

SYNTHESIS

ANTICOAGULANTS IN NON-VALVULAR ATRIAL FIBRILLATION



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■ FOREWORD

A good automatic pilot corrects the course as of the slightest deviation. A good thermostat doesn't; otherwise your refrigerator or heating boiler would constantly switch on and off, and that is not the intention. A certain 'slowness' is therefore built in. If you ask for 20°C, the boiler switches on only when the temperature drops below 19.5°, and it switches off only above 20.5°. In control technology this is referred to as 'hysteresis'. A bit of hysteresis is often very useful; but too much hysteresis makes things uncontrollable.

A good medication maintains an active and safe blood level without the need to take a pill exactly at a certain time. But if the response after administration is very slow and variable, and the half-life is very long, controlling the blood level becomes a difficult matter. And if moreover the therapeutic margin is very narrow, safety is also jeopardised. Not exactly a comfortable situation for the prescriber of such a product, let alone for the patient.

A good 'blood thinner' allows safe navigation between the risk of thrombosis to be avoided and too high a risk of haemorrhages. And that is precisely what the NOACs promise. These Novel Oral AntiCoagulants, in contrast to the 'standard' vitamin K antagonists, allow much more direct control of anticoagulation. No more stress of bleeding times that are difficult to stabilise. No more uncomfortable hassle with monthly blood tests. So there seems to be no turning back.

But the KCE wouldn't be the KCE if we hadn't looked at the results a bit closer too. Are patients on NOACs in fact better protected against stroke? And do they actually run less risk of haemorrhage? And, not unimportant, what are the consequences for the health insurance budget?

And medicine wouldn't be medicine if the conclusions were crystal-clear and unambiguous, just like that. As is so often the case, between the encouraging promises and the ultimate results in daily routine lies an obstacle course with contestable evidence, creative prescription, massive marketing, suboptimal compliance, and a lack of data. If with this report we have been able to provide you with some guidance through this labyrinth, we regard our effort as successful. All of this in the humble realisation that there can be quite a bit of hysteresis between a KCE recommendation and its effect in practice!

Christian LÉONARD
Deputy general director

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■ KEY MESSAGES

- International practice guidelines recommend prescribing anticoagulants to patients with non-valvular atrial fibrillation and a CHA₂DS₂-VASc score ≥ 2 (for men) and score ≥ 3 (for women). For a CHA₂DS₂-VASc score = 0 they are best not prescribed. In patients with a CHA₂DS₂-VASc = 1 (men) and = 2 (women), the risk of stroke due to atrial fibrillation (AF) is of the same order of magnitude as the risk of cerebral haemorrhage induced by anticoagulants. Hence, it is not certain whether the latter patients all benefit from treatment with anticoagulants. Therefore we conclude that these medications are not recommended for them.
- Based on randomised clinical trials (RCTs) in which NOACs are compared with VKAs, we can conclude that these two classes of medications are equivalent in preventing ischemic strokes in patients with atrial fibrillation (AF).
- In the area of adverse effects, the NOACs score better than VKAs in terms of tenths of a percent: the risk of cerebral bleeding is slightly (but statistically significantly) lower (-0.20 to -0.31% per year). However, NOACs appear to cause a higher number of gastrointestinal bleedings (+0.51 to -0.10% per year). It should be noted that these RCTs may favour the NOACs due to bias.
- With NOACs there are clearly fewer laboratory checks needed than with VKAs.
- The long-term effects of NOACs are not yet known, although these medications must be taken by some patients for 10 or 20 years or more.
- From the Belgian economic models it appears that NOACs extend the life of patients by 1 to 4 quality adjusted life months if their effects are extrapolated over an entire lifespan. The accumulated cost over this period are only slightly higher than those of the VKAs. For that reason these models consider the NOACs cost-effective compared to the VKAs. This holds only on the assumption that the anticoagulants are used in daily practice as they are in the RCTs, and that the results of the RCTs remain applicable in the long term.
- In contrast to what was expected, the persistence of patients on a NOAC is no better than with a VKA, although NOACs do not require regular blood testing. According to the figures of the IMA/AIM, 20 to 30% on anticoagulation treatment interrupt their treatment; these figures hold for both classes of medications.
- Due to the short duration of action of the NOACs, compliance is even more important with them than with the VKAs. A patient who forgets to take a NOAC only once already runs a higher risk of stroke, which is not the case for VKAs.
- In daily practice, a substantial number (43%) of Belgian patients have a lower dose prescribed than that in the RCTs. Moreover, even in the strict framework of the RE-LY study (dabigatran) it turned out that 20% of the patients who took the dose assigned to them fell outside the optimal therapeutic serum levels. That is a problem, because for NOACs it is impossible to check whether the patient is getting/taking the adequate dose



with coagulation tests. It cannot be excluded that some patients on a NOAC are no better protected than on a VKA.

- The NOACs are a good therapeutic choice for patients in whom a stable INR is difficult to achieve on a VKA, or for whom regular blood tests are problematic. The prerequisite is that these patients have the proper NOAC dose prescribed and show adequate persistence/compliance.



■ SYNTHÈSE

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1. OBJECTIVES OF THIS STUDY

Patients with atrial fibrillation run an increased risk of ischemic cerebrovascular accidents (stroke). Therefore many of them must use anticoagulants for the rest of their lives. The class of vitamin K antagonists (VKAs) used to be the drugs of choice: Sintrom® (acenocoumarol), Marevan® (warfarin) and Marcoumar® (phenprocoumon). Anticoagulants have certain disadvantages (blood must be drawn often for monitoring) and risks (especially cerebral haemorrhage). Several years ago a new family of anticoagulants appeared on the market: the "novel oral anticoagulants" or NOACs (*Novel Oral AntiCoagulants*). These medications were introduced on the Belgian market in 2009 to prevent thromboembolic accidents after orthopaedic surgeries (hip or knee prosthesis). In 2012 their indication was expanded to the prevention of ischemic stroke in persons with atrial fibrillation. At present four of these medicines are reimbursed: Eliquis® (apixaban), Pradaxa® (dabigatran), Xarelto® (rivaroxaban) and Lixiana® (edoxaban).

