(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☑ No ☐

The application addresses the public health issue of the prevalence of atrial fibrillation (AF) and the related risk of thromboembolic complications in high and low income countries. An adequate pharmacological treatment (on the basis of thromboembolic risk stratification) is needed in order to prevent thromboembolic stroke (principal consequence of AF). Novel oral anticoagulants (NOACs) have been allowed onto the market in the last few years as a new therapeutic option for the thromboembolic prophylaxis in AF. The application regards three of the four available NOACs: dabigatran (D), rivaroxaban (R) and apixaban (A). Edoxaban is not included because it has not yet been approved by the regulatory agencies.

Since NOACs are supposed not to require monitoring, the Applicants suggest that they offer convenient alternative to Vitamin K antagonists (VKA), like warfarin. The Applicants also argue that NOACs are cost-effective versus VKA in a variety of settings and perspectives. However, elsewhere in their submission the Applicants correctly suggest that NOACs represent a valid alternative to VKA in settings in which monitoring of anticoagulation is not available.

(2) Have all important studies that you are aware of been included in the application?

Yes ☐ No ☑

The applicants have reported the data from the three pivotal trials RCTs (RE-LY, ROCKET and ARISTOTLE) which led to marketing authorization of D, R and A respectively, in EU and US. The application also includes three smaller trials: PETRO (D+/ aspirin Vs. warfarin), and J-ROCKET and ARISTOTLE-J (assessing the efficacy and safety of R and A respectively in Japanese patients).

It is important to consider also post-authorization cohort studies that describe the clinical effectiveness of NOACs in the real world. There are several post-authorization cohort studies not included in the current application. At least two should have entered the literature search conducted by the Applicant up to January 2014 (Sorensen et al, BMJ Open. 2013 May 3; 3(5); Larsen et al, J Am Coll Cardiol, 2013; 61: 2264-73).

A meta-analysis of all RCTs with D was published in 2012 and it is not reported in this application (Uchino et al, Arch Intern Med. 2012;172:397-402).

A major shortcoming in the application is the lack of reference to the investigation of the BMJ on the behavior of the marketing authorization holder of D (Boehringer Ingelheim) which withheld from doctors and drug regulators the fact that monitoring the blood level of its new anticoagulant drug and adjusting its dose could substantially reduce major bleeds (Cohen D. BMJ 2014;349:g4670; Moore TJ, et al. BMJ 2014;349:g4517; and Charlton B, Redberg R. BMJ 2014;349:g4681.). The implications of the possible need for monitoring will be addressed later on in this report.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes ❌ for efficacy   No ❌ for effectiveness

The three NOACs substantially differ in terms of pharmacodynamic and pharmacokinetic characteristics (Table 1). D etexilate is an inactive pro-drug converted by plasma esterases to dabigatran, a reversible direct inhibitor of thrombin, whereas R and A are the direct inhibitors of Factor Xa that are active with no further metabolic transformation. There are some differences in the elimination mechanism, mainly through the kidney for D and R, less so for A. The high rate of renal elimination of D and R is not an ideal feature in patients with AF who, being often old, are likely to have some degree of renal insufficiency. In spite of similar pharmacokinetics (short Cmax and plasma-half life) their dosage differed in RCTs, R being the only one that was surprisingly tested in RCTs with a once daily dosing, whereas D and A were administered twice a day in the corresponding RCTs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Randomized, non inferiority trial, double blind for the two fixed doses of dabigatran and open-label for warfarin</td>
<td>Double-blind, randomized, non inferiority trial</td>
<td>Double-blind, randomized, non inferiority trial</td>
</tr>
<tr>
<td>150/110</td>
<td>110/110</td>
<td>200/150</td>
<td>200/150</td>
</tr>
<tr>
<td>twice</td>
<td>once</td>
<td>twice</td>
<td>twice</td>
</tr>
<tr>
<td>18,113</td>
<td>14,206</td>
<td>18,206</td>
<td>18,206</td>
</tr>
<tr>
<td>64%</td>
<td>58%</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>32%</td>
<td>87%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>% VKA naïve</td>
<td>% High risk patients (CHA2DS2-VASc 3 or higher)</td>
<td>% High risk patients (CHA2DS2-VASc 3 or higher)</td>
<td>% High risk patients (CHA2DS2-VASc 3 or higher)</td>
</tr>
<tr>
<td>50%</td>
<td>30%</td>
<td>50%</td>
<td>30%</td>
</tr>
</tbody>
</table>

VKA = vitamin K antagonist.
* Dose adjusted in patients with renal insufficiency.

