Medicines Adverse Reactions Committee

Meeting date	5 December 2019	Agenda item	3.2.2
Title	**Direct acting oral anticoagulants and risk of recurrent thrombotic events**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	**PHARMAC funded?**
Apixaban	Eliquis (2.5, 5 mg)	Pfizer New Zealand Limited	N
Dabigatran	Pradaxa Capsule (75, 110, 150 mg)	Boehringer Ingelheim (NZ) Ltd	Y
Rivaroxaban	Xarelto (10, 15, 20 mg)	Bayer New Zealand Limited	Y
* the products in this table are those available (status = consent given) at 8 October 2019			
Previous MARC meetings	Apixaban: Not previously discussed by the MARC. Dabigatran: • 176th meeting (6 December 2018) - Dose reductions for Pradaxa (dabigatran etexilate): DVT/PE indications • 175th meeting (13 September 2018) - Dabigatran and gout, gout aggravation and gout-like symptoms • 170th meeting (8 June 2017) - The risk of haemorrhage from concomitant use of statins and dabigatran • 148th meeting (8 December 2011) - Update on the safety profile of dabigatran (Pradaxa) • 147th meeting (8 September 2011) - Dabigatran safety profile Rivaroxaban: • 149th meeting (8 March 2012) - Risk management plan: rivaroxaban (Xarelto)		
International action	There has been some international action on this topic with a focus on patients with antiphospholipid syndrome however not more generally. TGA: Direct acting oral anticoagulants and risk of recurrent thrombotic events (in patients with antiphospholipid syndrome) (www.tga.gov.au/publication-issue/direct-acting-oral-anticoagulants-and-risk-recurrent-thrombotic-events). MHRA: www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-increased-risk-of-recurrent-thrombotic-events-in-patients-with-antiphospholipid-syndrome		
Prescriber Update	www.medsafe.govt.nz/profs/PUArticles/September2019/Direct-acting-oral-anticoagulants-and-antiphospholipid-syndrome.htm (as above this is specifically in patients with antiphospholipid syndrome not generally).		
Classification	Prescription medicine		
Usage data	See section 2.5.		
Advice sought	**The Committee is asked to advise:** • whether there is sufficient evidence of an association between apixaban, dabigatran or rivaroxaban and a rebound effect, and if so		

	o are data sheet updates required? o does this topic require any further communication, other than MARC's remarks in *Prescriber Update*?

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1 PURPOSE

In March 2019 at the 177th meeting, the Medicines Adverse Reactions Committee (MARC) discussed a case (CARM ID: 130309) where a patient suffered a thromboembolic stroke following cessation of dabigatran treatment two weeks prior. The Committee considered a potential rebound effect may occur upon stopping dabigatran. The Committee requested that Medsafe further investigates this safety concern.

The minutes of the 177th MARC meeting are available on the Medsafe website.

2 BACKGROUND

2.1 Apixaban, dabigatran and rivaroxaban

Apixaban, dabigatran and rivaroxaban are direct acting oral anticoagulants (DOACs) that are available in New Zealand. Anticoagulants are agents that inhibit one or more steps in the coagulation process, by varying mechanisms [1]. DOACs is used to collectively refer to direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban and rivaroxaban) [1]. These medicines block pro-coagulant activities involved in the generation of a fibrin clot [1].

This report focusses on apixaban, dabigatran and rivaroxaban as edoxaban is not currently available in New Zealand.

2.1.1 Apixaban

Apixaban is a reversible, direct factor Xa inhibitor [2]. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development [2].

Apixaban (brand name Eliquis) is indicated for the [2]:

- Prevention of venous thromboembolic events (VTE) in adults who have undergone elective total hip or knee replacement surgery
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adult patients
- Prevention of recurrent DVT and PE in adults.

2.1.2 Dabigatran

Dabigatran etexilate is a prodrug which is rapidly absorbed and converted to dabigatran after oral administration [3]. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor [3]. Through the inhibition of thrombin, dabigatran prevents the development of thrombus [3].

Dabigatran (brand name Pradaxa) is indicated for the [3]:

- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with non-valvular atrial fibrillation
- Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery
- Treatment of acute DVT and/or PE
- Prevention of recurrent acute DVT and/or PE and related death.

2.1.3 Rivaroxaban

Rivaroxaban is a selective direct factor Xa inhibitor [4].

Rivaroxaban (brand name Xarelto) is indicated for the [4]:

- Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors

- Treatment of DVT and PE and for the prevention of recurrent DVT and PE.

It has been reported that apixaban, dabigatran and rivaroxaban carry a risk of thrombotic events after *premature* discontinuation [1].

2.2 Vascular disorders

2.2.1 Venous thromboembolism

Venous thromboembolism is a term used to describe deep vein thrombosis (DVT) and pulmonary embolism (PE) [5]. A DVT occurs when a thrombus forms in a vein, most commonly in the legs, thighs or pelvis [5]. The blood clot can limit blood flow through the affected vein. DVTs are serious and potentially life threatening [5]. Blood clots can also form in other parts of the body and if the blood clot travels through the venous system and gets lodged in the lung it is called a PE [5].

3 to 6 months of anticoagulant treatment has been shown to be effective at reducing the risk of recurrent VTE but the clinical benefit is not maintained when anticoagulation treatment is stopped [6]. For patients with unprovoked VTE the optional duration of anticoagulant treatment is uncertain [6].

2.2.2 Stroke

The Stroke Foundation New Zealand define stroke as 'a sudden interruption of blood flow to part of the brain causing it to stop working and eventually damaging brain cells' [7]. The two main types of stroke are ischaemic and haemorrhagic [8]. Ischaemic stokes can be thrombotic or embolic [8]. Haemorrhagic strokes can be intracerebral or subarachnoid [8].

Ischemic stroke: a blockage in one of the blood vessels that supply oxygen and other nutrients to the brain [8]. These can be thrombotic (a problem within an artery that supplies blood to the brain) or embolic (when a blood clot breaks loose and gets stuck in a smaller blood vessel) [8].

Haemorrhagic stroke: these occur when a blood vessel in the brain leaks or ruptures causing bleeding in or around the brain [8]. When bleeding occurs within the brain it is called an intracerebral haemorrhage and when bleeding occurs on the surface of the brain it is called a subarachnoid haemorrhage [8].

2.3 Recurrent events

Granger et al, 1995, defined a true rebound as an increase followed by a subsequent decrease, in thrombin activity after discontinuation [9].

Patients with a first unprovoked VTE have a higher risk of recurrence compared to patients with VTE due to a major risk factor [6]. A weak recommendation is to discontinue anticoagulation treatment after 3 to 6 months in patients with VTE due to a major risk factor and to continue treatment for an extended time in patients with unprovoked VTE. Uncertainty remains over treating patients with a first episode of unprovoked VTE and whether they should receive indefinite anticoagulation (risk of major bleeding) or can stop treatment after the initial 3 to 6 months (long term risk of recurrent VTE if anticoagulation is discontinued) [6].

Randomised trials, meta-analyses and long-term epidemiologic studies of recurrence risk after cessation of a conventional course of anticoagulation suggest that prolonged periods of anticoagulation successfully reduces the rate of VTE recurrence [10]. Most studies are inadequately powered to assess mortality [10].

Using data from randomised control trials and meta-analyses, The American College of Chest Physicians estimated the risk of recurrence (see table below) [10].

[redacted]

Some clinical prediction rules have been developed to estimate the risk of recurrence in patients with unprovoked VTE following cessation of a conventional (3-6 month) course of anticoagulation but none have been validated for routine use in clinical practice [10]. It has been reported that VTE has the highest risk of recurrence in the first six months to one year following the first event and the annual rate then declines. However it is cumulative for many years beyond that [10]. For example a population-based cohort study of 1719 patients diagnosed with VTE estimated cumulative percentages of VTE recurrence as the following: 7 days (0.2 percent), 30 days (1 percent), and 180 days (4 percent), 1 year (6 percent), and 10 years (18 percent) [10].

Prolonged periods of anticoagulation, leading to a decrease in VTE recurrence, needs to be balanced up against the increased risk of bleeding [10]. Indefinite anticoagulation is most likely to benefit those with an increased risk of recurrence and a low risk of bleeding [10]. It is challenging however to precisely categorise a patient as having a provoked or unprovoked VTE or as having a high or low risk of bleeding and it is likely the risk of both recurrence and bleeding is on a spectrum that requires careful consideration by both the clinician and patient [10].

Hoffman and Monroe, 2017, report that a key property of NOACs is their reversibility [11]. They report that the consequences of the reversibility of a coagulation protease inhibitor are not clear but they make a hypothesis. The authors state that NOACs have short half-lives compared to vitamin K antagonists and therefore plasma levels rise and fall between doses leading to the rising and falling of the extent of thrombin inhibition. When the drug level falls, thrombin activity can increase and potentially this could have procoagulant activity and cause a rebound hypercoagulability if dabigatran levels fall sufficiently [11].

2.4 Product Information

2.4.1 New Zealand Data Sheets

2.4.1.1 Dabigatran

The data sheet for Pradaxa currently states no rebound effect was observed in the RE-SONATE study [3].

Section 5.1 of the Pradaxa data sheet discusses the RE-SONATE study and says the study included observational follow-up for 12 months after the conclusion of treatment. The study indicated that the initial treatment effect of dabigatran etexilate was sustained as after discontinuation of the medicine, the effect was maintained until the end of follow-up (12 months). No rebound effect was observed [3].

2.4.1.2 Apixaban

The current Eliquis data sheet does not mention rebound effect [12].

2.4.1.3 Rivaroxaban

The current Xarelto data sheet does not mention rebound effect [4].

2.4.2 International Product Information

2.4.2.1 FDA, United States

The product label for Xarelto (rivaroxaban), Pradaxa (dabigatran) and Eliquis (apixaban) include a black box warning of an increased risk of thrombotic events after premature discontinuation. The warning states 'Premature discontinuation of any oral anticoagulant, including [medicine], increases the risk of thrombotic

events. To reduce this risk, consider coverage with another anticoagulant if [medicine] is discontinued for a reason other than pathological bleeding or completion of a course of therapy.'

Further information regarding this risk is stated in the full prescribing information for Xarelto (Annex 1).

2.4.2.2 MHRA, United Kingdom

The Summary of medicinal Product Characteristics (SmPC) for Pradaxa mentions rebound in sections 4.9 (overdose) and 5.1 (pharmacodynamic properties).

Section 4.9 – management of bleeding complications.

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited.

Section 5.1

RE-SONATE study - The study included observational follow-up for 12 months after the conclusion of treatment. After discontinuation of study medication the effect was maintained until the end of the follow-up, indicating that the initial treatment effect of dabigatran etexilate was sustained. No rebound effect was observed. At the end of the follow-up VTE events in patients treated with dabigatran etexilate was 6.9% vs. 10.7% among the placebo group (hazard ratio 0.61 (95% CI 0.42, 0.88), p=0.0082).

2.4.2.3 Health Canada

Pradaxa is the only product monograph to mention rebound effect, out of the three DOACs viewed. As in the New Zealand and UK product information, the sentence relates to the RE-SONATE study.

2.5 Usage

2.5.1 Apixaban

Not funded so no data is available in the Ministry of Health Pharmaceutical Collection.