NOACs are promoted especially because they require no intensive monitoring of coagulation, which is indeed the greatest drawback of the VKAs. On the other hand, they are much more expensive. The RIZIV - INAMI budget for reimbursement for anticoagulants rose from 1.6 million euro in 2004 to 95.3 million euro in 2015 (this amount does not take into account the confidential discounts that have been negotiated with the NOAC manufacturers). This increase is admittedly not only attributable to the high price of the NOACs. The number of patients who have anticoagulants prescribed is also increasing, because of changing recommendations in international guidelines.

This report is a Rapid HTA on NOACs for patients with "non-valvular" atrial fibrillation.

2. ATRIAL FIBRILLATION

2.1. A silent disorder with potentially serious consequences

Atrial fibrillation (AF) is one of the most common heart rhythm disorders (in 1.5 to 2% of the western population), manifesting itself in an irregular heart rhythm, often in the form of tachycardia. Its prevalence increases with age and it occurs in 5 to 15% of persons older than 80 years. The disorder also occurs more often in patients who have associated cardiovascular problems. When it is accompanied by a cardiac valve disorder (mitral valve stenosis, heart valve prosthesis), it is called "valvular atrial fibrillation". All other forms fall under the heading of "non-valvular atrial fibrillation". This report concerns only the latter cases (we therefore indicate them by AF for short).

AF is often a discreet or even asymptomatic disorder. It may provoke complaints such as heart palpitations, shortness of breath or fatigue. It can also cause heart failure. The greatest risk of AF, especially in patients above 65 years of age, is thromboembolism. In this, blood clots that are formed in the left atrium can be taken to the brain via the cerebral arteries, where they cause an ischemic stroke. People in whom the estimated stroke risk is high are treated with an anticoagulant (see item 2.2).



Two categories of stroke:

- Ischemic stroke: interruption of arterial (oxygenated) blood supply to a part of the brain. In AF a brain artery becomes blocked by blood clots that are formed in the atrium and released into the blood circulation. The latter is then called an “embolism”. In practice this distinction is not always made and it is more generally referred to as a “thromboembolic complication” of AF.
- Haemorrhagic stroke, also called cerebral haemorrhage or (intra)cerebral bleeding: blood extravasation in the brain due to a small tear in an artery (e.g. due to hypertension) or a rupture of an aneurysm. Treatment with an anticoagulant increases the risk of a cerebral haemorrhage.

2.2. Assessment of the thromboembolic risk

Assessment of the thromboembolic risk is a required step for every patient with AF. Around the world, this assessment is done with a specific risk scale called CHA₂DS₂-VASc. This is a cumulative score based on the most important risk factors that may or may not be present. CHA₂DS₂-VASc is an acronym composed of the initial letters of the measured risk factors (see Table 1).

Table 1 – Calculation of the CHA₂DS₂-VASc-score

	CHA ₂ DS ₂ -VASc
Congestive heart failure (more specifically moderate to severe systolic dysfunction of the left ventricle, arbitrarily established on the basis of a left ventricular ejection fraction ≤ 40%).	1
Hypertension	1
Age > 74	2
Diabetes	1
History of stroke, transient ischemic attack (TIA) or thromboembolic problems	2
Vascular disorder (history of myocardial infarction, complex plaque in the aorta, peripheral artery disease)	1
Age between 65 and 74	1
Female gender	1

The risk scores are obtained by summing the numbers (1 of 2) for all the risk factors. When “female gender” is the only risk factor, it is not counted.

In comparison with the CHADS₂ score that was used until 2009, the CHA₂DS₂-VASc contains three additional risk factors: age between 65 and 74 (CHADS₂ started as of age 75), a known vascular disorder, and female gender. The latter factor must however not be taken into account if it is the only risk factor (a woman without other risk factors thus does not have the score 1 but the score zero).

CHA₂DS₂-VASc is more sensitive than CHADS₂, but with that increased sensitivity, the risk of overdiagnosis inevitably becomes greater.



3. EFFICACY OF ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION

For anticoagulant treatment of AF patients, oral anticoagulants from the two aforementioned classes are used: vitamin K antagonists (VKAs) and novel oral anticoagulants (NOACs). They block the action of certain blood constituents that are needed for blood clotting.

There is yet another category of medications that influence blood clotting, the platelet inhibitors, of which aspirin is the best known. They are not discussed in this report. This class of medications, which has different mechanisms of action (inhibition of platelet aggregation), is no longer recommended by the European Society of Cardiology (ESC) for preventing stroke in patients with AF. In 10 to 15% of cases however they are used *in combination* with oral anticoagulants, more specifically if the AF patient presents comorbidities that require their use (coronary disease, stents, or peripheral arterial disease).

3.1. Vitamin K antagonists

Vitamin K antagonists (VKAs) were for decades the standard treatment for venous thromboembolic disorders (deep venous thrombosis, pulmonary embolism) and for the prevention of thromboembolic events (ischemic stroke, systemic embolism) in patients with AF. Their efficacy is based on inhibiting the action of vitamin K, which is needed for production of various clotting factors.

The use of VKAs is fairly complex due to several special characteristics:

- Their long duration of action: 48 hours for acenocoumarol, 2 to 5 days for warfarin and 1 to 2 weeks for phenprocoumon. This means that discontinuation of the treatment (e.g. for the purpose of a surgical procedure) must be planned in advance. This long half-life however offers the advantage that a patient remains protected even when he missed a dose;
- Their narrow therapeutic margin: the concentration of VKAs in the blood is rather unstable and the effective dose needed to prevent clot formation is close to the dose that can cause haemorrhages. The clotting values must be checked monthly for patients who are treated with VKAs. This is done with the "INR" (*International Normalised Ratio*) blood test. The INR must be maintained at values between 2 and 3. For an INR <2 the risk of ischemic stroke increases; an INR >3 increases the risk of a haemorrhage. Patients preferably remain between 2 and 3 at least 70% of the time;
- Many interactions with other medications (aspirin, non-steroidal anti-inflammatory drugs) and with certain foods (alcohol, vegetables of the cabbage family, green tea, etc.).

