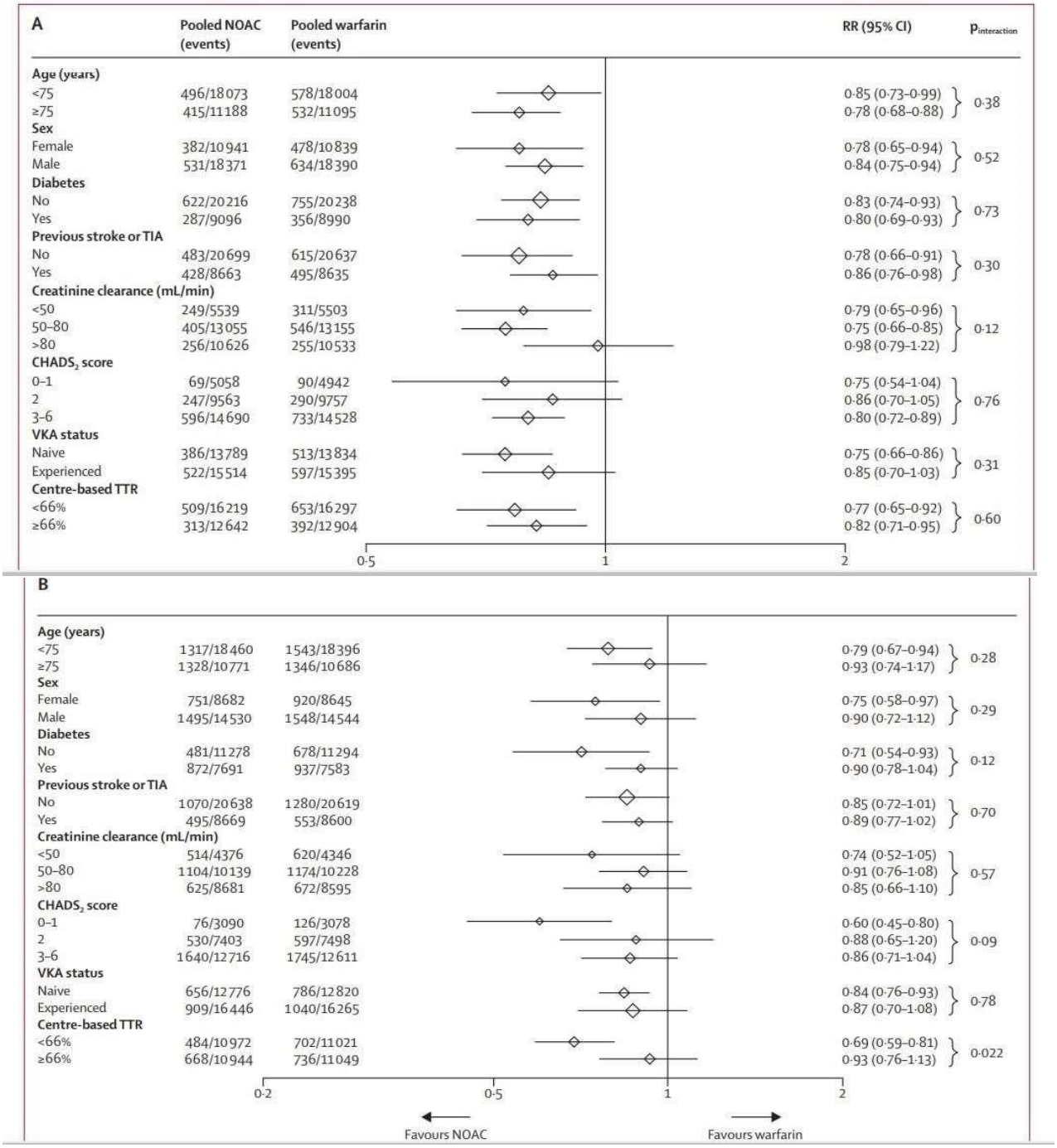


Figure 1: Stroke or systemic embolic events subgroups (Panel A) and major bleeding subgroups (Panel B) NOAC=new oral anticoagulant. RR=risk ratio. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range
Source: Ruff, Giugliano, Braunwald, et al. (2014). Figure 4, page 959.