In spite of their different features NOACs have been dealt with as if they were a homogeneous class in RCTs. All the three pivotal trials comparing NOACs with warfarin had in common as primary endpoint the prevention of stroke or systemic embolism. All reportedly aimed at proving the non-inferiority of NOACs Vs. warfarin but ended up claiming their superiority. The ARR ranged 0.3-0.5%. The secondary outcome events (all cause mortality and hemorrhagic stroke) were also reduced (ARR 0.4-0.5% and 0.2 %, respectively). However, reduction in mortality was statistically significant only in the pivotal
trial of A. The results were less homogenous pertaining to ischemic stroke, because only the highest 150 mg D dosage gave a statistically significant 0.44% ARR. In terms of major bleeding, ARR compared with warfarin was 0.65% for the lower D dose (110mg twice daily) and 0.96% for A.

The Applicants have made a meta-analysis of the six trials supporting the application (see point (2)) and found that the use of NOACs instead of warfarin can reduce the risk of death (5 fewer deaths per 1000 patients for a year; high quality evidence) and the risk of stroke (2-9 fewer strokes per 1000 patients for a year; high quality evidence). Additionally, the use of NOACs probably reduces the risk of major bleeding in comparison to warfarin (2 fewer bleeds per 1000 patients for a year; moderate quality evidence) (Table 2). The quality of the evidence according to GRADE was moderate to high for the main outcomes.

The recent meta-analysis by Ruff which includes data for four NOACs studied in the pivotal phase 3 clinical trials confirms that NOACs had a favorable risk–benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of NOACs was consistent across a wide range of patients.
However, both the homogeneous efficacy across the NOACs class and their effectiveness in the every-day clinical practice have been repeatedly questioned.

- The alleged consistent efficacy of the three NOACs included in the application seems to be challenged by the Conclusions of the report of the Canadian Agency for Drugs and Technologies in Health (CADTH) that are as follows.

Table 3

<table>
<thead>
<tr>
<th>1.7 Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>With only a few large randomized controlled trials, coupled with clinical and methodological heterogeneity, there will be uncertainty in any clinical conclusions. For the new oral anticoagulants, compared to adjusted dose warfarin:</td>
</tr>
<tr>
<td>• Dabigatran 110 mg bid did not significantly reduce all cause stroke/systemic embolism but was associated with significantly less major bleeding. It was also associated with significantly less intracranial bleeding but not major gastrointestinal bleeding or myocardial infarction. There was no significant reduction in all-cause mortality.</td>
</tr>
<tr>
<td>• Dabigatran 150 mg bid significantly reduced all cause stroke/systemic embolism. It was associated with significantly less intracranial bleeding but with significant more major gastrointestinal bleeding. There was no significant association with major bleeding or myocardial infarction, and there was no significant reduction in all-cause mortality.</td>
</tr>
<tr>
<td>• Apixaban significantly reduced all cause stroke/systemic embolism and was associated with significantly less major bleeding. It was also associated with significant less intracranial bleeding but not major gastrointestinal bleeding or myocardial infarction. There was no significant reduction in all-cause mortality.</td>
</tr>
<tr>
<td>• Rivaroxaban significantly reduced all cause stroke/systemic embolism compared to adjusted dose warfarin. It was associated with significantly less intracranial bleeding but with significant more major gastrointestinal bleeding. There was no association with major bleeding or myocardial infarction, and there was no significant reduction in all-cause mortality.</td>
</tr>
</tbody>
</table>

When considering subgroups for TTR, age and CHADS2, for all cause stroke/systemic embolism, compared to adjusted dose warfarin:

- For TTR≥66%, only dabigatran 150mg bid achieved a significant reduction in stroke/SE and for TTR>66%, no treatments achieved a significant reduction.

- For age<75y, only dabigatran 150mg bid achieved a significant reduction in stroke/SE and for age≥75y, only dabigatran 110mg bid did not achieve a significant reduction.

- For CHADS2 < 2, no treatments achieved a significant reduction in stroke/SE (rivaroxaban, results were not available since no patients with a CHADS2=2 were recruited into the study) and for CHADS2 ≥ 2, only dabigatran 110mg and rivaroxaban based on ITT analysis did not achieve a significant reduction.

When considering subgroups for TTR, age and CHADS2, for major bleeding compared to adjusted dose warfarin:

- For TTR≥66%, only rivaroxaban was not associated with statistically less major bleeding and for TTR>66%, only apixaban was associated with statistically less and rivaroxaban was associated with statistically more major bleeding.