3.2. Novel Oral AntiCoagulants (NOACs)

Approximately ten years ago the NOACs, a new class of anticoagulants, appeared on the market. They act directly on blood clotting factors (and not on their synthesis, as with VKAs), so that they are much more "flexible" in use. Their action begins immediately after ingestion and is quickly reversible after use is discontinued. Certain NOACs directly inhibit the activity of thrombin (Direct Thrombin Inhibitors: dabigatran); others work by blocking clotting factor Xa (Factor Xa Inhibitors: rivaroxaban, apixaban and edoxaban). They have a duration of action of 7 to 17 hours. Because their blood concentrations and effects are predictable, the clotting values of patients need not be monitored. On the other hand, strict compliance is necessary, as the anticoagulant effect wears off quickly.

Severe renal insufficiency (creatinine clearance < 15 mL/min) is a contraindication for use of this therapeutic class. In the event of moderate renal insufficiency (creatinine clearance between 15 and 30 mL/min), lower doses are recommended.

Note that NOACs are not used in patients with mechanical artificial valves. In these persons they are less effective than VKAs, which remain the reference anticoagulants for them.



3.3. Comparison of the efficacy of VKAs and NOACs

Table 2 summarises the most important outcomes of the randomised controlled trials (RCTs) in which NOACs and VKAs were compared. Summarising, we can state that NOACs are in general as effective as VKAs for the prevention of ischemic strokes. With regard to safety, the risk of cerebral haemorrhages is significantly lower for NOACs, although the difference in absolute numbers is very small and varies between 0.20 and

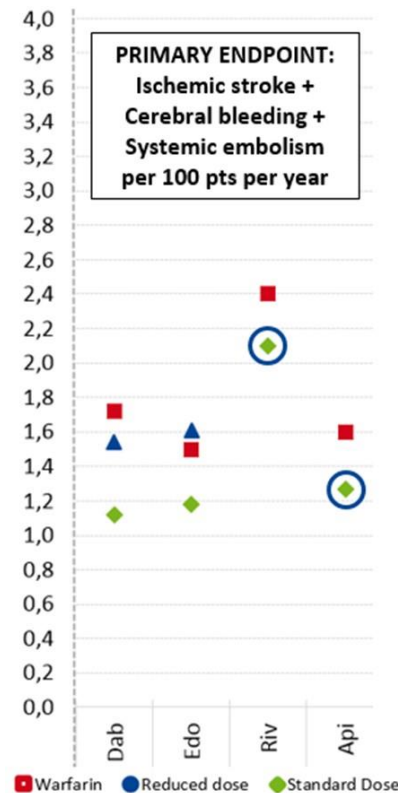
0.31% per year. For gastrointestinal bleeding, NOACs in standard doses score somewhat less well than VKAs with a risk difference varying between -0.10 and +0.51% per year.

Of note, these RCTs have a short time horizon (approximately two years). The only data we have available for the NOACs over a longer term come from observational studies (which are scientifically less conclusive).

Table 2 – Absolute risks of the most important outcomes in the RCTs comparing NOACs with VKAs

	Relative Risk (95% CI)			
	Stroke + SE (Primary outcome)	Ischemic stroke	Haemorrhagic stroke	Gastrointestinal bleeding
Dabigatran 110 *	0.89 (0.73–1.09)	1.11 (0.89-1.40)	0.31 (0.17-0.56)	1.10 (0.86-1.41)
Dabigatran 150	0.65 (0.52–0.81)	0.76 (0.60-0.98)	0.26 (0.14-0.49)	1.50 (1.19-1.89)
Rivaroxaban	0.88 (0.75-1.03)	0.94 (0.75-1.17)	0.67 (0.47-0.93)	1.54 (1.19-1.78)
Apixaban	0.78 (0.66-0.95)	0.92 (0.74-1.13)	0.51 (0.35-0.75)	0.89 (0.70-1.15)
Edoxaban 30 *	1.07 (0.87-1.31)	1.41 (1.19-1.67)	0.33 (0.22-0.50)	0.67 (0.53-0.83)
Edoxaban 60	0.79 (0.63-0.99)	1.00 (0.83-1.19)	0.54 (0.38-0.77)	1.23 (1.02-1.50)

Sources: Connolly et al.¹ for dabigatran; from Patel et al.² for rivaroxaban; from Granger et al.³ for apixaban, and from Giugliano et al.⁴ for edoxaban. Stroke + SE: Stroke and Systemic Embolism, this includes ischemic and haemorrhagic strokes. GI bleeding: gastrointestinal bleeding. °Δ = (NOAC-VKA). * reduced dose. Definitions of the outcomes can differ depending on the RTC. We found a meta-analysis of these RCTs not to be indicated given the methodological differences between the studies and the heterogeneous basic characteristics of the participants.

**Figure 1 – Absolute incidence rate of primary endpoint in pivotal RCTs**

Source: Phase 3 RCTs that compared a NOAC with a VKA (dabigatran: Connolly et al.¹; rivaroxaban: Patel et al.²; apixaban: Granger et al.³ and edoxaban: Giugliano et al.⁴) as shown in Table 2. In the dabigatran and edoxaban studies one-third of the patients got the standard dose of the NOAC, one-third the reduced dose of the NOAC, and one-third, warfarin.

◉ In the studies on rivaroxaban and apixaban only the combined results of the standard and the reduced doses were defined as the study endpoint. In the rivaroxaban study, 20.7% of the patients got the reduced dose; in the apixaban study, 4.7%.

A critical analysis of the various RCTs reveals that they involve a **substantial risk of bias in favour of the NOACs:**

- The RCTs took place in 40 to 50 countries with a mutually very heterogeneous quality of healthcare. In addition to western countries, centres in China, India, Bulgaria, Taiwan, Ukraine and the Philippines also participated. This fact is especially important for patients who were treated with warfarin in the RCTs, for whom strict monitoring of the INR is crucial.
- Although it can be expected that the monitoring of haemostasis is very strict in the framework of a RCT, it appears that the treatment of the patients in the VKA group of the RCTs was not optimal. That applies in particular to the ROCKET-AF study, where a TTR^a of only 55% was reported.
- The high percentage of dropouts in de RCTs is problematic in both the NOAC arm and the VKA arm, especially for the ROCKET-AF (rivaroxaban 23%), ARISTOTLE (apixaban 25%) and ENGAGE (edoxaban 34%) studies.
- In the RE-LY study (dabigatran) there was no double-blind dose adjustment in patients in the warfarin arm. Moreover, the results of this study had to be corrected twice over the years. Although these new data reportedly did not change the original conclusions, questions arise about the integrity of the data in this study.