2.5.2 Dabigatran

Table 2 The number of people who received a dispensing of dabigatran (all strengths) (from the Pharmaceutical data web tool) [13]

Year	Number of people who received a dispensing
2014	26183
2015	34361
2016	45840
2017	58046
2018	66681

Source: Ministry of Health's Pharmaceutical Collection, extracted on 26 March 2019

2.5.3 Rivaroxaban

Table 3 The number of people who received a dispensing of rivaroxaban (from the Pharmaceutical data web tool) [13]

Year	Number of people who received a dispensing
2014	1052
2015	1400
2016	1329

2017	1418
2018	9135

Source: Ministry of Health's Pharmaceutical Collection, extracted on 26 March 2019

Comment:

In 2018, 66,681 people received a dispensing of dabigatran. If all patients were taking dabigatran for unprovoked VTE, based the rates of recurrence (see Table 1) for the first episode of unprovoked VTE after stopping treatment (10% first year, 5% year after), we would expect to see 6668 people in the first year experiencing recurrent VTE (if none were on indefinite coagulation). Note that this would be a maximum estimate.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Dabigatran

3.1.1.1 Vene et al, 2016 [14]

The aim of this study was to investigate the incidence of thromboembolic events in patients with non-valvular atrial fibrillation treated with non-vitamin K/new oral anticoagulants (NOAC) who had a discontinuation or cessation of treatment in comparison to patients on continuous treatment.

The study notes that the half-life of NOAC is short compared to warfarin meaning interruption of treatment rapidly reverses the anticoagulant effect.

Registry data from 866 patients with non-valvular atrial fibrillation (AF not associated with artificial heart valves or mitral stenosis) taking dabigatran or rivaroxaban were analysed for thromboembolic events and survival. Patients who had temporary or permanent discontinuation of NOAC were compared to patients on continuous NOAC treatment. The Trombo registry is a registry of outpatients on anticoagulant treatment from a region of Slovenia serving about 700000 inhabitants.

Out of the 866 patients, 84 patients had temporary interruption and 77 had permanent cessation of NOAC therapy (meaning 705 patients were treated without interruption). 84 patients had 98 temporary treatment interruptions with a median duration of 7 days (Figure 1).

Anticoagulation treatment was intentionally stopped in 46 patients on NOAC (34% of all anticoagulant treatment discontinuations), 1–2 months after successful conversion of atrial fibrillation into sinus rhythm in patients with a low thromboembolic risk and a $CHADS_2$ score of 0–1. For 5 patients, death was the cause of permanent discontinuation of NOAC treatment (1 death due to ischemic stroke, 1 due to myocardial infarction, 3 due to non-cardiovascular cause). An additional 26 patients were switched from NOAC to long-term warfarin because of worsening renal function, or to low molecular weight heparin because of newly diagnosed malignancies.

Two thromboembolic events occurred during interruption of NOAC treatment among patients with persistent / chronic AF and 5 events occurred among 64 patients with paroxysmal AF. However, the authors could not prove a difference in the incidence of thromboembolic events between patients with persistent/chronic or paroxysmal AF: 12.2 (95%CI 3.2– 51.6) events per 100 patient years of observation (pty) vs. 31.0 events (95%CI 13.0–78.2) per 100 pty, p = 0.269.

In the subgroup of patients with an interruption due to bleeding there were 4 thromboembolic events among 10 patients with a cumulative follow up of 0.59 pty, while for planned interruptions due to invasive procedures there was only 1 event among 69 patients with a cumulative follow up of 0.93 pty. The proportion of thromboembolic events during NOAC interruption among bleeders was significantly higher than in those with planned invasive procedures however when the longer duration of interruption was taken into account, the difference in incidence was not significant (6.7 (95% CI 2.5–17.9) per pty vs. 1.1 (95% CI 0.15–7.6) per pty, p =

0.40). The different proportions of patients suffering a thromboembolic event after NOAC discontinuation because of bleeding or due to planed invasive procedures could not be explained by different baseline risk. The authors found no significant differences in age, proportion of females, HAS BLED score ≥ 2 or distribution of $CHADS_2$ scores. The authors state that the association between bleeding and increased thrombotic risk is biologically plausible, since vascular injury activates platelets and coagulation.

In patients without interruptions, the incidence of thromboembolic events was 1.0 (95% CI 0.4–2.1) per 100 patient-years, while in patients with interruption/cessation the rate of thromboembolic events was 21.6 (95% CI 10.3–45.2) per 100 patient-years, $p < 0.001$. There was a distinct clustering of thromboembolic events in the first weeks of NOAC discontinuation with the median occurring on day 14 (range 1–37 days) after discontinuation.

[redacted]

Seven thromboembolic events (95% CI 3.3–14.7 events) occurred during NOAC interruption/cessation among 161 patients with a cumulative follow-up of 32.5 patient years of observation (pty), while 6 (95% CI 2.7–13.4) thromboembolic events occurred during uninterrupted NOAC treatment among 705 patients with a cumulative follow-up of 621.7 pty. The incidence of thromboembolic events in patients with interruption/cessation of any cause was thus 21.6 (95% CI 10.3–45.2) per 100 pty, while in patients without interruptions it was 1.0 (95% CI 0.4–2.1) per 100 pty, $p < 0.001$.

The observed incidence of thromboembolic events during interruptions of treatment was significantly higher than the predicted "natural-course" incidence based on the $CHADS_2$ scores and lengths of observation (Table 4). On the other hand, in patients with uninterrupted NOAC treatment the incidence of thromboembolism was significantly lower than the incidence predicted by the $CHADS_2$ score for untreated patients (Table 4).

[redacted]

The study notes thrombin generation is increased in the presence of low concentrations of dabigatran and no such effect has been noted with rivaroxaban. A potential for rebound hypercoagulability to be a possible

reason for the increased risk after discontinuation was highlighted, as one of the patients had a very low stroke risk and no obvious inducers of a hypercoagulable states but suffered an ischemic stroke ten days after dabigatran discontinuation. One of the limitations of the study is that dabigatran and rivaroxaban were not able to be analysed separately due to the low number of events.

Planned invasive procedures, the most common causes of temporary interruptions of NOAC treatment, were short, with a mean duration of only 4 days. The observed incidence of thromboembolic events of 1.1 (95% CI 0.15–7.6) per pty is consistent with observations of other authors who report low risk (around 1%) of post-procedural stroke, systemic embolism or cardiovascular events during 30-day follow up after brief interruptions of NOAC or warfarin treatment due to invasive procedures, indicating that short periprocedural interruptions of any type of oral anticoagulation in daily care are safe.

The authors concluded that dabigatran and rivaroxaban offered good protection against thromboembolic events during treatment, but interruption of NOAC treatment increased the short-term thromboembolic risk more than 20-fold. The proportion of patients who suffered a thromboembolic event was higher among patients with interruptions due to bleeding in comparison to those with interruption due to planned invasive procedures.

Comments:

The authors don't mention the relevance for including patients who switched to warfarin.

The study authors were not able to explain the increase in thromboembolic events during NOAC interruption among bleeders than in those with planned invasive procedures.

The numbers were also small, so the estimate is not stable.

3.1.1.2 Thorne et al, 2012 [15]

This letter published in the BMJ raises the question of how to stop dabigatran safely if true rebound exists. The letter states that over a 6 month period, 3 cases of arterial or venous thromboembolism within one month of stopping dabigatran have been seen. The REMODEL trial suggested that stopping dabigatran does not produce a rebound thrombotic effect however others have raised this as a possibility. The letter notes that it is difficult to prove whether the events in the three cases mentions were related to rebound, resumption of events associated with the primary condition or underlying hypercoagulability. The letter concludes further studies and prospective pharmacovigilance may be needed to clarify this matter.

3.1.1.3 Weiler et al, 2014 [16]

An 84 year old man had been taking dabigatran for 3 months for non-valvular atrial fibrillation. He had been experiencing 2 days of abdominal pain, nausea and vomiting. His partial thromboplastin time confirmed a subtherapeutic level of dabigatran as he was unable to keep his medicines down due to the vomiting.

A Ct angiogram demonstrated a thrombus just beyond the origin of the superior mesenteric artery (SMA). Further findings supported a diagnosis of LV thrombus complicating MI.

The authors reported that the patient most likely experienced a small bowel obstruction attributable to adhesions from a prior surgery and as a result was unable to continue taking dabigatran. The patient subsequently experienced an acute MI complicated by an LV thrombus with embolism to the SMA. The authors state that this case highlights previously raised concerns over the possibility of rebound hypercoagulability following cessation of dabigatran.

Comments:

The authors state that this case highlights the possibility of a rebound effect however the case equally shows that anticoagulation was needed for the atrial fibrillation.

3.1.1.4 Benhayon et al, 2018 (Abstract) [17]

This study compared periprocedural heparin requirements during different pre-procedure anticoagulation regimens and the potential clinical implications.

Every case of atrial fibrillation ablation performed at their institution over the last 2 years, was retrospectively analysed. The amount of unfractionated heparin (UFH) per kilogram needed to achieve the target activated clotting time (ACT) was collected. Groups were compared based on periprocedural anticoagulation strategy (warfarin v dabigatran v rivaroxaban) and the number of doses held before the procedure.

584 patients were included. Of those 391 (67%) were on warfarin, 162 (28%) were receiving dabigatran and 31 (5%) rivaroxaban. Baseline characteristics were not significantly different.

Patients that held ≥2 doses of dabigatran needed significantly more UFH-per-kilogram-per-procedure, as compared to patients on warfarin with INR <1.5. (15% more; p=0.029).

No differences were observed between those on warfarin with INR ≤1.5 and those holding ≥2 doses rivaroxaban (p=0.56). No significant differences were observed in the rate of bleeding or TE complications between groups (P=0.18).

The authors concluded that interrupted dabigatran is associated with a significantly increased need for UFH compared to those functionally off warfarin, which may suggest a slight rebound procoagulant effect due to dabigatran interruption.

3.1.2 Direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban)

3.1.2.1 Cavallari et al, 2018 (edoxaban – not approved in New Zealand)

Oral anticoagulation is the basis of treatment for patients with atrial fibrillation to reduce the risk of cardioembolic stroke. However, one quarter of patients on warfarin interrupt the drug in the first year, for multiple reasons including bleeding, and therefore these patients don't benefit from the risk reduction for cardioembolic stroke. Given the elevation of blood markers of thrombin generation and activity seen soon after stopping warfarin, some people have argued for the existence of transient rebound hypercoagulability after discontinuing warfarin.

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial demonstrated the non-inferiority of edoxaban, an oral direct factor Xa inhibitor, compared to well-managed warfarin for the prevention of stroke/SEE in patients with moderate-to high-risk atrial fibrillation. This study is a three-arm, randomised, double-blind, double-dummy trial which compared two dose regimens of edoxaban with warfarin.

In this analysis from ENGAGE AF-TIMI 48, the authors characterised patients who interrupted study drug, examined reasons for interruption, estimated thromboembolic risk associated with interruption of study drug, and compared the outcomes after interruption of edoxaban and warfarin.

The study population included 21,105 atrial fibrillation patients with $CHADS_2$ score ≥ 2 followed for a median of 2.8 years. Eligible patients were randomly assigned, in a 1:1:1 ratio, to receive warfarin, titrated to achieve an INR of 2.0 to 3.0; higher-dose edoxaban regimen (60 mg daily, HDER) or lower-dose edoxaban (30mg daily, LDER). The edoxaban dose was halved if any of the following characteristics were present at the time of randomisation or during the trial: estimated creatinine clearance of 30 to 50ml/min, a body weight ≤ 60 kg, or the concomitant use of verapamil, quinidine or dronedarone. The primary efficacy endpoint was the time to the first stroke adjudicated and categorised as ischemic or haemorrhagic or systemic embolic events (SEE). The principal safety endpoint was major bleeding, defined by the International Society on Thrombosis and Hemostasis.

The interruption cohort was derived from the modified intention-to-treat population, i.e. 21,026 patients who took at least one dose of study drug. Patients with at least one interruption of study drug for >3 consecutive days were identified; patients with no discontinuations or discontinuations <3 consecutive days, since the latter likely had some residual anticoagulant effect, were considered to have remained "on-treatment". Clinical events were analysed during the first at-risk time window, from day 4 after last dose of study drug until day 34 or study drug resumption, whichever occurred first. Patients who received any open-label anticoagulant at any time during the first at-risk time window, including non-study vitamin K antagonists or other oral or parenteral anticoagulants, or who died before day 4 were excluded.