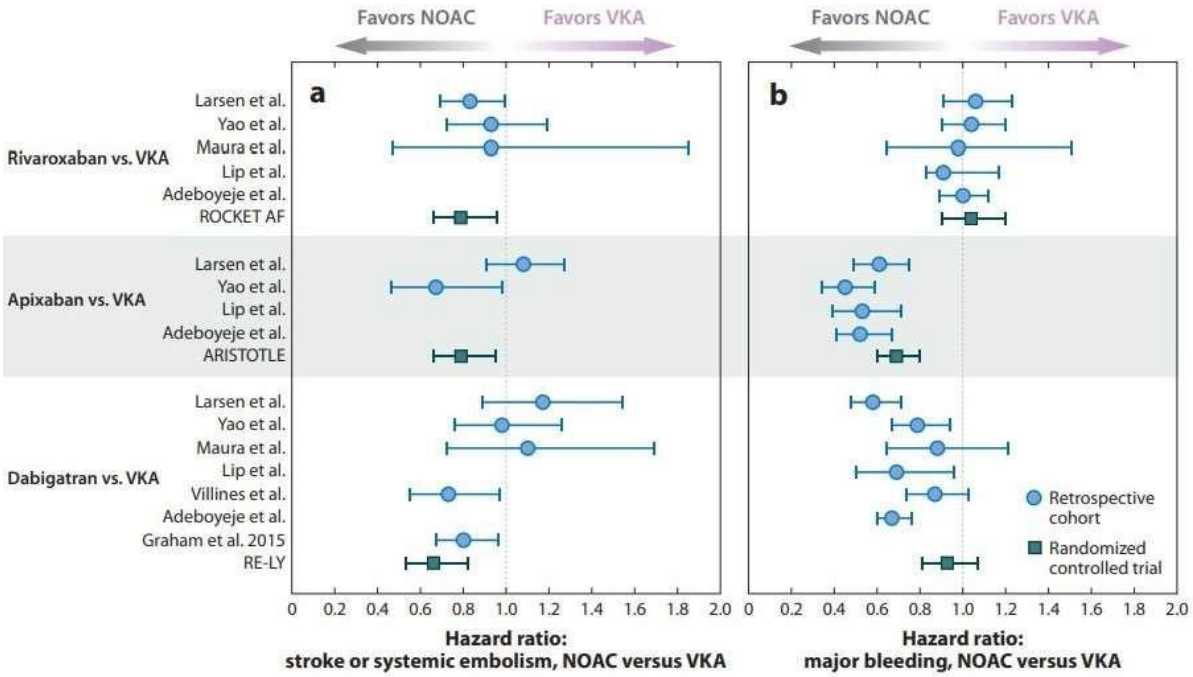


Figure 2 Comparative effectiveness (panel a) and safety (panel b) of non–vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin (vitamin K antagonist, VKA) in selected observational studies and pivotal clinical trials. Observational studies, in general, have overestimated the effectiveness of NOACs and underestimated their safety compared with pivotal randomized clinical trials.
Source: Fanaroff & Ohman (2019) Figure 4, page 8.

Results

**Clinical Results Intention to Treat**

Table 1

**Clinical Data from Original CPAMS Study**

| Clinical Data Variable | Full-Year Sample Mean/% | Full-Year Sample Std.Dev. | Last Five-Months Sample Mean/% | Last Five-Months Sample Std. Dev. |
|---|---|---|---|---|
| TTR | 68.75 | 16.93 | 75.35 | 21.18 |
| % INR in range | 62.90 | 16.61 | 72.03 | 20.81 |
| % INR below range | 19.49 | 13.80 | 17.42 | 17.53 |
| % INR over range | 17.62 | 12.59 | 10.55 | 13.65 |
| % INR <1.5 | 2.85 | 6.19 | 1.97 | 5.88 |
| % INR >4.0 | 4.10 | 7.65 | 1.55 | 4.82 |
| # INR tests | 19.80 | 7.74 | 7.30 | 3.11 |
| Days INR in Range | 226.75 | 77.36 | 92.56 | 29.90 |
| Days in Study | 322.00 | 78.71 | 122.27 | 22.22 |
| #observations | 928 | | 783 | |