^a TTR: time period expressed as a % during which a patient has an adequate anticoagulant level, i.e. INR values between 2 and 3. With good follow-up, this number lies above 70%.



- In December 2014 – four years after the end of the ROCKET-AF study – the American Food and Drug Administration (FDA) had the device that was used to measure the INR value in this study removed from the market because it gave unreliable INR measurements. According to the authors of this study the use of this device had no impact on the previously published study results. Various other authors have complained that an independent review of these data was denied.
- In all the studies we note a high percentage of combined use of oral anticoagulants and aspirin (ASA), varying from 29% in ENGAGE to 40% in RE-LY. That combined use doubles the risk of haemorrhage, which means an increase by 2% in absolute numbers. We do not know whether the ASA+NOAC combination is as detrimental as the ASA+VKA combination.

4. PRACTICAL: PRESCRIBE ANTICOAGULANTS OR NOT?

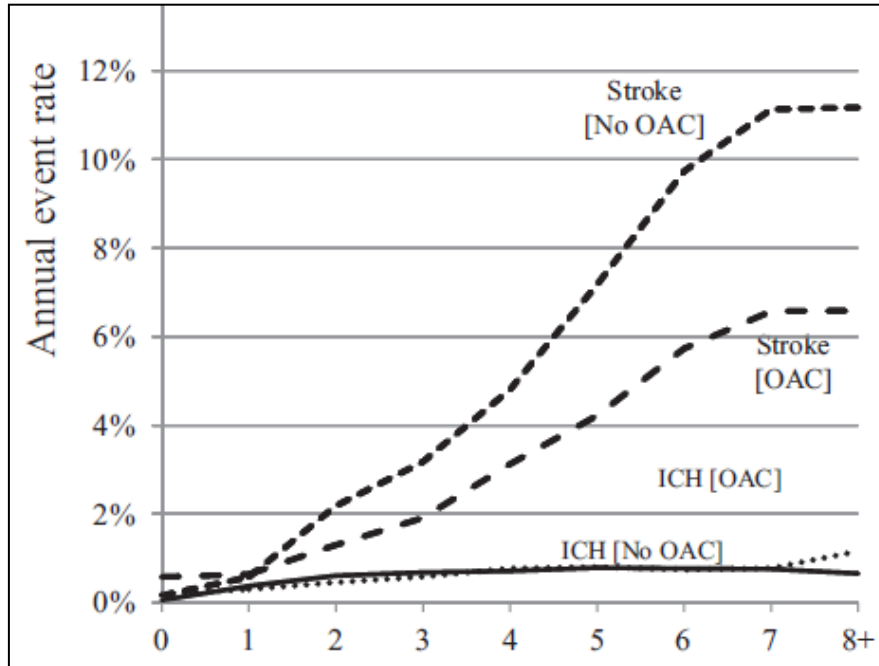
4.1. Finding the balance between the risk of ischemic and haemorrhagic stroke

A physician who treats a patient with AF with anticoagulants does this primarily to prevent ischemic stroke. However, a risk of haemorrhages, in particular cerebral haemorrhage (haemorrhagic stroke), is related to that treatment. That risk is estimated at 0.1 - 0.7% per year (see Table 3). From the RCTs it appears that this risk is somewhat lower for NOACs than for VKAs (cf. paragraph 3.3).

The concept of net clinical benefit has been introduced to indicate the actual benefit a patient receives from anticoagulant treatment. It corresponds to the difference between the percentage of ischemic strokes that were prevented by anticoagulants, and the percentage of haemorrhagic strokes that are attributable to it. Given that the risk of haemorrhage is rather constant regardless of the CHA2DS2-VASc score of the patient, the net clinical benefit of the anticoagulant is primarily determined by the risk of ischemic stroke. Fig. 1 illustrates this: the percentage of ischemic strokes increases with the CHA2DS2-VASc. It rises from 0% to almost 12% per year for patients who are not treated with anticoagulants, and to 7% for patients who are treated with anticoagulants.



Figure 2 – Relation between the CHA2DS2-VASc score and the risk of ischemic stroke and intracranial haemorrhage



Source: Friberg et al. X-axis: CHA2DS2-VASc-score. Stroke = ischemic stroke. OAC = oral anticoagulant. ICH = intracranial haemorrhage (this includes both intracerebral (haemorrhagic strokes) and meningeal haemorrhages). The data in this figure come from a cohort of Swedish patients with AF who were admitted to hospital in the period 2005-2008 (n = 182,678).

Various patient registries around the world show that a considerable number of AF patients with high thromboembolic risk receive no treatment with anticoagulants (undertreatment), while conversely some patients at low risk do have them prescribed (overtreatment).

4.2. Overtreatment

International guidelines recommend prescribing *no* anticoagulants when the CHA2DS2-VASc-score = zero.

In the present report the number of patients in Belgium with a CHA2DS2-VASc score = 0 being treated long-term with anticoagulants could not be calculated because the data from the IMA/AIM [*Inter-Mutual Agency*] contain no diagnostic information.

INTEGO (network of general practitioners in Flanders) data over the period 2013-2014 suggest that 15% of AF patients with a CHA2DS2-VASc score = 0 receive anticoagulants. There is a favourable downward trend over time when we compare this percentage with previously published figures from the same source. It is however not certain whether the INTEGO data can be simply extrapolated to the entire Belgian population.

4.3. Undertreatment

International guidelines recommend prescribing anticoagulants to patients with a CHA2DS2-VASc score ≥ 2 (men) or ≥ 3 (women).

According to the INTEGO data (2013-2014), anticoagulants were started in 74.5% of patients with a CHA2DS2-VASc score ≥ 2 , which is an improvement compared to previous years. Apparently the treatments are also started sooner after the diagnosis was made than previously. The same data also show however that this percentage falls to 50% again after one year has passed, which means that a large number of the treatments are interrupted at some point. The reasons for this cannot be deduced from the data we have available.