Events of interest in this analysis were: 1) ischemic stroke or SEE; 2) major adverse cardiac and cerebrovascular events (MACCE), defined as a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), ischemic stroke or SEE; 3) the primary net clinical outcome, a composite of stroke or SEE, major bleeding and all-cause death. Of note, the composite endpoint of ischemic stroke or SEE was the focus of this analysis since interruption of OAC should not result in an increase in the occurrence of haemorrhagic stroke. There were significant reductions in major and intracranial bleeding and cardiovascular mortality with edoxaban.

Clinical events (ischemic stroke/systemic embolism, major cardiac and cerebrovascular events [MACCE]) were analysed from day 4 after interruption until day 34 or study drug resumption. 21,026 patients (7012 warfarin; 7012 high dose edoxaban; 7002 low dose edoxaban) received at least one dose of study anticoagulant.

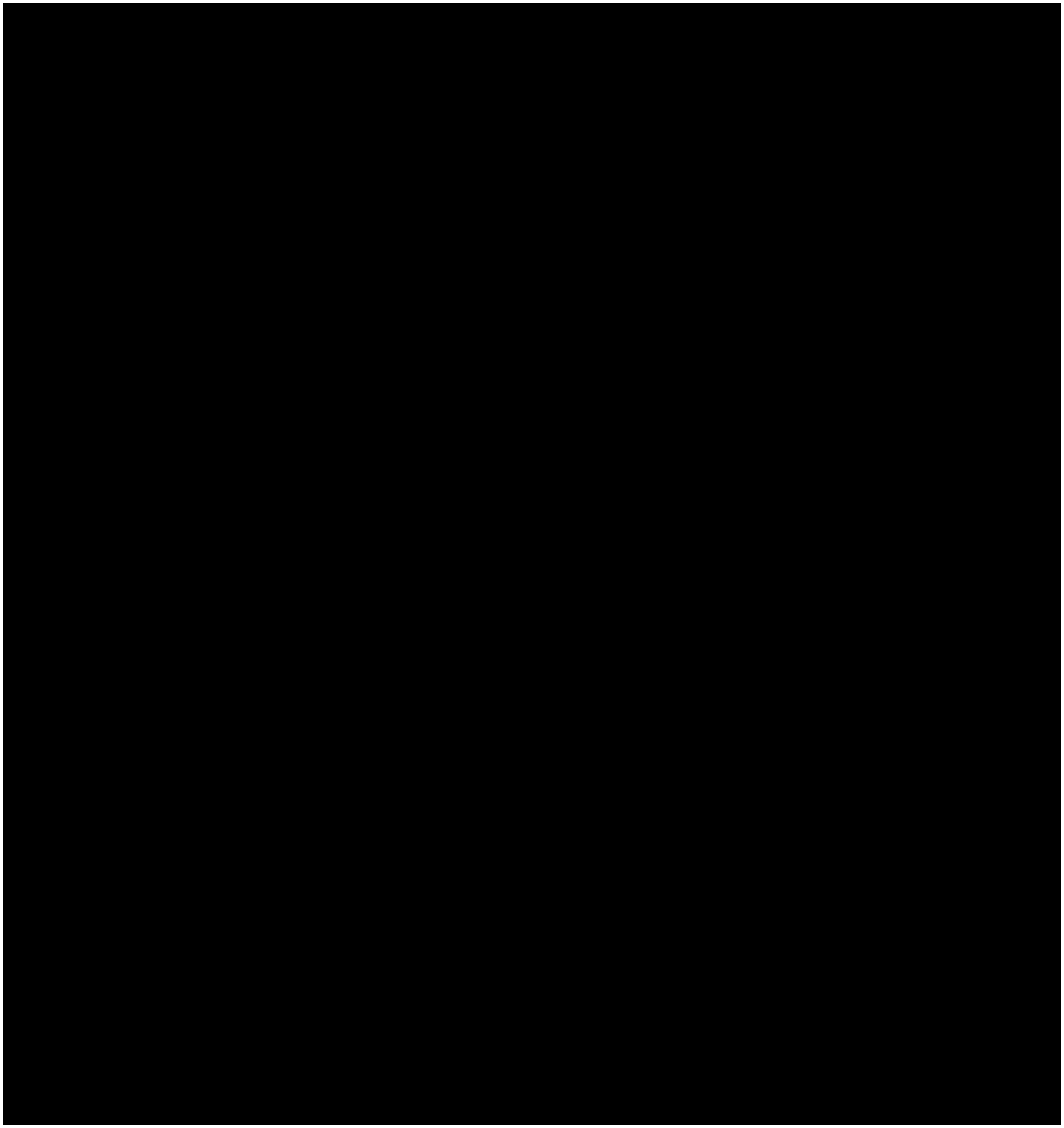
During 2.8 years median follow-up, 36.7% of patients (N = 7715) never interrupted study drug and 13,311 (63%) patients interrupted study drug for >3 days. After excluding those who received open-label anticoagulation during the at-risk window, the population for analysis included 9148 patients (baseline characteristics shown in Table 5).

[redacted]

Patients who interrupted study drug were more likely to be older, female, have higher $CHADS_2$ and HAS-BLED scores, have impaired renal function and be on aspirin at randomisation, compared to those who never interrupted study drug. The most frequent reasons for study drug interruption in the 9148 patients were adverse events (N=4038, 44.1%) and physician decision (N = 3553, 38.8%) (Figure 3).

The rates of ischemic stroke/systemic embolism and MACCE post interruption were substantially greater than in patients who never interrupted (15.42 vs. 0.26 and 60.82 vs. 0.36 per 100 patient-years, respectively, $p_{adj} <$ .001). Patients who interrupted study drug for an adverse event (44.1% of the cohort), compared to those who interrupted for other reasons, had an increased risk of MACCE (HR_{adj} 2.75; 95% CI 2.02–3.74, $p < .0001$), but similar rates of ischemic stroke/systemic embolism. Rates of clinical events after interruption of warfarin and edoxaban were similar (Figure 4).

Patients who interrupted study drug due to a transient ischemic attack, ischemic stroke or SEE had significantly higher rates of MACCE and all-cause mortality through 30 days and numerically, but not significantly, higher rates of a second recurrent thromboembolic event (28.36%, 29.26%, 2.06%, respectively), compared to those who interrupted for other reasons (4.49%, 5.26%, 1.25%; p_{adj} values b.001, b.001 and 0.49, respectively) (Figure 5).



Baseline characteristics of patients who interrupted study drug did not differ across the three randomization arms. More patients in the warfarin arm interrupted study drug compared to patients in the HDER group (65.5% vs. 62.6%; p b .001). The risks of ischemic stroke or SEE and MACCE through 30 days were similar following interruption of HDER and warfarin (1.23% vs. 0.93%, p_{adj}=.36 and 4.75% vs. 4.54%, p_{adj} = .75, respectively). Fewer patients in the lower-dose edoxaban regimen (LDER) than the warfarin arm interrupted

study drug (61.8% vs. 65.5%; p b .001). The incidence of ischemic stroke/SEE and MACCE after interruption of LDER were numerically, although not statistically higher, compared to warfarin.

In this large trial of oral anticoagulant therapy for atrial fibrillation, interruption of study drug occurred in approximately two-thirds of all patients during almost three years of follow-up was slightly but significantly more frequent in patients treated with warfarin than either regimen of edoxaban. Interruptions of both warfarin and edoxaban were associated with poorer outcomes and an elevated thromboembolic risk through 30 days that was markedly higher than the event rate of patients who never interrupted study drug.

The authors consider their study highlights the importance of close monitoring during OAC interruption and support guideline recommendations to minimize the frequency and duration of interruptions, especially in patients who experience adverse events. In patients with atrial fibrillation, temporary interruption of OACs should be restricted to selected scenarios, such as patients with active major bleeding or with acute stroke, and OACs should be resumed as soon as possible, i.e. approximately 2 weeks after an extracranial bleed. In case of gastrointestinal bleeding, resumption of OAC after 7 days is associated with a reduction in thromboembolic events and mortality without a statistically significant increase in recurrent bleeding. When OAC interruption is considered to be mandatory, in particular as a result of an adverse event, patients should be followed closely given the substantial risk of major cardiac and cardiovascular events within 30 days. Further studies exploring the optimal duration of OAC interruption after an adverse event are needed.

The authors state that overall their findings with respect to higher interruption rates with warfarin and the increased risk of thromboembolism following OAC interruption among moderate- to high-risk patients with AF are consistent with previous studies with both warfarin and two other NOACs (rivaroxaban and apixaban).

Several limitations are noted in the article. This is a retrospective analysis of post-randomization subgroups of patients. Despite adjustment for differences in baseline characteristics between treatment groups and by reason for discontinuation, unmeasured confounders influencing outcomes cannot be excluded. Also, there is likely to be a selection bias with respect to patients with AF participating in a clinical trial, who are followed closely and who may have lower rates of discontinuation compared to patients in the community. Reasons for interruption or discontinuation of OAC are often complex and multifactorial. Finally, it is not possible to disentangle whether the elevated mortality risk after study drug interruption was due to the baseline risk profile of the patients who required interruption, a direct consequence of the adverse event leading to the interruption, or a combination of these factors.

Interruption of study drug was frequent in patients with AF and was associated with a substantial risk of major cardiac and cerebrovascular events over the ensuing 30 days. This risk was particularly high in patients who interrupted as a result of an adverse event; these patients deserve close monitoring and resumption of anticoagulation as soon as it is safe to do so. In clinical practice, interruption of OAC in patients with AF should be avoided or as brief as possible, especially following non-serious adverse events. Considering the increased risk of ischemic events after interruption of OAC, NOACs represent an attractive alternative to vitamin K antagonists given their better safety and tolerability profiles.

3.1.2.2 Li et al, 2018 [18] (rivaroxaban)

This is a letter to the editor in response to the letter by Bakhit et al (section 3.1.2.4). The authors state that the existence of a phenomenon of rebound hypercoagulability after cessation of oral anticoagulant therapy is controversial. Previous research has shown that some atrial fibrillation patients enter a hypercoagulable state after oral anticoagulant therapy discontinuation. They also note a study that found abrupt cessation of oral anticoagulant treatment may trigger a hypercoagulable rebound phenomenon however there is little research on the mechanism for this. The authors conclude to be able to demonstrate a clinical mechanism of the phenomenon, studies with large patient numbers are required.

3.1.2.3 Nagasayi et al, 2017 [19] (rivaroxaban)

A case report concerning an 88 year old Chinese woman with a permanent pace maker and on rivaroxaban for atrial fibrillation suffered from a fall and a small subdural haematoma. Her rivaroxaban was discontinued.

Pacemaker thrombosis may develop within days immediately following or even years after device implantation. This is attributed to a combination of endothelial damage and change of blood flow characteristics resulting in a local procoagulant environment. In this patient, the authors state the prior anticoagulant use may have protected her against thrombosis until the withdrawal.

The authors report that newer oral anticoagulant withdrawal is associated with rebound hypercoagulability as evidenced by post-hoc analysis of the ROCKET study.

Only case reports of episodes of atrial or arterial thrombosis were found from a PubMed search on the risk of venous thrombosis after rivaroxaban withdrawal and interruption.

The discussion concludes that rebound hypercoagulability and risk of thrombosis upon discontinuation of anticoagulants and its consequences should be recognised by physicians.

Comments:
Rivaroxaban is not indicated in patients with pacemakers.