Table 2

**Clinical Data for CPAMS Patients☆Scenario A**

| Clinical Data Variable | Full-Year Sample Mean/% | Full-Year Sample Std.Dev. | Last Five-Months Sample Mean/% | Last Five-Months Sample Std. Dev. |
|---|---|---|---|---|
| TTR | 73.15 | 13.83 | 83.89 | 16.04 |
| % INR in range | 66.72 | 14.38 | 79.33 | 17.88 |
| % INR below range | 17.75 | 12.70 | 12.55 | 14.40 |
| % INR over range | 15.53 | 10.11 | 8.12 | 11.52 |
| % INR <1.5 | 2.07 | 4.40 | 0.99 | 4.03 |
| % INR >4.0 | 3.00 | 4.81 | 0.86 | 3.55 |
| # INR tests | 19.67 | 7.05 | 6.75 | 1.98 |
| Days INR in Range | 244.05 | 65.74 | 103.41 | 23.84 |
| Days in Study | 332.13 | 61.51 | 123.62 | 17.90 |
| #observations | 595 | | 514 | |

Table 3

**Intention-to-treat sample sizes and Scenario proportions**

| Sample/Scenario | Sample | Proportion CPAMS Full-Year | Proportion CPAMS 5-month | Proportion To NOACs |
|---|---|---|---|---|
| CPAMS full-year sample | 928 | 1.00 | - | |
| CPAMS five-month sample | 783 | 0.84 | 1.00 | |
| Scenario A full-year sample | 595 | 0.64 | - | 0.36 |
| Scenario A five-month sample | 514 | 0.55 | 0.66 | 0.34 |

## Costs

Table 4

**Pharmaceutical/Monitoring Costs^**

| Pharmaceutical/Monitoring | Monthly Costs | | |
|---|---|---|---|
| | | Generic Prices | |
| | Formulary Price | 75% Price~ | 25% Price~ |
| Apixaban | $ 99.38 | $ 74.53 | $ 24.84 |
| Rivaroxaban | $ 86.38 | $ 64.79 | $ 21.60 |
| Dabigatran | $ 76.29 | $ 76.29 | $ 25.43 |
| Edoxaban | $ 88.97 | $ 66.73 | $ 22.24 |
| Warfarin | $ 6.11 | $ 6.11 | $ 6.11 |
| CPAMS Monitor | $ 50.00 | $ 50.00 | $ 50.00 |

^dispensing fees are assumed similar across drugs and thus not included in calculations. Dosages are: Apixaban: 5 mg BID; Rivoraban: 20 mg OD; Dabigatran: 150 mg BID; Edoxaban: (Giugliano, Ruff, Braunwald,et al., 2013) 60 mg, OD. Mean warfarin dose from CPAMS data. Pharmaceutical prices were calculated for the year then divided by 12 to obtain a monthly price. ~Generic price range is assumed to be 75% and 25% of the original formulary brand name cost except Dabigatran which is now available at single generic price and warfarin which has many generic forms.

Table 5

**Estimated Monthly Treatment Costs for Scenarios (/patient/month)**

| CPAMS Comparators | | | | |
|---|---|---|---|---|
| Full-Year Sample | $56.11 | | | |
| 5-Month Sample | $56.11 | | | |
| Scenario A | **Apixaban** | **Rivaroxaban** | **Dabigatran** | **Edoxaban** |
| Full-Year Sample | $67.75 | $64.25 | $61.54 | $64.95 |
| 5-Month Sample | $67.26 | $63.91 | $61.31 | $64.57 |
| Scenario B | $99.38 | $86.38 | $76.29 | $88.97 |

Cost includes XX proportion of patients in CPAMS and XX proportion of patients on NOACs (see table 3).
Costs include NSDHW payment and pharmaceutical costs for CPAMS and pharmaceutical costs for NOACs.
Medical treatment other than adverse events (see tables 6, 7, 8) are assumed similar across treatments.