Older persons with AF often take no anticoagulants although they have de facto a high CHA2DS2-VASc score. The reasons that are put forth for this are reluctance to prescribe them due to age itself, or the fact that the elderly have a higher risk of falling (and thereby bleeding). Moreover scientific knowledge of the effects of anticoagulants in this patient group is highly incomplete, among other things because the RCTs included few patients older than 85. Nevertheless, a recent observational study in the Netherlands shows that the risk of haemorrhages during treatment with VKAs increases



only very slightly after the age of 80, while the thromboembolic risk becomes significantly greater. IMA/AIM data in Belgium point to a favourable tendency to treat **older patients** with AF with anticoagulants. The percentage of persons older than 80 who use anticoagulants rose from 29.6% in 2005-2011 to 35.6% in 2012-2014.

It is also encouraging to note that the period between diagnosis of AF and the start of treatment has become much shorter in recent years. INTEGEO data show that for patients who were diagnosed with AF in 2007 and who had a CHA2DS2-VASc ≥ 2 , it took 8 years on average before 50% of them were treated long-term. This period fell to 4 years in 2010-2012, and to 1 year in 2013-2014.

The numbers suggest that physicians have become more aware in recent years of the need to treat AF patients with anticoagulants. We can assume that the introduction of the NOACs has contributed to this.

4.4. Special case: patients with a CHA2DS2-VASc score = 1 (for men) and = 2 (for women)

In patients with a CHA2DS2-VASc score of 1 (men) or 2 (women), the risk of ischemic stroke due to AF according to our analysis is of the same order of magnitude as the risk of haemorrhagic stroke caused by anticoagulants (Table 3). For Western populations^b the risk of ischemic stroke amounts to 0.08% to 1.03% per year, and that of haemorrhagic stroke, 0.10 to 0.70% per year. As these numbers overlap a great deal, it is unclear whether these patients have a net clinical benefit from treatment with anticoagulants.

b Asian populations run a much greater risk of ischemic stroke; for a CHA2DS2-VASc score = 1 this risk amounts to 2.22% on average (0.84% -3.59%).



Table 3 – Absolute risk of stroke in patients with CHA2DS2-VASc = 1 (men) or = 2 (women) treated with an anticoagulant

Yearly risk (%)	0	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1,00	1,1	1,2
Risk of ischemic stroke		[Blue bar representing risk from 0.10 to 1.00]											
Haemorrhagic stroke risk in the original studies on VKAs		[Red bar representing risk from 0.20 to 0.70]											
Haemorrhagic stroke risk in the VKA arm of pivotal NOACs RCTs		[Red bar representing risk from 0.30 to 0.80]											
Haemorrhagic stroke risk in the NOAC arm of pivotal NOACs RCTs		[Red bar representing risk from 0.10 to 0.60]											

Sources: Ischemic strokes in patients with CHA2DS2-VASc = 1 according to a meta-analysis of cohort studies on Western patients. The percentages are derived from hospitalised AF patients who were not being treated with anticoagulants. In view of the worldwide downward trend in strokes, the actual percentages in the long term are probably lower than these estimates. Figures on haemorrhagic strokes are extracted from the original RCTs on VKAs (combined for all risk scores). The data from the RCTs on NOACs are summarised in Table 2.

Our analysis shows that it is not certain that patients with a CHA2DS2-VASc-score of 1 (men) or 2 (women) derive a net benefit from treatment with anticoagulants. International guidelines however propose that this be considered. Making reference to David Sackett, we do not concur with this, as anticoagulation is a purely preventive treatment, with potentially serious adverse effects, with no hard scientific evidence that the benefit of anticoagulation in this stroke risk stratum exceeds its harms.

The decision to start a preventive treatment must - even more than in curative medicine - be justified by hard scientific evidence from RCTs that demonstrate that a treatment does not do more harm than good to the patient.

David Sackett, founder of Evidence-Based Medicine

4.5. Additional observations

- Since the beginning of the 2000s, the number of prescriptions for anticoagulants in Belgium has steadily increased. At present almost 2.5% of the population is being treated with anticoagulants (all indications combined). Since the introduction of the NOACs for AF in 2012, that increase has accelerated to the extent that three years later the NOACs accounted for 60% of long-term anticoagulant treatments. In 2014 - only a few years after their introduction - NOACs generated a worldwide turnover of 5.8 billion USD. In Belgium this translates into 100 million euro in extra yearly costs in the years to come for the RIZIV - INAMI.
- The rise in the number of prescriptions for NOACs, both in Belgium and abroad, is at least partly due to gradually **expanding indications for anticoagulants in international guidelines**. These indications were initially limited to chronic AF, but were later extended to paroxysmal AF and atrial flutter. Moreover it cannot ruled out that an increasing number of asymptomatic patients with accidentally discovered AF are also being treated with anticoagulants. By replacing the CHADS2 score by the CHAD2S2-VASc, the guidelines implicitly have purely arbitrarily reduced the risk threshold for thromboembolism that justifies prescription of anticoagulants by half (from 2% to 1% annual estimated stroke risk).



- **The involvement of the pharmaceutical industry** in drafting the guidelines and the **conflicts of interest** within the Guidelines Development Groups are worrying. Thus, the guideline of the European Society of Cardiology (ESC) for treatment of AF is a 90-page document with an (online) 47-page appendix that contains the declarations of interest of the members of the working group^c. It is supplemented by a "Practical Guide" from the ESC that has been drafted in collaboration with the NOAC producers, allegedly "to guarantee the accuracy and integrity of the data" (sic).
- European guidelines devote too little attention to the uncertainties on the use of anticoagulants in patients with low thromboembolic risk and too strongly favour NOACs over VKAs.
- Despite all this, the Belgian authorities decided to reimburse a fourth NOAC, edoxaban, before the present report was published.