3.1.2.4 Bakhit et al, 2016 (rivaroxaban)

This article discusses a case of a 65 year old female who had been taking rivaroxaban 20 mg once daily for 5 months before a scheduled radiofrequency catheter ablation procedure. The patient had a medical history of obesity, diabetes, hypertension, hypothyroidism, tachycardia-bradycardia syndrome status post permanent pacemaker placement, paroxysmal atrial fibrillation on chronic anticoagulation with rivaroxaban and stage 2 infiltrative ductal carcinoma of right breast 17 years ago treated with radio and chemotherapy without evidence of recurrence. The procedure was scheduled as her atrial fibrillation had been symptomatic with significant burden that persisted despite trialling different anti-arrhythmics. Rivaroxaban was stopped the day before the scheduled procedure. Heparin was given during the procedure. An aneurysm and large thrombus was noted. The procedure was stopped due to the high risk of thromboembolic complications. The patient was started on IV heparin with warfarin and discharged on warfarin.

The authors note that some data raised concerns regarding increased risk of thrombosis after abrupt discontinuation of rivaroxaban compared to warfarin and the risk of rebound thrombosis after discontinuation of different oral anticoagulants remains a controversial issue. The US FDA have issued a black box warning (see also Annex 1 and section titled 'International Product Information' above).

The authors consider that their case highlights the acute formation of atrial thrombus within 24 hours after temporary interruption in therapy with rivaroxaban prior to radiofrequency catheter ablation of atrial fibrillation. The patients' intrinsic stroke risk was considered an unlikely cause of the acute thrombosis as it was reported as intermediate. The mechanism is still unknown however some suggestions are that decreased plasma concentration of rivaroxaban after its discontinuation results in loss of prothrombinase/factor Xa inhibition at the thrombotic site, leading to prothrombic activity.

The authors conclude that although data and clinical experience with rivaroxaban and other novel oral anticoagulant agents (such as dabigatran and apixaban) are still limited, emerging data demonstrate similar safety and effectiveness of uninterrupted approach. It is therefore critical to bear in mind the potential risk of rebound thrombosis after discontinuation of oral anticoagulants especially in high-risk patients, and to consider uninterrupted approach in the management of anticoagulation in the peri-procedural period. More importantly, such risks should be discussed with the patients in order to avoid unnecessary interruptions of oral anticoagulation therapy.

3.1.2.5 Perzborn et al, 2014 [20] (rivaroxaban)

The objective of this study was to compare the effects of rivaroxaban with those of melagatran and dabigatran on thrombin generation and tissue factor-induced hypercoagulability and to explore the possible involvement of the thrombin-thrombomodulin/activated protein C system.

Increased hypercoagulability has been reported with low doses of direct thrombin inhibitors but not with direct factor Xa inhibitors.

Methods: In normal human plasma and in protein C-deficient plasma, thrombin generation was investigated *in vitro* in the presence and absence of recombinant human soluble thrombomodulin (rhs-TM). Thrombin generation was determined by calibrated automated thrombography and an ELISA for prothrombin fragments 1+2 (F1+2). In an *in vivo* rat model, hypercoagulability was induced by tissue factor; levels of thrombin–antithrombin (TAT) and fibrinogen and the platelet count were determined.

Results: Rivaroxaban inhibited thrombin generation in a concentration-dependent manner. In the absence of rhs-TM, melagatran and dabigatran also inhibited thrombin generation concentration dependently. However, in the presence of rhs-TM, lower concentrations of melagatran (119–474 nmol L^{-1}) and dabigatran (68–545 nmol L^{-1}) enhanced endogenous thrombin potential, peak thrombin generation, and F_{1+2} formation in normal plasma but not in protein C-deficient plasma. *In vivo*, rivaroxaban dose-dependently inhibited TAT generation, whereas melagatran showed a paradoxical effect, with an increase in TAT and a small decrease in fibrinogen and platelet count at lower doses.

Conclusion: In conclusion, the present study indicates a paradoxical activation of coagulation at low plasma concentrations of melagatran and dabigatran, which may be caused by suppression of the thrombin–TM/activated protein C feedback system. In contrast, rivaroxaban did not exhibit such an effect, suggesting that direct FXa inhibition may not be associated with a paradoxically increased prothrombotic state. However, the clinical relevance remains to be evaluated in clinical studies measuring prothrombotic markers.

3.1.2.6 Sherwood et al, 2014 [21]

The Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), a randomized, double-blind, double-dummy study of rivaroxaban and warfarin in nonvalvular atrial fibrillation, baseline characteristics, management, and outcomes, including stroke, non–central nervous system systemic embolism, death, myocardial infarction, and bleeding, were reported in participants who experienced temporary interruptions (TI) (3–30 days) for any reason. The at-risk period for outcomes associated with TI was from TI start to 30 days after resumption of study drug. In 14 236 participants who received at least 1 dose of study drug, 4692 (33%) experienced TI. Participants with TI were similar to the overall ROCKET AF population in regard to baseline clinical characteristics. Only 6% (n=483) of TI incidences involved bridging therapy. Stroke/systemic embolism rates during the at-risk period were similar in rivaroxaban-treated and warfarin-treated participants (0.30% versus 0.41% per 30 days; hazard ratio [confidence interval] =0.74 [0.36–1.50]; P=0.40). Risk of major bleeding during the at-risk period was also similar in rivaroxaban-treated and warfarin-treated participants (0.99% versus 0.79% per 30 days; hazard ratio [confidence interval] =1.26 [0.80–2.00]; P=0.32).

The 30 day stroke rate or non-CNS embolism in the study population was 0.36%. The observed embolic event rates are high if prorated over a 1-year period but are consistent with findings in other populations in which there is TI of anticoagulant therapy. The authors note the patients enrolled in the ROCKET-AF trial are considered high risk and the embolic event rate during the temporary interruption likely reflects their intrinsic susceptibility to these outcomes. The authors consider that their finding neither supports nor refutes a 'rebound effect' for either anticoagulant and the clinical evidence for this phenomenon remains tenuous.

The authors conclude in the ROCKET AF study, a large international population of participants with nonvalvular AF, TI of oral anticoagulation occurred in ≈ 10% of patients per year, with only a minority of patients (<10%) receiving bridging therapy. During the at-risk period associated with TIs, the authors observed a 30-day stroke/systemic embolism rate of 0.4% and a major bleeding rate of 0.9%. The risks of thrombotic and bleeding complications were comparable between rivaroxaban- and warfarin-treated participants experiencing TI. TI of oral anticoagulation should be avoided to minimise adverse outcomes.

3.1.2.7 Agarwal et al, 2013 [22] (rivaroxaban)

This case report concerns a 65 year old male who received rivaroxaban prior to and for 12 days after left knee replacement surgery. The patient developed generalised weakness soon after stopping rivaroxaban. The patient was reported to have developed an acute coronary event after rivaroxaban cessation. A subsequent coronary angiogram revealed two-vessel coronary thrombosis. This case illustrates a temporal relationship of coronary thrombosis following rivaroxaban cessation.

The authors of this article note the black box warning issued about the increased risk of thrombotic events with cessation of rivaroxaban therapy (see section 'International product information').

During follow up in a phase III clinical trial for rivaroxaban, 8 events (4 coronary events) occurred in seven patients in the rivaroxaban group compared to one event in the enoxaparin group. The authors view is that it seems counterintuitive to explain the excess strokes in rivaroxaban patients as a result of under anticoagulation in the post-trial period and the high bleeding risk in these patients at the same time.

The authors conclude acute coronary event is a possible post marketing adverse event after discontinuation of rivaroxaban therapy. Individual risk factors would increase the risk of these adverse events and alternative therapy is yet to be considered in high risk patients. Van Thiel et al have previously raised the concern about the cardiovascular rebound phenomenon and recommends additional clinical validation to establish the safety of rivaroxaban.

The above case report is in a patient who received rivaroxaban for knee replacement surgery. This patient is likely to have a lower background risk of thromboembolic events compared to other patients taking an anticoagulant for a thromboembolic event and therefore this case may be stronger evidence of a possible rebound effect. Alternatively, the patient may not have mobilised well after surgery and been at a high risk of a clot.

The studies discuss the possibility of a rebound effect after cessation of DOAC treatment. No clear mechanism has been identified. The issue of rebound effect has also been discussed with relation to warfarin and older anticoagulants.

Some papers consider that available data together with the FDA black box warning shows that a possible risk of a rebound effect with anticoagulants is controversial. The FDA black box warning however doesn't refer to a rebound effect as it is referring to an increased risk of thrombotic events following premature discontinuation of anticoagulants (see section 2.4.2.1 for the FDA wording).

3.1.2.8 Patel et al, 2013 [23]

Rivaroxaban is an oral direct factor Xa inhibitor with consistent and predictable anticoagulation effects. In the double-blind 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), rivaroxaban was found to be noninferior to warfarin for the prevention of stroke and systemic embolism in patients with moderate- to high-risk nonvalvular AF. The ROCKET AF findings resulted in rivaroxaban being approved as an alternative to warfarin for stroke prevention. However, concerns regarding a potential increased risk of events after discontinuation led the United States Food and Drug Administration to require a boxed warning on the package insert stating "discontinuing rivaroxaban places patients at an increased risk of thrombotic events," and "an increased risk of stroke was observed following rivaroxaban discontinuation in clinical trials in atrial fibrillation patients".

In an effort to understand the possible risk of discontinuation in the context of clinical care, the authors evaluated patients who had a temporary interruption or an early permanent study drug discontinuation and all patients who completed the ROCKET AF and transitioned to open-label therapy for the primary event of stroke and non–central nervous system (CNS) embolism and other thrombotic events, including myocardial infarction (MI) and death, up to 30 days after discontinuation.

To understand the risk of discontinuation of rivaroxaban compared with warfarin, the authors evaluated 3 clinically relevant situations during the ROCKET AF (see section 3.1.2.9 'Patel et al, 2011' for additional information on this trial) (Figure 6). The first was patients with temporary interruptions, defined as any interruption of more than 3 days. The second was patients with early permanent study drug discontinuation who were analysed for clinical events from 3 to 30 days after discontinuation. The third was patients completing the study, defined as receiving the study drug at site notification of study end.

Key clinical characteristics of patients who received study drug and had any type of discontinuation (n = 8,261 [rivaroxaban: 4,021, warfarin: 4,240]) compared with patients who did not have any discontinuation (n = 5,882 [rivaroxaban: 3,040, warfarin: 2,842]) are shown in Table 6.

The most common reasons for early permanent study drug discontinuation included adverse events (39%), both nonbleeding and bleeding. Additionally, investigators were instructed to stop study drug permanently when a primary end point was suspected, which occurred in 12.9% (n = 632) of discontinuations. The most common reasons for temporary interruption were surgical or invasive procedures (38.2%) and adverse events (40.2%), both bleeding and nonbleeding. The median duration for all temporary interruptions was 6 days.

Stroke and non-CNS embolism occurred at similar rates after temporary interruptions (rivaroxaban: n = 9, warfarin: n = 8, 6.20 vs. 5.05 per 100 patient-years, HR: 1.28, 95% CI: 0.49 to 3.31, p = 0.62) and after early permanent discontinuation (rivaroxaban: n = 42, warfarin: n = 36, 25.60 vs. 23.28 per 100 patient-years, HR: 1.10, 95% CI: 0.71 to 1.72, p = 0.66) (Table 7).

[redacted]

Patients transitioning to open-label therapy at the end of the study had more strokes with rivaroxaban (n = 22) versus warfarin (n = 6, 6.42 vs. 1.73/100 patient years, HR: 3.72, 95% CI: 1.51 to 9.16, p = 0.0044) and took longer to reach a therapeutic international normalized ratio with rivaroxaban versus warfarin. All thrombotic events within 30 days of any study drug cessation (including stroke, non-CNS embolism, myocardial infarction, and vascular death) were similar between groups (HR: 1.02, 95% CI: 0.83 to 1.26, p = 0.85).