Table 6

**Adverse Events* per patient per year  Warfarin given TTR**

| TTR | IS | HS | SE | MBEHS | CRNB | MBld |
|---|---|---|---|---|---|---|
| 55% | 0.0136 | 0.0048 | 0.0015 | 0.0290 | 0.0488 | 0.1324 |
| 60% | 0.0125 | 0.0044 | 0.0014 | 0.0289 | 0.0485 | 0.1317 |
| 65% | 0.0115 | 0.0040 | 0.0012 | 0.0287 | 0.0483 | 0.1310 |
| 70% | 0.0104 | 0.0037 | 0.0011 | 0.0286 | 0.0480 | 0.1303 |
| 75% | 0.0094 | 0.0033 | 0.0010 | 0.0284 | 0.0478 | 0.1296 |
| 80% | 0.0083 | 0.0029 | 0.0009 | 0.0283 | 0.0475 | 0.1290 |
| 85% | 0.0073 | 0.0026 | 0.0008 | 0.0281 | 0.0473 | 0.1283 |
| 90% | 0.0062 | 0.0022 | 0.0007 | 0.0280 | 0.0470 | 0.1276 |

Notes: TTR=Time in Therapeutic Range; IS=Ischemic stroke; HS=hemorrhagic stroke; SE=systemic embolism; MBEHS=Major Bleed except HS; CRNB=Clinically Relevant Non-major Bleed; MBld=Minor Bleed.;
*Source: Amin et al., 2014

Table 7

**Adverse Events per patient per year  NOACs**

| NOAC | IS | HS | SE | MBEHS | CRNB | MBld |
|---|---|---|---|---|---|---|
| Api* | 0.0140 | 0.0022 | 0.0012 | 0.0207 | 0.0330 | 0.0935 |
| Riv* | 0.0170 | 0.0026 | 0.0003 | 0.0320 | 0.0504 | 0.1527 |
| Dab* | 0.0094 | 0.0011 | 0.0009 | 0.0297 | 0.0441 | 0.1198 |
| Edo~ | 0.0125 | 0.0026 | 0.0008 | 0.0275 | 0.0400 | 0.1110 |

Notes: IS=Ischemic stroke; HS=hemorrhagic stroke; SE=systemic embolism; MBEHS=Major Bleed except HS; CRNB=Clinically Relevant Non-major Bleed; MBld=Minor Bleed.;
Api=Apixaban, Riv=Rivaroxaban Dab=Dabigatran Edo=Edoxaban
*Amin et al., 2014
~Giugliano, Ruff, Braunwald,et al., 2013.

Table 8

**Annual Costs ($2018 CDN) per Event**^

| IS | HS | SE | MBEHS | CRNB | MBld |
|---|---|---|---|---|---|
| $71,455 | $75,453 | $17,120 | $21,465 | $897.50 | $45.28 |

^From Original CPAMS Costing Study. Canadian Costs IS and HS (Goere et al., 2005); SE (Regier et al., 2006); MBEHS (Brown et al., 2007; CADTH, 2009); CRNB (Nova Scotia Health Authority, 2019); MBld (Amin et al., 2014).

Table 9

Annual Event Costs per patient for Different Scenarios and samples ^

| **Scenarios** | Event Costs |
|---|---|
| **Full-Year Sample** | |
| CPAMS (comparator) | $ 1,730.39 |
| Scenario A with APIXABAN | $ 1,645.14 |
| Scenario A with RIVAROXABAN | $ 1,820.10 |
| Scenario A with DABIGATRAN | $ 1,568.51 |
| Scenario A with EDOXABAN | $ 1,671.34 |
| **5-Month Sample** | |
| CPAMS (comparator) | $ 1,588.29 |
| Scenario A with APIXABAN | $ 1,493.19 |
| Scenario A with RIVAROXABAN | $ 1,660.70 |
| Scenario A with DABIGATRAN | $ 1,419.83 |
| Scenario A with EDOXABAN | $ 1,518.27 |
| **All patients prescribed NOACs** | |
| Scenario B with APIXABAN | $ 1,661.30 |
| Scenario B with RIVAROXABAN | $ 2,148.89 |
| Scenario B with DABIGATRAN | $ 1,447.74 |
| Scenario B with EDOXABAN | $ 1,734.30 |

^Scenario costs extrapolated linearly given TTRs and probabilities (see table 6,7,8).