5. MONITORING A PATIENT ON ANTICOAGULANTS

5.1. Monitoring coagulation

From the point of view of the patient the most important advantage of the NOACs over the VKAs is that they do not **need regular blood tests for dosage adjustments of the anticoagulant**. This argument plays a central role in the marketing campaigns of the NOACs. Nevertheless, kidney function must still be monitored and patients must come for consultation every 3 to 6 months to follow up on compliance, adverse effects, and use of other medication.

Belgian IMA/AIM data show that patients on NOACs have an annual median of 8 visits to the general practitioner (IQR 5-13), versus 17 (IQR 9-24) for patients who are being treated with VKAs.

5.2. Monitoring compliance

Although NOACs are clearly easier to use than VKAs, the RCTs show no difference as far as persistence is concerned. In the pivotal RCTs, the percentage of patients that interrupted anticoagulation treatment ranged from 16.6 to 35.5% for VKAs, and from 20.7 to 34% for NOACs. The Belgian IMA/AIM data are in line with this, with **20 to 30% of patients considered non-persistent in the two categories**. For the NOACs this could be explained by the fact that a patient who no longer has a regular follow-up feels less "monitored" and deals less diligently with this preventive treatment from which he experiences no physical benefit. Unfortunately significant risks are connected with that laxity that are even greater for NOACs than for VKAs. NOACs have a short half-life, and **skipping even one dose can reduce the protection against strokes**. Two of the NOACs available in

c

https://www.escardio.org/static_file/Escardio/Guidelines/DOI/DOI_Summary_2016_AFIB.pdf



Belgium must moreover be taken twice a day, which is a risk factor for reduced compliance.

5.3. A new form of undertreatment with NOACs

Although the NOACs probably have helped making physicians more aware of the need for anticoagulants in many AF patients, this **new therapeutic class has introduced a new form of undertreatment.**

Shortly after the NOACs appeared on the European and American markets, a large number of severe haemorrhages were reported to the EMA and the FDA. This led to an **increased prescription of the reduced dose** of the NOACs as documented in recent data from the United Kingdom, France and Germany. That also holds for Belgium, where IMA/AIM data show **that 43% of patients take the reduced dose.** With the exception of dabigatran and edoxaban, these reduced doses have however only been evaluated in a small number of patients in the RCTs. **It is therefore not proven that their efficacy and safety compared to VKAs is as good as in the RCTs that were conducted with higher average doses.**

That is all the more worrying because **prescription of NOACs is not accompanied by monitoring of coagulation.** There is no routine test with which, as with the INR for VKAs, coagulation can be accurately monitored in patients on a NOAC^d. The prescribing physician thus cannot check in any way whether his patient is properly (too much or too little) treated. An additional problem is that data from the RE-LY-study (dabigatran) show that, even in the strict framework of a RCT, **up to 20% of the patients fell outside the optimal concentrations** of 35 to 300 ng/mL.

The prescription of reduced NOAC doses for which the efficacy profiles are not well known, combined with the absence of routine monitoring, means that a substantial number of patients on a NOAC are not being optimally treated.

d An analysis of the BMJ from 2014 revealed that monitoring of dabigatran serum levels is in fact possible, and can even reduce the risk of haemorrhage

5.4. Reversibility of the anticoagulant effect and antidotes

In the event of bleeding, or of a surgical procedure, a clotting problem is presented in patients who are being treated with an anticoagulant. The short half-life of NOACs is an advantage here.

The anticoagulant effect of VKAs can be reversed by administration of vitamin K, which costs approximately €10 per treatment. For NOACs, specific antagonists have recently been developed. Idarucizumab, a monoclonal antibody for dabigatran, costs € 2687 for a treatment. For the other NOACs an antagonist (andexanet) has also been developed, but this is not yet available in Belgium.

compared to VKAs. This fact was however initially concealed by the manufacturer (Boehringer Ingelheim) because it weakened their most important marketing argument.



6. ECONOMIC ASPECTS

6.1. Reimbursement of NOACs in Belgium

NOACs have been reimbursed in Belgium since 2009. At first that was the case only for prevention of venous thrombosis after a hip or knee replacement; later also for the prevention of venous thrombosis in general. In 2012 the prevention of ischemic stroke in patients with AF was added as an indication for NOACs.

When this report was initiated (at the end of 2015) three NOACs were reimbursed in Belgium: dabigatran (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®). In the meantime a fourth has been added, namely edoxaban (Lixiana®), which has been reimbursed since 1 October 2016.

The conditions for reimbursement of NOACs are rather restrictive and not in accordance with the international guidelines (see Table 4). For a diabetes patient 60 years of age with hypertension and AF, for example, the physician has no choice but to prescribe a VKA.

Table 4 – Conditions for reimbursement of NOACs in atrial fibrillation in Belgium (1 May 2016)

	< 65 years	65-74 years	≥75 years
	Secondary prevention	Secondary prevention	
OR	EF < 40%	EF < 40%	
OR	NYHA heart failure ≥2	NYHA heart failure ≥2	No additional requirements
OR		Diabetes	
OR		Coronary artery disease	
OR		Hypertension	