[redacted]

The authors state that the most important finding in this analysis is that there were no significant differences between rivaroxaban and warfarin in the rates of stroke or non-CNS embolism after temporary interruption or early permanent discontinuation, when both blinded therapies were stopped. After the end of the study and after mandatory withdrawal of blinded study drug, when patients treated with rivaroxaban frequently were transitioned to open-label vitamin K antagonists and patients treated with warfarin were continued on vitamin K antagonist prophylaxis, there were significantly more strokes and non-CNS embolism events in patients who had received rivaroxaban compared with those who had received warfarin. Finally, when all thrombotic events that included stroke, non-CNS embolism, MI, and vascular death were evaluated for interruptions and discontinuation both during and after the study, there was no significant difference between rivaroxaban and warfarin.

The rate of stroke and systemic embolism observed was similar between therapies and likely represents the intrinsic stroke rate for patients at moderate to high risk who are without therapeutic anticoagulation. Even with short temporary interruptions, the protection from anticoagulant therapy for AF is lost and the baseline patient risk becomes evident when observed over several thousand interruptions. These findings draw

attention to the potential value of adequate anticoagulation coverage during interruptions, an aim of ongoing studies, and the importance of minimizing interruptions.

Patients undergoing early permanent study drug discontinuation had high rates of both stroke and systemic embolism and all thrombotic events within 30 days of cessation of therapy. Clinicians and patients should be aware of the significant risk of stroke, non-CNS embolism, and thrombotic events when anticoagulation, including rivaroxaban or warfarin, is stopped on either a temporary or permanent basis.

This study is limited by the observational nature of the analysis. Additionally, there may be unmeasured confounders that are associated with discontinuation. However, the blinded nature of the study should provide reassurance regarding decisions to discontinue therapies.

In atrial fibrillation patients who temporarily or permanently discontinued anticoagulation, the risk of stroke or non-CNS embolism was similar with rivaroxaban or warfarin. An increased risk of stroke and non-CNS embolism was observed in rivaroxaban-treated patients compared with warfarin-treated patients after the end of the study, underscoring the importance of therapeutic anticoagulation coverage during such a transition.

3.1.2.9 Patel et al, 2011 [24]

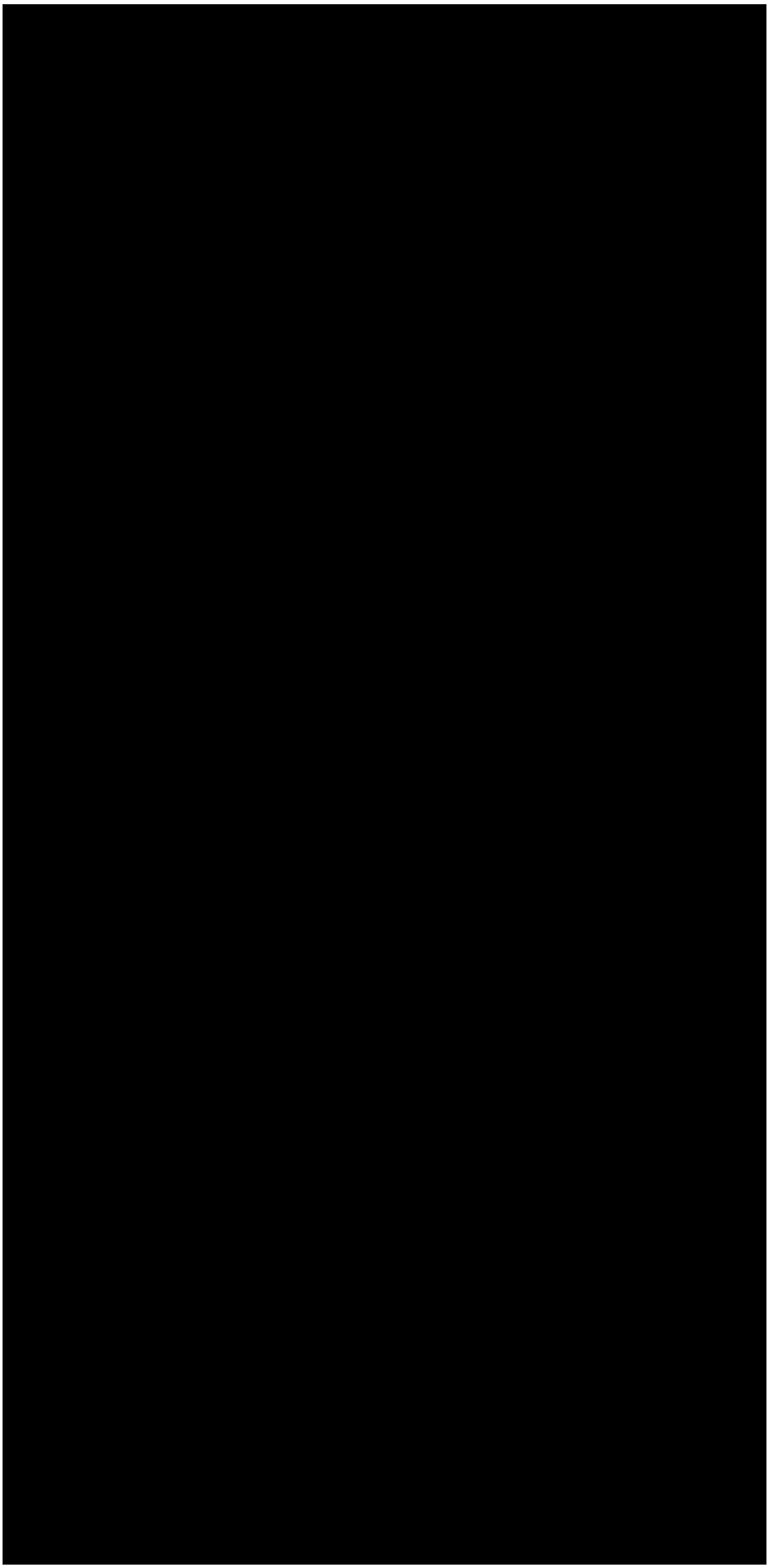
The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin. This trial was designed to compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke.

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicentre, randomised, double-blind, double-dummy, event-driven trial that was conducted at 1178 participating sites in 45 countries.

Patients with nonvalvular atrial fibrillation, as documented on electrocardiography, who were at moderate-to-high risk for stroke were recruited for the study. Elevated risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus (i.e., a $CHADS_2$ score of 2 or more, on a scale ranging from 1 to 6, with higher scores indicating a greater risk of stroke).

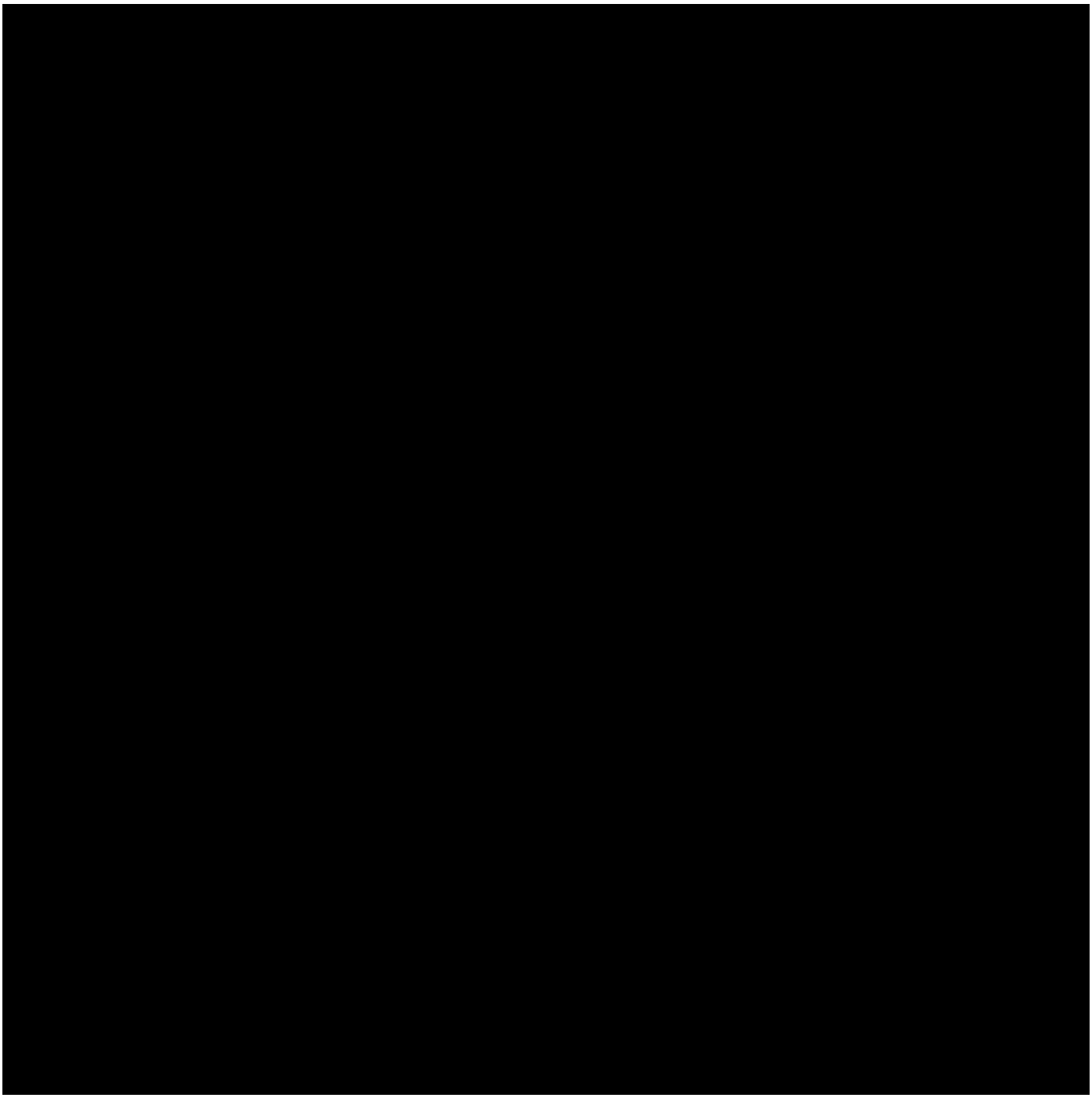
In this double-blind trial, 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke were randomly assigned to receive either rivaroxaban (at a daily dose of 20 mg or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary efficacy end point of a composite of stroke (ischemic or haemorrhagic) and systemic embolism. Secondary efficacy end points included a composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular causes, or myocardial infarction; and individual components of the composite end points. The principal safety end point was a composite of major and non-major clinically relevant bleeding events.

Key clinical characteristics of the patients who underwent randomisation are shown in Table 9. The median age was 73 years (a quarter of the patients were 78 years of age or older), and 39.7% of the patients were women. The patients had substantial rates of coexisting illnesses: 90.5% had hypertension, 62.5% had heart failure, and 40.0% had diabetes; 54.8% of the patients had had a previous stroke, systemic embolism, or transient ischemic attack. The mean and median $CHADS_2$ scores were 3.5 and 3.0, respectively.