Table 10

Scenarios A and B compared to CPAMS (full-year and five-month sample)
NSDHW payment of $50 per month per patient for CPAMS
CPAMS is Comparator^

| **Full-year Sample** | Difference Event Costs | Difference Treatment Costs | Costs-Benefits* |
|---|---|---|---|
| Scenario A - APIXABAN | -$ 7.10 | $ 11.65 | $ 4.54 |
| Scenario A - RIVAROXABAN | $ 7.48 | $ 8.15 | $ 15.62 |
| Scenario A - DABIGATRAN | -$ 13.49 | $ 5.43 | -$ 8.06 |
| Scenario A - EDOXABAN | -$ 4.92 | $ 8.84 | $ 3.92 |
| **LAST 5 MONTHS Sample** | | | |
| Scenario A - APIXABAN | -$ 7.92 | $ 11.15 | $ 3.23 |
| Scenario A - RIVAROXABAN | $ 6.03 | $ 7.80 | $ 13.83 |
| Scenario A - DABIGATRAN | -$ 14.04 | $ 5.20 | -$ 8.84 |
| Scenario A - EDOXABAN | -$ 5.83 | $ 8.47 | $ 2.63 |
| **Full-year Sample** | | | |
| Scenario B - APIXABAN | -$ 5.76 | $ 43.27 | $ 37.51 |
| Scenario B - RIVAROXABAN | $ 34.87 | $ 30.27 | $ 65.15 |
| Scenario B - DABIGATRAN | -$ 23.55 | $ 20.18 | -$ 3.37 |
| Scenario B - EDOXABAN | $ 0.33 | $ 32.86 | $ 33.19 |
| **LAST 5 MONTHS Sample** | | | |
| Scenario B - APIXABAN | $ 6.08 | $ 43.27 | $ 49.36 |
| Scenario B - RIVAROXABAN | $ 46.72 | $ 30.27 | $ 76.99 |
| Scenario B - DABIGATRAN | -$ 11.71 | $ 20.18 | $ 8.47 |
| Scenario B - EDOXABAN | $ 12.17 | $ 32.86 | $ 45.03 |

^Difference = Alternative - CPAMS --> Negative ==> CPAMS > Alternative (event costs or treatment costs). Rounding may occur.

*lower event costs are a positive benefit; higher event costs are a negative benefit

Alternative is Dominant: More effective & Less costly.

Alternative is Cost Effective: More Effective & More Costly but Benefits>Costs.

Alternative is Not Cost Effective: More Effective and More Costly (Benefits<Costs).

Alternative is Not Effective: Less Effective but Less Costly; Less Effective and More Costly

Table 11

Scenario B compared to Scenario A (full-year and 5-month sample)
NSDHW payment of $50 per month per patient for CPAMS
Scenario A is Comparator^ (/patient/month)

| **Full-year Sample** | Event Costs | Treatment Costs | Costs-Benefits* |
|---|---|---|---|
| Scenario B - APIXABAN | $ 1.35 | $ 31.63 | $ 32.97 |
| Scenario B - RIVAROXABAN | $ 27.40 | $ 22.13 | $ 49.52 |
| Scenario B - DABIGATRAN | -$ 10.06 | $ 14.75 | $ 4.69 |
| Scenario B - EDOXABAN | $ 5.25 | $ 24.02 | $ 29.27 |
| **Last 5 Months Sample** | | | |
| Scenario B - APIXABAN | $ 14.01 | $ 32.12 | $ 46.13 |
| Scenario B - RIVAROXABAN | $ 40.68 | $ 22.47 | $ 63.15 |
| Scenario B - DABIGATRAN | $ 2.33 | $ 14.98 | $ 17.31 |
| Scenario B - EDOXABAN | $ 18.00 | $ 24.40 | $ 42.40 |

^Difference = Alternative - CPAMS --> Negative ==> CPAMS > Alternative (events or treatment costs).

*lower event costs are a positive benefit; higher event costs are a negative benefit

Alternative is Dominant: More effective & Less costly.

Alternative is Cost Effective: More Effective & More Costly but Benefits>Costs.

Alternative is Not Cost Effective: More Effective and More Costly (Benefits<Costs).