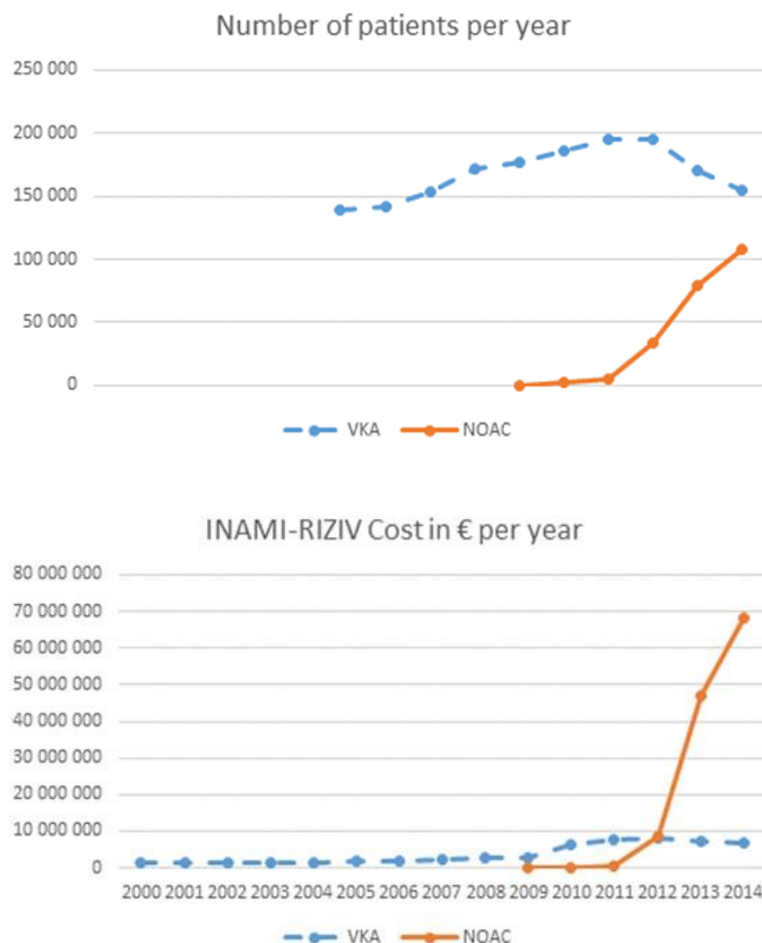
Source: RIZIV - INAMI (<https://www.riziv.fgov.be/webprd/appl/pssp/ssp/cns2/pages/DemandFormStandard.asp>). EF: left ventricular ejection fraction. Secondary prevention = prevention after ischemic stroke or systemic embolism. NYHA: functional classification of the New York Heart Association that classifies patients with heart failure into four categories on the basis of their limitations as to physical activity.

Figure 2 shows that the use of anticoagulants in Belgium has increased substantially since 2012, the year in which NOACs for AF became reimbursed. The RIZIV - INAMI data show that the number of patients who are being treated with anticoagulants almost doubled between 2004 and 2015, and that the share of the NOACs has increased at the expense of the VKAs as of 2012. During the same period the expenditures of the RIZIV - INAMI for anticoagulants increased sixty-fold, from € 1.6 to 95.3 million. It is expected that in the years to come the total expenditures of the RIZIV -

INAMI for NOACs will reach € 100 million. These expenditures are based on the official prices, without taking account of discounts that are kept confidential for commercial reasons. (The RIZIV - INAMI MORSE report of 2015 shows that the budgetary compensation for pharmaceuticals in ATC class B in the framework of an "Article 81/81bis agreement" came to 29.1% overall.) The expenditures also do not take account of any savings that result from the use of NOACs instead of VKAs.



Figure 3 – Annual expenditures of the RIZIV – INAMI for anticoagulants



Source: Farmanet, RIZIV - INAMI. 2015 data are not yet fully available; by extrapolating the data from 11 months, we can estimate the expenditures for 2015 at € 6.1 million for VKAs and € 89.2 million for NOACs.

6.2. Economic evaluations

Our literature study of economic cost-effectiveness analyses is based on 41 studies from 17 countries. The oldest date from 2011, and 24 of them were published in 2014 or 2015 (see scientific report, section 8.3, for detailed information on the studies).

Although a daily dose of a NOAC costs 10 times as much as a daily dose of VKAs (€ 2.85 per day for a NOAC versus € 0.28 per day for VKAs - 2016 prices), according to the published economic models, the overall costs for the rest of the life of the patient are not much higher for NOACs than for VKAs if we take account of monitoring and the adverse effects. Because NOACs are according to the RCTs somewhat more effective than VKAs, **the international economic evaluations conclude that NOACs are cost-effective when compared to VKAs.**

Three economic studies have been published in which the data from the RCTs were extrapolated over the lifespan of a Belgian patient. The authors conclude that NOACs yield **1 to 4 extra high-quality months of life on average compared to VKAs.** They calculated an ICER (incremental cost-effectiveness ratio) between € 2807 and € 12,564 per quality adjusted life year (QALY) gained.

However, it cannot be ruled out that these economic models **are too optimistic.** The RCTs on NOACs display a number of biases due to which they present them in too favourable a light (see 3.3). Moreover, these studies are based on use of NOACs under the very strict conditions of an RCT, which do not correspond to daily practice and with the fact that physicians often make use of reduced doses. The uncertainties about the efficacy and safety of this class of medications in the long term should also be pointed out. **At present it has also not been demonstrated that NOACs are clinically more beneficial than VKAs over a time horizon that corresponds to the life expectancy of AF patients (10 years or longer).**



7. CONCLUSIONS

7.1. Anticoagulants or not?

- For patients with a **CHA2DS2-VASc score = 0** (including women without another risk factor) guidelines clearly recommend prescribing no anticoagulants.
- For patients with a **CHA2DS2-VASc score > 2 (men) and > 3 (women)** guidelines clearly recommend prescribing an anticoagulant.
- For patients with a **CHA2DS2-VASc score = 1 (men) and = 2 (women)** the risk of the ischemic stroke to be prevented is of a similar magnitude as the risk of haemorrhagic stroke caused by anticoagulants. There is no hard evidence supporting the use of anticoagulants in these patients.

7.2. VKA or NOAC?

7.2.1. Advantages of NOACs compared to VKAs

- In terms of **prevention of ischemic stroke in patients with AF**, it can be accepted that NOACs and VKAs have a comparable efficacy.
- In terms of risks, according to the RCTs, NOACs offer a slight advantage, expressed in tenths of a percent. With NOACs the risk of cerebral haemorrhages is significantly less, although the difference is very slight in absolute numbers (-0.20 to -0.31% per year). The risk of gastrointestinal bleeding is somewhat greater with NOACs compared to VKAs (+0.51 to -0.10% per year).
- Haemostasis monitoring is not needed for NOACs, but kidney function and compliance must be monitored.
- In terms of cost-effectiveness, modelling the data of the RCTs on the Belgian population shows that the gain with NOACs compared to VKAs amounts to 1 to 4 quality adjusted *months* of life. Because the estimated costs over the entire lifespan is estimated to be only slightly higher for the NOACs, the NOACs are regarded as cost-effective compared to the VKAs. However, this holds only if the NOACs are used under the same

conditions as in the RCTs, and if the RCT data also hold over the long term. Moreover, there is also the problem of the possible bias in the RCTs in favour of the NOACs in the RCTs.