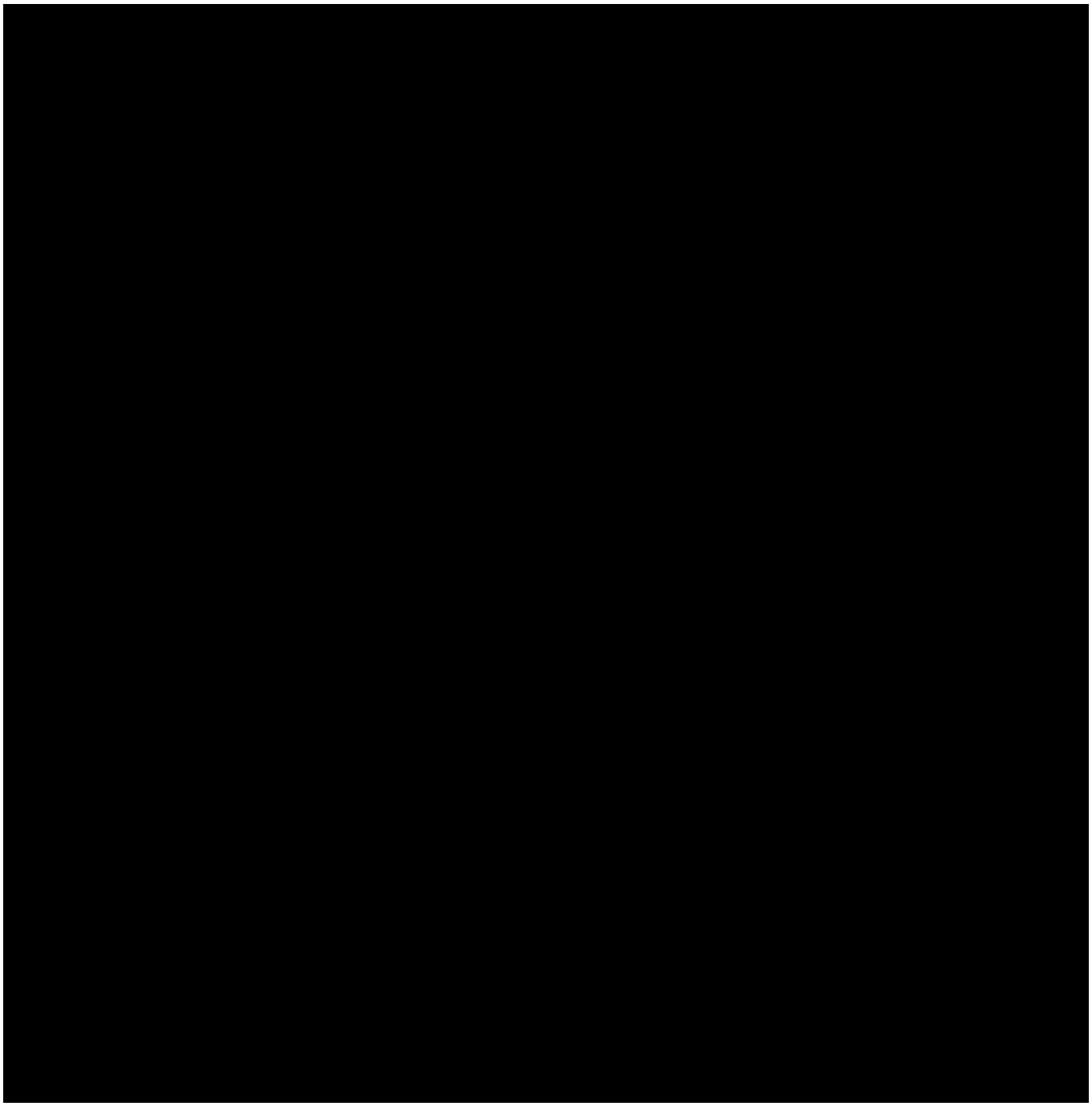


In the per-protocol population (the patients included in the primary efficacy analysis), the primary endpoint (stroke or systemic embolism) occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority).

In the as-treated safety population, primary events occurred in 189 patients in the rivaroxaban group (1.7% per year) and in 243 patients in the warfarin group (2.2% per year) (hazard ratio, 0.79; 95% CI, 0.65 to 0.95; P = 0.01 for superiority). Among all randomized patients in the intention-to-treat analysis, primary events occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P = 0.12 for superiority) (Table 10).



During treatment in the intention-to-treat population, patients in the rivaroxaban group had a lower rate of stroke or systemic embolism (188 events, 1.7% per year) than those in the warfarin group (240 events, 2.2% per year) (P = 0.02) (Figure 7).



Major and clinically relevant non-major bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P = 0.44). Rates of major bleeding were similar in the rivaroxaban and warfarin groups. Rates of intracranial haemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs. 0.7% per year; hazard ratio, 0.67; 95% CI, 0.47 to 0.93; P = 0.02). Major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, P<0.001) with significant reductions in intracranial haemorrhage (0.5% vs. 0.7%, P = 0.02) and fatal bleeding (0.2% vs. 0.5%, P = 0.003) in the rivaroxaban group.

In both the primary analysis, which included patients in the per-protocol population, and in the intention-to-treat analysis, the authors found that rivaroxaban was noninferior to warfarin. In the primary safety analysis, there was no significant difference between rivaroxaban and warfarin with respect to rates of major or nonmajor clinically relevant bleeding.

In the intention-to-treat population, we found no significant between-group difference in a conventional superiority analysis. In contrast, in the analyses of patients receiving at least one dose of a study drug who were followed for events during treatment, the authors found that rivaroxaban was superior to warfarin. The difference between these results reflects the fact that among patients who discontinued therapy before the conclusion of the trial, no significant difference in outcomes would have been anticipated, and none was seen.

Rates of major and nonmajor clinically relevant bleeding, the main measure of treatment safety, were similar in the rivaroxaban and warfarin groups.

The authors conclude in this trial comparing a once daily, fixed dose of rivaroxaban with adjusted dose warfarin in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke, rivaroxaban was noninferior to warfarin in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant nonmajor bleeding between the two study groups, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Comment:

Many articles retrieved from a literature search focus on recurrence in different populations to assist decision making around the risks and benefits of long-term anticoagulation but not many focus on, or can make a clear decision on, whether a rebound effect is a true effect and a possible reason for recurrence.

3.1.3 Anticoagulants excluding dabigatran, rivaroxaban, apixaban

3.1.3.1 Khan et al, 2019 [6]

The objective of this systematic review and meta-analysis was to determine the rate of a first recurrent venous thromboembolism (VTE) event after discontinuation of anticoagulant treatment in patients with a first episode of unprovoked VTE, and the cumulative incidence for recurrent VTE up to 10 years.

A comprehensive systematic search of Embase, Medline and the Cochrane Central Register of Controlled Trials was conducted (from inception to 15 March 2019). Randomised controlled trials and prospective cohort studies reporting symptomatic recurrent VTE after discontinuation of anticoagulant treatment in patients with a first unprovoked VTE event who had completed at least three months of treatment were selected in this review. A standardised form was used to extract data by two independent authors. The same authors assessed the risk of bias of the studies. All studies, including each arm of a randomised trial were evaluated as an independent observational cohort.

For each study cohort the authors calculated the rates of recurrent VTE (number of events per 100 person years) from the number of first recurrent VTE events divided by the person years of follow-up. Random effects meta-analyses were used to pool rates from each study cohort. Heterogeneity between studies was assessed using the I^2 statistic, with values of 75% or greater indicating substantial heterogeneity.

1034 articles were identified by the literature search. After removing duplicates, title and abstract screening and after full text screening, 24 studies were identified as eligible for inclusion in the meta-analysis. 6 of these 24 studies were excluded because the published manuscript did not provide the data required for the analysis which left 18 studies with a total of 7515 patients included in the analysis. Four studies were prospective observational cohort studies and 14 were RCTs. 15 studies met the criteria for the International Society on Thrombosis and Haemostasis definition of unprovoked VTE or VTE associated with minor transient risk factors. This definition as reported by the authors is:

VTE is defined as unprovoked if the following provoking risk factors are absent:

Persistent

Active cancer, defined as:
- cancer that has not received potentially curative treatment, or
- treatment is ongoing, or
- evidence that treatment has not been curative

Major transient

Surgery with general anaesthesia for more than 30 minutes

Confined to bed (only "bathroom privileges") for at least three days with an acute illness

Caesarean section

Minor transient

Surgery with general anaesthesia for less than 30 minutes

Admission to hospital for fewer than three days with an acute illness

Oestrogen treatment

Pregnancy or puerperium

Confined to bed out of hospital for at least three days with an acute illness

Leg injury associated with reduced mobility for at least three days

All 18 studies with 24 independent cohorts followed patients for one year after discontinuation of anticoagulation treatment. 13 studies followed patients for 2 years, four studies followed patients for 5 years, and three studies followed patients for 10 years after discontinuation of anticoagulation treatment.

The characteristics of studies included in the meta-analysis is shown in Table 11.

The risk of recurrent VTE after discontinuation of anticoagulation in patients with a first unprovoked VTE event can be seen in Table 12 below.

The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 10.3 events (95% confidence interval 8.6 to 12.1, I^2=81%) in the first year. The rate of recurrent VTE events per 100 person years for deep vein thrombosis was 6.2 (95% confidence interval 4.8 to 7.7; I^2=79%), for pulmonary embolism was 3.3 (2.4 to 4.2; I^2=68%), and for pulmonary embolism plus deep vein thrombosis was 0.3 (0.1 to 0.5; I^2=44%).

The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 6.3 events (5.1 to 7.7, I^2=56%) in the second year. The rate of recurrent VTE events per 100 person years for deep vein thrombosis was 3.7 (2.8 to 4.7; I2=55%), for pulmonary embolism was 2.0 (1.4 to 2.6; I2=36%), and for pulmonary embolism plus deep vein thrombosis was 0.2 (0.1 to 0.4; I2=0%).

The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 3.8 events/year (95% CI 3.2 to 4.5, I^2=24%) in years 3-5. The recurrent VTE events annually per 100 person years for deep vein thrombosis was 2.5 (95% confidence interval 2.0 to 2.9; I^2=0%), for pulmonary embolism was 1.0 (0.4 to 1.8; I^2=83%), and for pulmonary embolism plus deep vein thrombosis was 0.1 (0.0 to 0.3; I^2=71%).

The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 3.1 events/year (1.7 to 4.9, I^2=84%) in years 6-10. The recurrent VTE events annually per 100 person years for deep vein thrombosis was 2.2 (95% confidence interval 1.0 to 3.8; I^2=86%), for pulmonary embolism was 0.7 (0.2 to 1.6; I^2=79%), and 0.0 for pulmonary embolism plus deep vein thrombosis was 0.0 (0.0 to 0.1; I^2=0%).

The cumulative incidence for recurrent VTE was 16% (95% confidence interval 13% to 19%) at 2 years, 25% (21% to 29%) at 5 years, and 36% (28% to 45%) at 10 years.

The pooled rate of recurrent VTE per 100 person years in the first year was 11.9 events (9.6 to 14.4) for men and 8.9 events (6.8 to 11.3) for women, with a cumulative incidence for recurrent VTE of 41% (28% to 56%) and 29% (20% to 38%), respectively, at 10 years. Compared to patients with isolated pulmonary embolism, the rate of recurrent VTE was higher in patients with proximal deep vein thrombosis (rate ratio 1.4, 95% confidence interval 1.1 to 1.7) and in patients with pulmonary embolism plus deep vein thrombosis (1.5, 1.1 to 1.9). In patients with distal deep vein thrombosis, the pooled rate of recurrent VTE per 100 person years was 1.9

events (95% confidence interval 0.5 to 4.3) in the first year after anticoagulation had stopped. The case fatality rate for recurrent VTE was 4% (95% confidence interval 2% to 6%).

The authors concluded that they found the long term risk for recurrent VTE was substantial based on this meta-analysis of 7515 patients with a first unprovoked VTE event who had completed at least three months of anticoagulant treatment. The risk was 10.3% in the first year after discontinuing treatment and 36% at 10 years. The authors consider that unprovoked VTE is a chronic disease imposing a substantial long term burden. The case fatality rate was determined to measure the clinical impact of VTE recurrence in this patient population. 3.8% of recurrent VTE events are fatal.

The authors consider that their results provide a management framework in which to consider the long term risks and consequences of recurrent VTE if anticoagulation is stopped. These need to be weighed against the risks and consequences of major bleeding if anticoagulation is continued. The overall reduction in mortality with indefinite anticoagulation is small, other factors that affect the risk of recurrence (eg sex, sit of initial VTE) and the risk of bleeding, as well as patient preferences, could influence decisions about whether to continue or stop treatment.