- For age<75y, all treatments were associated with statistically less major bleeding with the exception of rivaroxaban, and for age≥75y, only apixaban was associated with statistically less major bleeding.

- For CHADS2 < 2, all treatments with the exception of dabigatran 150mg bid had statistically less major bleeds (results for rivaroxaban were not available since no patients with a CHADS2=2 were recruited into the study) and for CHADS2 ≥ 2, only apixaban was associated with statistically less major bleeding.

- As for the effectiveness, Larsen et al. reported the first nationwide registry study from a large Danish cohort (n= 13,914) showing that there were similar stroke and systemic embolism incidence in patients treated with D compared with warfarin and adjusted
mortality was lower with both D doses compared with warfarin (J Am Coll Cardiol, 2013; 61: 2264-73).
Sorensen et al. (BMJ Open 2013;3:e002758) also published a study based on nationwide administrative registers from Denmark identifying 2,726 D users (naïve or VKA experienced) and 49,640 warfarin users. The paper cautiously concluded that in naïve patients D is as effective as warfarin in reducing the risk of thromboembolic events. An unexpected increased risk of thromboembolic events was observed among D users VKA experienced with both doses, probably reflecting patient selection and “drug switching” practices.

The unsettled efficacy profile of NOACs as compared with warfarin along with the open questions regarding their safety (see section (5)) may have led the scientific community to consider NOACs equivalent to warfarin. This is reflected in the recommendations offered by scientific societies in their guidelines for the prevention of stroke in AF (see the Table below from Semin Thromb Hemostas, 2015). All the guidelines but the European Society of Cardiology’s never suggest the use NOACs instead of warfarin.

Table 4.

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHAD_{2}DS_{2}-VASc ≥2</td>
<td>CHAD_{2}DS_{2}-VASc = 1</td>
<td>CHAD_{2}DS_{2}-VASc = 0</td>
</tr>
<tr>
<td>ESC 2012⁴</td>
<td>NOAC</td>
<td>NOAC</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td>Warfarin (alternative)</td>
<td>NOAC (D/ A/ W/R)</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOAC (D/A) W/R (alternative)</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHA/ACC/HRS 2014⁵</td>
<td>OAC (D/R/A/W)</td>
<td>OAC (D/R/A/W)</td>
<td>No Tx (class I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC (D/R/A/W) or No</td>
<td>(can be considered)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tx or aspirin</td>
<td>(class III)</td>
</tr>
<tr>
<td>NICE 2014⁶</td>
<td>OAC (D/R/A/W)</td>
<td>Women: No Tx</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men: OAC (D/R/A/W) (can be considered)</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS 2012⁷</td>
<td>OAC⁸</td>
<td>* Age 65–74</td>
<td>No risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Female and Vascular disease⁹</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC⁹</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin (can be</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>considered)</td>
<td></td>
</tr>
<tr>
<td>ICS 2014ⁱ⁰</td>
<td>D/R/A/EW⁴</td>
<td>D/R/A/EW* (can be</td>
<td>No Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>considered)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A, apixaban; AHA/ACC/HRS, American Heart Association/American College of Cardiology/American College of Cardiologists/Heart Rhythm Society; AP/HRS, Asia Pacific Heart Rhythm Society; CCS, Canadian Cardiovascular Society; CHA_{2}DS_{2}-VASc score, Congestive heart failure, Hypertension, Age ≥75 years (double), Diabetes mellitus, previous thomboembolism (doubled), Vascular disease, Age 65–74 years, and female gender; CHA_{2}DS_{2} score, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (doubled); D, dabigatran; E, edoxaban; ESC, European Society of Cardiology; ICS, Japanese Circulation Society; NICE, National Institute for Health and Care Excellence; NOAC, non-VKA oral anticoagulants; OAC, oral anticoagulants; R, rivaroxaban; W, warfarin.

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes ☒ No ☐

RCTs were conducted in different countries including high and low income countries.
Although there are no specific efficacy studies in different settings or populations, subgroup analyses of data from all reported RCTs revealed no statistically significant differences. However, elderly people, patients with renal insufficiency and African Americans seem to be more prone to bleeding if treated with NOACs instead of warfarin. The efficacy of NOACs was not tested in pregnant or breast feeding women, and subjects with age less than 18 years.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ✗ applies to the 2nd Q

No □

On the basis of the published RCTs the application considers as adequate the safety of NOACs.

In line with the applicants’ view the cohort study by Larsen et al (Larsen et al, J Am Coll Cardiol, 2013; 61: 2264-73) showed that intracranial bleedings and myocardial infarctions were fewer with D compared with warfarin. No evidence of an excess of bleeding events in D treated patients were found.