7.2.2. Disadvantages of NOACs compared to VKAs

- A great disadvantage of NOACs is that we do not know their effects in the long term, while medications that theoretically must be prescribed for 10 years or longer are involved.
- It was expected that not requiring monitoring of blood clotting in patients who use NOACs would encourage persistence/compliance. Nevertheless, the percentages of patients who stop treatment are comparable for the two classes of medications. According to the Belgian data of the IMA, in the two classes of medications 20 to 30% of patients interrupt treatment.
- Due to the short duration of action of the NOACs, conscientious administration of them is even more important than for the VKAs. When a patient skips one dose of a NOAC, he is already exposed to an increased thromboembolic risk, which is not the case for VKAs.
- The absence of monitoring can be to the detriment of the NOACs. It leaves the physician unaware whether the appropriate dose is prescribed, which can lead to undertreatment in a significant number of patients.
- A large proportion of patients (43% in Belgium) receive a reduced dose of NOAC compared to the dose that was studied in the RCTs. Moreover, even in the framework of a RCT (RE-LY) it has been demonstrated that 20% of the patients fell outside the optimal blood concentrations. It is thus possible that some patients who use NOACs are in fact no better protected than they would be with VKAs.



7.2.3. Conclusion

Our analysis demonstrates that, under optimal RCT conditions, NOACs perform better than VKAs only to a limited extent. The fact that NOACs require no monitoring of haemostasis is an important advantage that makes them more acceptable for patients and physicians. It might be expected that this would favour persistence/compliance. Yet this is not the case in practice. The absence of monitoring moreover led to an unexpected undesirable effect: physicians, on their guard for the risk of bleeding, prescribe doses of NOAC that are too low and cannot check whether their patients are adequately protected against stroke.

Due to this, the limited advantage that the NOACs have in RCTs may no longer exist in daily practice. It is therefore difficult to justify the extra costs that they entail for our health insurance. The RIZIV - INAMI budget spent on NOACs should reflect their limited added value as compared to VKAs.

NOACs are a good choice for patients in whom it is difficult to achieve a stable INR with VKAs, or for persons for whom regular blood collections are a problem, but only on condition that they receive a proper dose and carefully take the prescribed dose every day or twice per day.



RECOMMENDATIONS^e

To the prescribing physicians:

- Anticoagulants should be prescribed very cautiously for patients with non-valvular AF and a CHA2DS2-VASc = 1 (men) or 2 (women), because these people receive on average no net benefit with this treatment.
- Strict follow-up is just as necessary for patients on a Novel Oral Anticoagulant (NOAC) as for those on a vitamin K antagonist (VKA), with attention to kidney function and compliance.

To guideline developers:

- In practice guidelines, the absolute risk of stroke in relation to the CHA2DS2-VASc score should be clearly stated. Moreover the uncertainties in this, and the probable overestimate of this risk in people with a low CHA2DS2-VASc score, must be reported.
- Methodological experts should be involved in the Guideline Development Groups, and the input of industry should be limited.

To decision makers:

- There are no documented arguments that justify the official price at which the NOACs are marketed. The budget that the RIZIV - INAMI devotes to this class of medications is not known, but it appears to lie significantly higher than that for the VKAs. In new negotiations between the RIZIV - INAMI and industry, the fact that it is uncertain whether patients in daily practice are better off with a NOAC than with a VKA should be taken into account.

Research agenda:

- It should be recommended to conduct studies that examine the extent to which the pharmacist and resources in the Electronic Medical Record such as pop-ups can contribute to optimising patient compliance.

^e The KCE has sole responsibility for the recommendations.



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COLOPHON

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Acknowledgements:	We thank the Southampton Health Technology Assessments Centre (SHTAC) for their commentary and advice on the chapter on cost-effectiveness. We thank Dominique Roberfroid (KCE) for calculating the pooled risk estimates per CHA2DS2-VASc stratum. We thank Carine Pochet (IMA) for running the analyses on Belgian data (IMA database).
Other reported interests:	<p>Fees or other compensation for writing a publication or participating in its development: Rob Cook (Bazian will be paid a fee by the KCE to deliver the chapter 8 of this report)</p> <p>A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Rob Cook (Bazian are paid to deliver a range of scientific research projects), Olivier Gurné (Yearly grant from Bayer for research in cardiology at Cliniques universitaires Saint-Luc)</p> <p>Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Olivier Gurné (consultancy for Boehringer and Pfizer), Lieven Annemans (evaluations in health economy)</p> <p>Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Marnix Goethals (participation to the BeHRA congress – inscription sponsored), Olivier Gurné (participation to scientific meetings with Boehringer and Pfizer), Lieven Annemans (evaluations in health economy)</p> <p>Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Rob Cook (Bazian lead on a range of scientific research projects)</p> <p>Participation in scientific or experimental research as an initiator, principal investigator or researcher: Philippe Hainaut (Principal Investigator for most NOACs trials in VTE), Olivier Gurné (RELY and ARISTOTLE studies), Lieven Annemans (evaluations in health economy)</p> <p>Other possible interests that could lead to a potential or actual conflict of interest: Philippe Hainaut (Advisory boards NOACs pharmaceutical companies)</p>



Layout: Ine Verhulst, Joyce Grijseels

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Publication date: 9 januari 2017
Domain: Health Technology Assessment (HTA)
MeSH: atrial fibrillation; anticoagulants; secondary prevention; Belgium; cost-benefit analysis; Practice Patterns, Physicians'; Practice Guidelines as Topic
NLM Classification: QV 193
Language: English
Format: Adobe® PDF™ (A4)
Legal depot: D/2016/10.273/100
ISSN: 2466-6459
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How to refer to this document?

Van Brabandt H, San Miguel L, Fairon N, Vaes B, Henrard S, Boshnakova A, Cook R, Davies R, Karnad A, Lovell A, Dubois C. Anticoagulants in non-valvular atrial fibrillation – Synthesis. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2016. KCE Reports 279Cs. D/2016/10.273/100.

This document is available on the website of the Belgian Health Care Knowledge Centre.