Strengths of the study were identified as being an ability to obtain and pool data from a large number of patients and the ability to capture accurately the time varying risk for recurrent VTE by standardising the varying durations of follow-up across patient cohorts.

Limitations of the study included the high heterogeneity, the authors were unable to account for death from causes other than pulmonary embolism as a competing event for recurrent VTE, adjust for other potentially confounding variables such as patient's age, and explore the potential effect of an age-sex interaction on the differences in the risk of recurrent VTE observed between men and women. Lastly, the authors did not assess the risk of major bleeding during extended anticoagulant treatment, as well as other long term consequences of recurrent VTE that should also be considered in weighing the long term risk and benefits of anticoagulation.

The authors concluded that in patients with a first episode of unprovoked VTE who have completed at least three months of anticoagulant treatment, the risk of recurrent VTE after discontinuing anticoagulation reached 10% in the first year, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent VTE events resulting in death. These findings provide rigorous benchmarks of the long term risks and consequences of recurrent VTE that should inform clinical practice guidelines, enhance confidence in counselling patients of their prognosis, and help guide decision making about long term management of unprovoked VTE.

Comments:

This article does not comment on possible reasons for recurrent VTE after discontinuation of treatment with anticoagulants. Instead it aims to guide decision making around the long term management of unprovoked VTE.

This study also does not appear to analyse whether there are differences in treatment duration or between treatments.

3.1.3.2 Rivera-Caravaca et al, 2017 [25] (acenocoumarol)

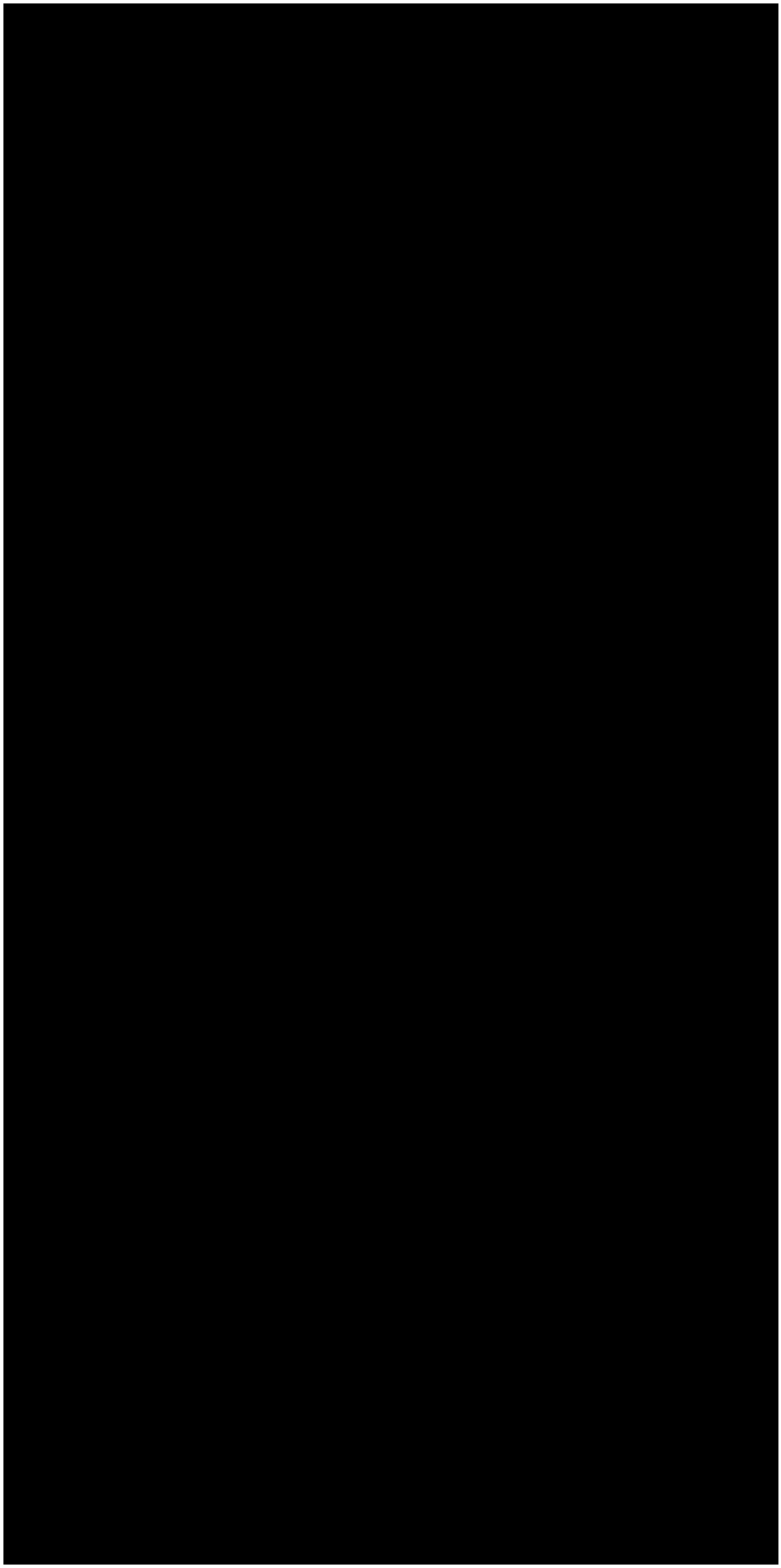
In this study, the authors analysed the rate of cessation of oral anticoagulant (OAC), predisposing factors to OAC cessation and the relation to clinical outcomes in a large 'real world' cohort of atrial fibrillation patients over a long follow-up period. Atrial fibrillation patients in 'real life' clinical practice tend to be older, with associated comorbidities and polypharmacy.

From 1 May 2007 to 1 December 2007 consecutive patients with paroxysmal, persistent or permanent non-valvular AF who were stable with VKA (INR 2.0–3.0) for at least six months, in our single anticoagulation centre at a tertiary Hospital in Murcia (Southeastern Spain) were included in the study.

All patients were receiving anticoagulation therapy with acenocoumarol (the most common VKA used in Spain) and consistently achieved an INR between 2.0 and 3.0 during the previous six months of clinic visits. Thus, for this analysis all patients were established on VKA to ensure homogeneity at baseline, which corresponds to approximately 1/3 of all the whole non-valvular AF patients treated in the clinic.

Follow-up was performed by personal interview at each visit to the anticoagulation clinic and through medical records. The primary endpoints were adverse cardiovascular events (the composite of stroke/transient ischaemic attack [TIA], as well as systemic embolism, ACS, acute heart failure [HF] and cardiac death) and major bleeding events.

Rates of cardiovascular events, major bleeding and mortality were recorded and related to OAC cessation. The authors included 1361 patients (48.7% male; aged 76, IQR 71–81), followed-up for a median of 6.5 years. Baseline characteristics can be seen in Table 13.



During follow-up, 244 (17.9%) patients suffered thrombotic episodes, of which 130 (9.6%) were ischaemic strokes/TIAs, 250 (18.4%) sustained a major bleeding event, of these, 78 [5.7%] were intracranial haemorrhage and 97 [7.1%] were gastrointestinal haemorrhage) and 551 (40.5%) patients died (of these 75 [5.5%] were from a cardiovascular cause. Following cessation of OAC, there were 36 (2.6 %) thromboembolic events (of which 22 [1.6 %] were strokes), 10 (0.7 %) major bleeding events and 75 (5.5 %) deaths (8 [0.6 %] by a cardiovascular cause). OAC cessation was independently associated with adverse cardiovascular events (HR 1.45; 95 % CI 1.01–2.08), stroke/TIA (HR 1.85; 1.17–2.94) and all-cause mortality (HR 1.30; 1.02–1.67). Independent predictors of OAC cessation were age ≥80 (HR 2.29; 1.60–3.29), previous coronary artery disease (HR 0.32; 0.15–0.71), major bleeding (HR 5.00; 3.49–7.15), heart failure (HR 2.38; 1.26–4.47), cancer (HR 5.24; 3.25–8.44) and renal impairment developed during follow-up (HR 2.70; 1.26–5.75). In conclusion, in non-valvular AF patients, cessation of OAC was independently associated with the risk of stroke, adverse cardiovascular events and mortality. Bleeding events and some variables associated with higher bleeding risk are responsible for OAC cessation.

Comments:
Acenocoumarol is an unapproved section 29 medicine.

3.1.3.3 Douketis et al, 2015 [26] (warfarin, heparin)

This study hypothesised that forgoing bridging anticoagulation would be non-inferior to bridging with low-molecular weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding.

A randomized, double-blind, placebo-controlled trial was conducted in which, after perioperative interruption of warfarin therapy, patients were randomly assigned to receive bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. Follow-up of patients continued for 30 days after the procedure. The primary outcomes were arterial thromboembolism (stroke, systemic embolism, or transient ischemic attack) and major bleeding.

In total, 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI], −0.6 to 0.8; P=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005 for superiority).

In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was non-inferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.

The authors state that the premise that warfarin interruption leads to rebound hypercoagulability and that the milieu of the procedure confers a prothrombotic state, which in turn leads to arterial thromboembolism, is not supported by the results of this trial.

3.1.3.4 Verhovsek et al, 2008 [27]

BACKGROUND: The optimal duration of anticoagulation for a first episode of unprovoked venous thromboembolism (VTE) is uncertain. Methods for predicting risk for recurrence may identify low-risk patients who are less likely to benefit from prolonged anticoagulation.

PURPOSE: To synthesize evidence evaluating the value of D-dimer as a predictor of recurrent disease in patients who have stopped anticoagulant therapy after a first unprovoked VTE.

DATA SOURCES: The MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched until March 2008 without language restrictions. The strategy was supplemented with manual review of reference lists and contact with content experts.

STUDY SELECTION: Randomized, controlled trials or prospective cohort studies that measured D-dimer after anticoagulant therapy in patients who received at least 3 months of anticoagulant treatment of unprovoked VTE.

DATA EXTRACTION: Two authors independently reviewed articles and extracted data.

DATA SYNTHESIS: Seven studies, totalling 1888 patients with a first unprovoked VTE, were eligible for analysis. During 4500 person-years of follow up, annual rates of recurrent VTE differed statistically significantly: 8.9% (95% CI, 5.8% to 11.9%) in patients with positive D-dimer results and 3.5% (CI, 2.7% to 4.3%) in patients with negative D-dimer results.

LIMITATION: The duration of anticoagulation, timing of D-dimer testing, and D-dimer assay varied across studies.

CONCLUSION: In patients who have completed at least 3 months of anticoagulation for a first episode of unprovoked VTE and after approximately 2 years of follow-up, a negative D-dimer result was associated with a 3.5% annual risk for recurrent disease, whereas a positive D-dimer result was associated with an 8.9% annual risk for recurrence. These rates should inform decisions about the balance of risks and benefits of prolonging anticoagulation.

3.1.3.5 Hermans et al, 2006 [28]

The objective was to review pharmacological and clinical data describing the rebound effect associated with new and standard anticoagulant drugs.

The search terms used were 'rebound, 'anticoagulant' and 'heparin'. The two new anticoagulants available at the time were fondaparinux and ximelagatran. These two anticoagulants had been compared in phase III clinical trials with warfarin, low molecular weight heparin (LMWH) or unfractionated heparin (UFH).

Available data in relation to a possible rebound phenomenon following cessation of active treatment are very limited. Results mainly from orthopaedic surgery trials suggest an increased rate of venous or arterial thromboembolic events with newer anticoagulants compared with standard anticoagulant therapy. An increase in the rate of serious arterial adverse events has, for example, been observed in VTE patients treated with ximelagatran relative to those receiving warfarin/placebo (short-term exposure: 0.75% vs 0.26%, $p < 0.05$; long-term exposure: 1.70% vs 0.70%, $p \leq 0.1$) (Table 14).