However, there are a number of reports questioning this view. The excess of gastrointestinal bleeding and myocardial infarction associated with D have been of particular concern.

➢ Bleeding

In the retrospective cohort study of Hernandez (JAMA Intern Med 2015; 175:18-24) in “real world” clinical practice D was associated with a higher risk of bleeding relative to warfarin (regardless of the anatomical site): HR 1.30 (95% CI, 1.20-1.41) for any bleeding event, 1.58 (95% CI, 1.36-1.83) for major bleeding, and 1.85 (95% CI, 1.64-2.07) for gastrointestinal bleeding. The risk of intracranial hemorrhage was higher among warfarin users, with a HR of 0.32 (95% CI, 0.20-0.50) for D compared with warfarin. D was consistently associated with an increased risk of major bleeding and gastrointestinal hemorrhage for all subgroups analyzed. The risk of major bleeding among D users was especially high for African Americans and patients with chronic kidney disease.

A report of the FDA of May 2014 http://www.fda.gov/downloads/Drugs/DrugSafety/UCM397606.pdf) states that the FDA study of Medicare patients found risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin.

An analysis of the risk of bleeding with both doses of D (110 mg and 150 mg) compared to warfarin in older and younger patients (Eikelboom et al, Circulation 2011; 123: 2363-2372) showed that D is as safe as warfarin in patients < 75 years old. Whereas in individuals ≥ 75 years old intracranial bleeding risk is lower but extracranial bleeding risk is higher with both doses.

Sorensen et al. (BMJ Open, 2013 May 3; 3(5)) also reported an excess of bleeding in VKA experienced patients treated with D 110 mg compared to warfarin.
Myocardial infarction
The nationwide Danish registry reported an increased risk of any type of coronary myocardial ischemic events in VKA experienced patients receiving D at both doses compared to warfarin (Larsen et al. Am J Med, 2014; 127:329-336).

The meta-analysis of Douxfils (J Am Heart Assoc.2014;3:e000515 oi:0.1161/JAHA.113.000515) confirms that D (both any dose and 150mg BID) increases the risk of myocardial infarction (respectively, OR 1.41, 95% CI 1.11 to 1.80, P=0.005 and 1.43 (95% CI 1.08 to 1.89, P=0.014). Neither any dose nor 150mg BID significantly reduced overall mortality and the 150mg BID did not reduce major bleeding.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒ No ☐

Careful selection of patients suitable to treatment with NOACs involves expert cardiologists and hemostasiologists. As reported in the NICE consensus statement on the use of NOACs in non-valvular atrial fibrillation, there may be a need for dose reduction in renal impairment as the NOACs are at least partially cleared by the kidney. Patients with chronic kidney disease will need careful monitoring of renal function. ([https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2](https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2)).

The management of clinical emergencies should involve adequate expertise. Should titration and monitoring of the anticoagulant effect of NOACs turn out to be needed, further expertise and facilities would be required.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☒ No ☐

Different dosages of D were approved by the FDA (75 and 150 mg BID) and the EMA (110 and 150 mg BID). The 75 mg regimen was never tested in clinical trials. It is not sure when the 110mg should be used instead of the 150 mg regimen.

The issue of the excess of GI bleeding and myocardial infarction associated with D is of concern and should be monitored. In addition the question should be addressed whether the plasma levels of D and other NOACs need to be titrated and monitored in order to optimize the benefit-risk profile of these products (see section (10)).

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☒
No current WHO guidelines address issues related to NOACs

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The daily cost of NOACs is about 50 times higher than warfarin’s. Possibly considering the need for monitoring INR in patients treated with warfarin, the Applicants argue that the cost of NOACs is only two-three times higher with respect to warfarin. Although cost is a perceived barrier to the use of NOACs, the NICE has concluded that these drugs are cost-effective and must be available to patients within their licensed indications (https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2.). Cost-effectiveness studies comparing the treatment of each NOACs and warfarin in various settings in Western countries concluded that NOACs are cost-effective. However, one cost-utility study concluded that in Thailand warfarin is still the most cost-effective medication (Jarungsuccess S et al. Clin Ther. 2014; 36:1389-94.e4).

The cost-effectiveness of NOACs should be re-evaluated in the light of the possible need for monitoring of their plasma levels and of the future availability and use of antidotes. In any case, however cost-effective, their net price make them hardly affordable in many countries.

(10) Any additional comments?