Alternative is Not Effective: Less Effective but Less Costly; Less Effective and More Costly

Table 12

Sensitivity Analysis: Scenarios compared to CPAMS when generics available (/patient/month)

CPAMS is the Comparator^

| | Costs-Benefits* | |
|---|---|---|
| | 75% Generic | 25% Generic |
| **FULL-YEAR SAMPLE** | | |
| Scenario A with APIXABAN | -$ 2.15 | -$ 15.52 |
| Scenario A with RIVAROXABAN | $ 9.81 | -$ 1.81 |
| Scenario A with DABIGATRAN | -$ 8.06 | -$ 21.75 |
| Scenario A with EDOXABAN | -$ 2.06 | -$ 14.04 |
| **LAST 5-MONTH SAMPLE** | | |
| Scenario A with APIXABAN | -$ 3.18 | -$ 15.98 |
| Scenario A with RIVAROXABAN | $ 8.27 | -$ 2.86 |
| Scenario A with DABIGATRAN | -$ 8.84 | -$ 21.94 |
| Scenario A with EDOXABAN | -$ 3.10 | -$ 14.56 |
| **FULL-YEAR SAMPLE** | | |
| Scenario B with APIXABAN | $ 12.66 | -$ 37.03 |
| Scenario B with RIVAROXABAN | $ 43.55 | $ 0.36 |
| Scenario B with DABIGATRAN | -$ 3.37 | -$ 54.23 |
| Scenario B with EDOXABAN | $ 10.95 | -$ 33.54 |
| **LAST 5-MONTH SAMPLE** | | |
| Scenario B with APIXABAN | $ 24.51 | -$ 25.18 |
| Scenario B with RIVAROXABAN | $ 55.39 | $ 12.20 |
| Scenario B with DABIGATRAN | $ 8.47 | -$ 42.39 |
| Scenario B with EDOXABAN | $ 22.79 | -$ 21.70 |

^Difference = Scenario A - CPAMS.

*lower event costs are a positive benefit; higher event costs are a negative benefit

Alternative is Dominant: More effective & Less costly.

Alternative is Cost Effective: More Effective & More Costly but Benefits>Costs.

Alternative is Not Cost Effective: More Effective and More Costly (Benefits<Costs).

Alternative is Not Effective: Less Effective but Less Costly; Less Effective and More Costly

Table 13

Scenario B compared to Scenario A when generics available (/patient/month)
Scenario A is the Comparator^

| | Costs-Benefits* | |
|---|---|---|
| | 75% Generic | 25% Generic |
| **Full-Year Sample** | | |
| Scenario B with APIXABAN | $ 14.81 | -$ 21.51 |
| Scenario B with RIVAROXABAN | $ 33.74 | $ 2.17 |
| Scenario B with DABIGATRAN | $ 4.69 | -$ 32.49 |
| Scenario B with EDOXABAN | $ 13.01 | -$ 19.50 |
| **Last 5 Months 5-Month Sample** | | |
| Scenario B with APIXABAN | $ 27.68 | -$ 9.20 |
| Scenario B with RIVAROXABAN | $ 47.12 | $ 15.06 |
| Scenario B with DABIGATRAN | $ 17.31 | -$ 20.45 |
| Scenario B with EDOXABAN | $ 25.89 | -$ 7.14 |

^Difference = Scenario B – Scenario A.

*lower event costs are a positive benefit; higher event costs are a negative benefit

Alternative is Dominant: More effective & Less costly.

Alternative is Cost Effective: More Effective & More Costly but Benefits>Costs.

Alternative is Not Cost Effective: More Effective and More Costly (Benefits<Costs).

Alternative is Not Effective: Less Effective but Less Costly; Less Effective and More Costly

Table 14

5-year Costing for Dabigatran==> Scenario B relative to Scenario A*+

| | Y1 | Y2 | Y3 | Y4 | Y5 | /patient/5 years |
|---|---|---|---|---|---|---|
| Full-year Sample | $ 56.28 | $ 101.49 | $ 96.87 | $ 92.66 | $ 88.80 | $ 436.10 |
| Full-year Sample (25% generic) | -$ 389.88 | -$ 271.20 | -$ 258.87 | -$ 247.62 | -$ 237.30 | -$ 1,404.87 |
| 5-month Sample | NOT EFFECTIVE^ | | | | | |
| 5-month Sample (25% generic) | NOT EFFECTIVE^ | | | | | |

*Higher TTRs in Scenario A after year 1 as the mean TTRs for those able to maintain TTR>64 is higher in years 2 through 5.

+5% discount rate. Positive value indicates Scenario B (all patients prescribed NOACs is more costly over 5 years)

^Given the higher TTRs in the 5-month sample Scenario B is not as effective as Scenario A thus not cost effective

Note: costs discounted using 5% discount rate.