It is not possible to state that an increase in venous thromboembolic events following cessation of anticoagulant treatment is linked to a rebound effect because it could also be due to a paradoxical prothrombotic effect. Both characteristics inherent to individual anticoagulants together with length of treatment may affect the delayed occurrence of thromboembolic events after cessation of treatment – the so-called 'rebound effect'.

Limited information is available regarding the potential of new anticoagulants to induce a rebound effect. It this effect is confirmed, it will be important to determine whether long-term prophylaxis will improve long-term outcomes and whether these benefits will be significant enough to offset a possible reduction in tolerability. In addition, the use of concomitant anticoagulant therapies should be considered when discontinuing anticoagulant treatment.

This review highlights the difficulty of distinguishing a 'true' rebound effect (due to a peak in coagulation factors after a drug is stopped abruptly) from a return to the natural state of thrombus formation when the period of prophylaxis is shorter than the duration of hypercoagulability. Future clinical trials should record all arterial and venous thrombotic events occurring up to 30 days after treatment cessation. It would be useful to have information on distribution of events according to time. As VTE is rare, a meta-analysis should help to increase the power of the analysis.

[redacted]

Comments: This review aimed to describe a rebound effect. The authors note the limited information available and the difficulty in determining a 'true' effect.

3.1.3.6 Genewein et al, 1996 [29]

In 1996, the authors stated that the controversy over a rebound phenomenon after cessation of oral anticoagulant therapy has expanded over more than three decades and it is still unclear whether or not the phenomenon is real.

Some clinical studies have demonstrated a transient increase of thrombotic events after cessation of anticoagulation whereas others do not or are inconclusive. The interpretation is difficult because the pre-thrombotic states may simply reappear (and is not transient) after a phase of suppression by oral anticoagulants, or the pathological vascular process has silently proceeded further and becomes over again. The authors consider that both these are a 'catching up' to the initial levels rather than being consistent with a transient overshooting of coagulation and subsequent normalisation. Nevertheless, some data suggest a potential rebound phase may represent a pre-thrombotic state which could become apparent only in high-risk groups. Large populations will be needed to see these effects.

The authors hypothesised that if a relevant rebound phenomenon was real, it should be measurable by careful daily monitoring of thrombin and fibrin formation after cessation of coumarin therapy as a significant increase and later as a decrease or normalisation. 19 patients on and off coumarin were participants in this study.

The 19 patients were seven females and 12 males aged between 30-64 years old and had been taking either acenocoumarol or phenprocoumon because of a thrombotic episode (13 phlebothromboses of lower extremities, one had pulmonary embolism and five had myocardial infarctions). Patients were invited to participate in the study when their treating physician independently decided to terminate oral anticoagulation. Patients were followed by laboratory monitoring for at least 30 days after cessation of anticoagulation and clinically for an average of 12 months (range 9–18).

Blood was taken from the patients during stable anticoagulation, after cessation of anticoagulation (on days 1, 2, 3, 4, 5, 7, 9, 11, 13 and 15) and after day 30 (range 30-51). Blood was also drawn from 20 healthy subjects without anticoagulant therapy on 10 consecutive days by the same person prior to the beginning of the study, in order to analyse the effect of repetitive blood sampling and the influence of training. Prothrombin time and coagulation factors II, V, VII and X were determined in duplicate using immune adsorbed, factor deficient plasmas in in a Schnittger and Gross coagulometer, thrombin–antithrombin III complex (TAT) by ELISA and fibrinopeptide A (FPA) by RIA.

The mean values before and after day 30 were compared with the peak value on day 4 and analysed by the Student's t-test for paired data. Similarly, the differences between the peak value and the value before and after day 30 following cessation of anticoagulation were calculated and analysed versus 0 by the Wilcoxon signed rank sum test.

The patients were followed clinically for 9–18 months after cessation of anticoagulation and none of the 19 patients had a thrombotic event. The prothrombin time normalised completely over the following 13 days after cessation and the coagulation factors reached normal levels (>70%) after an average of 4 d (FVII), 9 d (FX) and 9 d (FII), FV did not change over time (Figure 9).

TAT levels were all in the normal range under stable oral anticoagulation (Figure 10). The mean values increased significantly to a maximum by day 4 (Figure 11) and returned to normal levels by day 15 and after day 30. The peak TAT levels were above the normal range in 17/19 patients and reached a 2–3-fold increase over the baseline level. All peak-values were found between day 3 and 11 after cessation (Figure 10).

[redacted]

[redacted]

Mean FPA levels from all 19 patients increased non-significantly between days 5 and 11 and returned by day 13, 15 and 30 (Figure 12). 8/19 patients reached peak levels above the normal range and returned to normal

values after day 30, suggesting transient incomplete thrombin neutralisation and, as a consequence, increased fibrin formation.

Figure 13 below shows an example of two cases demonstrating a rebound of the TAT levels with and without a transient increase of FPA.

The determination of TAT and FPA enables a direct estimate of the actual thrombin and fibrin generation *in vivo*. The general relevance is supported by their continuous increase with age and progressive atherosclerosis, their higher levels in the so-called pre-thrombotic states and their suppression by anticoagulation therapy.

Rosenberg & Bauer (1992) have defined a prethrombotic state to have a 2–4-fold increased prothrombin to thrombin conversion rate and an approximately 10-fold rate for overt thrombosis. This is confirmed by clinical studies in which manifest thromboembolic events before anticoagulant treatment had TAT levels of 4–5 times the upper normal limit (The DVTENOX Study Group, 1993) and it is thought that the conversion rate of prothrombin to thrombin has to increase ±5-fold in order to result in a systemic fibrin formation as indicated by increased concentrations of FPA.

The data collectively suggest that a general, narrow, well-defined critical threshold level of thrombin generation resulting in fibrin formation does not exist, but that a working definition of a~3-fold increase of the TAT levels above baseline may be a useful guideline.

In this study, the authors found pathological TAT levels in 17/19 patients, but 8/19 patients also developed increased FPA levels. Increases were 2–3 times the baseline levels, and this is consistent with the abovementioned definition of a pre-thrombotic state (Rosenberg & Bauer, 1992). Since the TAT levels reached their maximum mostly between day 4 and 6, this period may represent the most critical phase.

Other groups also have tried to analyse the phenomenon biochemically. The data collectively suggested that tapering the anticoagulant dose may efficiently suppress the biochemical rebound.

This study was not designed to evaluate a clinical endpoint and the number of patients is too small to draw a clinical conclusion. Some studies have identified high risk groups with high relapse rates and overall it appears that the patients in this group would be considered as candidates for long term anticoagulation or they had to be withdrawn prematurely from treatment (for example bleeding). The authors consider that this implies that clinical studies may not be able to distinguish between the 'catching up' phenomenon (the return to the former prethrombotic state) and true rebound (the transient overshooting with subsequent normalisation including reduction of coagulation). It is important to distinguish between these two possibilities in terms of the need for long term anticoagulation or whether gradual withdrawal would suffice in the latter case.

The underlying mechanism for such a coagulation phenomenon remains obscure. If a constant rate of 0.1% of prothrombin is converted into thrombin, the presence of supranormal prothrombin levels could be a simple but valid explanation. In fact, coumarin treatment increases the intracellular pool of prothrombin in a hepatoma cell line, whereas vitamin K administration increases its secretion thus providing a potential mechanism for the observed prothrombin rebound. In summary, the authors believe that the results of their analysis of TAT and FPA demonstrates the existence of a significant rebound thrombin generation in most patients, which appears to be only partially neutralized by endogenous inhibitors and will induce an increase of fibrin formation in a subgroup of 40% of the patients. In order to demonstrate a clinical relevance of the phenomenon, studies with large patient numbers are required.

Comments:

This study also aims to explore whether there is a true rebound phenomenon. Only 19 patients participated in this study (12 received oral acenocoumarol, seven received phenprocoumon).

3.2 Company reports

3.2.1 Dabigatran (brand name Pradaxa, Boehringer Ingelheim)

[redacted]

[redacted]

[redacted]

3.2.2 Apixaban (brand name Eliquis, Pfizer)

[redacted]

[redacted]

3.2.3 Rivaroxaban (brand name Xarelto, Bayer)

[redacted]

3.3 International reviews

3.3.1 International Information

[redacted]

[redacted]

[redacted]

3.4 CARM data

CARM advised Medsafe at 30 September 2019, there are 117 cases reporting at least one thromboembolic type reaction with dabigatran as a suspect medicine, 3 cases reporting at least one thromboembolic type reaction with apixaban as a suspect medicine and 8 cases reporting at least one thromboembolic type reaction with rivaroxaban as a suspect medicine.

Medsafe manually reviewed these cases to identify the cases more likely to be consistent with a rebound effect, ie those with dates reported and where the onset date of the ADR is after the stop date of the medicine. The 7 cases that were identified can be seen in the table. An eighth case (CARM ID: 130309) has been included because this is the index case that was discussed in the March 2019 MARC meeting.

Date	Gender	Age	[redacted]	Medicine	Reaction	[redacted]
08/2011	M	64	[redacted]	Dabigatran* Warfarin	Venous thromboembolism	[redacted]
03/2012	F	79		Dabigatran* Warfarin	Medication error Embolism mesentric	[redacted]
04/2012	M	84	[redacted]	Dabigatran* Digoxin Quinapril Frusemide	Thrombosis cerebral arterial	[redacted]
04/2012	F	64	[redacted]	Rivaroxaban* Enoxaparin* Bendrofluazide Fluoxetine Omeprazole	Embolism pulmonary	[redacted]
08/2017	M	69	[redacted]	Dabigatran*	Venous thrombosis Rebound effect Amputation	[redacted]
09/2017	M	79	[redacted]	Dabigatran*	Melanoma malignant Stroke Pain neck/shoulder Medication error	[redacted]
10/2018	M	75	[redacted]	Dabigatran*	Embolism cerebral Thrombosis	[redacted]
07/2019	M	75		Dabigatran*	Medication error Stroke	[redacted]

* = suspect drug

reported dates are unclear however the narrative of the report states the patient had 'stopped dabigatran two weeks prior to the event for a number of days'. The reporter considered that the 'blood clot was formed while the patient was off Pradaxa.'

4 DISCUSSION AND CONCLUSIONS

Deep vein thrombosis and acute pulmonary embolism are serious, life-threatening events and anticoagulants are effective at reducing recurrent events. There is uncertainty around the optimal treatment duration which needs to be balanced against the risk of excessive bleeding and a potential rebound effect. A rebound effect phenomenon has been discussed for a number of years with relation to both older and newer anticoagulants however the evidence remains inconclusive. It is challenging to distinguish between a true rebound effect and the possible increased risk of thromboembolic events an individual taking an anticoagulant might have. It is also noted that rebound effect is not listed in the warfarin data sheet.

International product information does not mention the risk of a rebound effect. The US FDA has a black box warning on the product label of anticoagulants stating 'Premature discontinuation of any oral anticoagulant, including [medicine], increases the risk of thrombotic events' however this is not about rebound but about premature discontinuation and this may be a return to the pre-treatment state.

Articles identified during a literature search are frequently unable to make a conclusive opinion on whether a rebound effect is a true effect and no clear mechanism has been identified. Additionally, most studies identified are in patients being treated with anticoagulants for thromboembolic events rather than hip or knee replacement surgeries. It is expected that patients taking anticoagulants for thromboembolic events are at a greater risk of recurrence.

There is only one New Zealand case report of rebound effect in association with apixaban, dabigatran or rivaroxaban.

5 ADVICE SOUGHT

The Committee is asked to advise:

- whether there is sufficient evidence of an association between apixaban, dabigatran or rivaroxaban and a rebound effect, and if so
    - are data sheet updates required?
    - does this topic require any further communication, other than MARC's remarks in *Prescriber Update*?

6 ANNEXES

1. Xarelto (rivaroxaban) US FDA Product Label
2. Boehringer Ingelheim Signal Assessment Report for Pradaxa (dabigatran)

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