In pivotal RCTs NOACs resulted to be non-inferior in reducing thromboembolic events and safer in reducing intracranial bleedings with respect to warfarin. The major advantage offered by these medicines is the claimed unnecessary monitoring of anticoagulation. According to NICE NOACs could represent a valid and essential therapeutic option for patients who, despite the adequate adherence, spend less than 65% of time in therapeutic range (TTR), indicating suboptimal anticoagulant control, patients with allergic reactions or intolerance to warfarin, patients who have genuine difficulty in attending for INR monitoring (https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2.). However, most indications recommended by NICE would be questioned if monitoring proved necessary for NOACs too. This might be the case with D.

In 2014 an article published in BMJ reported that Boeringer Inghelheim, the D’s manufacturer, had hidden internal data which documented that “... if the plasma levels of the drug were measured and the dose was adjusted accordingly, major bleed could be reduced by 30-40% compared with well controlled warfarin. The adjustment would have little or no effect on the risk of ischemic stroke. It has also identified the plasma levels at which the dose adjustment should occur to reduce the risk of major bleed.” (Cohen. BMJ 2014 Jul 23;2349:g4670)

In a press release the company replied as follows: “In 2012, our scientists performed preliminary, exploratory simulations with mathematical models to understand whether dose adjustments based on plasma concentrations might further improve the efficacy and
safety profile of Pradaxa®. The initial hypothesis from this mathematical model could not be supported when applied to the actual clinical data from the RE-LY® population. Therefore, they were not provided to regulators. The totality of scientific evidence does not support dosing decisions for Pradaxa® based solely on blood levels. The research shows that individual patient characteristics, such as age, kidney function and certain medications, are critical factors in contributing to the risk of bleeding.” (http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/23_july_2014_Detexilate.html).

However the scientific community keeps being concerned about the lack of published studies on dose adjustment for NOACs and wonders what price, in terms of preventable hemorrhage and death, is being paid for each of the new drugs in the name of ease of use. The question of monitoring combined with the lack of antidote is seen as a “major hurdle in the safe introduction of NOACs (Hugo ten Cate, medical director of the Maastricht thrombosis anticoagulation clinic and co-editor in chief of Thrombosis Journal, 2012). Unlike bleeds related to warfarin which can be reversed using Vitamin K, there are no currently approved agents for reversing bleeds or reversing the anticoagulant effects of NOACs in case of emergency.

(11) Please summarise the action you propose the Expert Committee takes.

This reviewer favors the view that NOACs are not seen as essential medicines. However, the reasons for including them in the EML are acknowledged.

The reasons for not taking into consideration the NOACs as essential medicines relies on the fact that

1. contrary to what reported in RCTs the cohort studies conducted in the real life setting could not confirm substantial advantages over warfarin in terms of both thromboembolic and hemorrhagic prevention;
2. the alleged better convenience of use of NOACs due to the unnecessary monitoring has been questioned for D but could well apply to R and A too;
3. the uncertain impact of plasma levels of NOACs on their safety is critical in the absence of antidotes, while Vitamin K is the obvious and cheap antidote of warfarin;
4. the NOACs included in the application are seen as if they were all the same, while possibly they are not because of the several differences in terms of pharmacodynamic and pharmacokinetic properties (Table 1) and of clinical outcomes (Table 3). Although it would be preferable to select one product instead of the entire class, it is difficult to establish which NOAC should be adopted in the EML: D involves uncertainties regarding the optimal dose and its titration; R has uncertainties regarding the optimal dosage (twice instead of once a day?) and the clinical performance; A is possibly the best one (potential safer use in elderly patients and in those with renal insufficiency, proved better efficacy than aspirin in AVERROES trial, which is important for patients to be switched from aspirin to anticoagulant prophylaxis), but there is no comparative evidence supporting its selection.
5. last but not least, NOACs are considered cost-effective but their cost is about 50 times higher than warfarin cost, which can make them not affordable however cost-effective.
The argument in favor of including NOACs in the EML is that
6. their distinctive feature of needing no monitoring candidates them for the situations in which monitoring is not feasible.

The latter argument is questioned by the above point 2. but supported by point 1. However, one wonders whether standard not titrated doses of warfarin (the condition that possibly are experiencing patients currently treated with NOACs) or dual antiplatelet therapy with low dose aspirin and clopidogrel (which is not ruled out by the NICE Guideline on AF, June 2014) could do as well at much lower cost. Clearly RCTs are needed to explore these hypotheses. Comparative trials are also needed to understand better which NOAC and in which clinical conditions should be preferred.

In short, the present knowledge about the clinical effectiveness and cost-effectiveness of NOACs seems to be immature to support any decision about their inclusion in the EML. The cost of NOACs may hamper their affordability in low- and medium-income countries.