5 Patented medicines that have clinical benefits but did not meet the EML Expert Review committee's comparative cost-effectiveness criterion: *Case study on novel oral anticoagulants*

5.1 Background

One of the criteria used by the WHO EML Expert Committee is that of comparative cost-effectiveness.[1] Comparative cost-effectiveness is assessed when multiple treatments are available for the same indication. In some cases, the WHO Expert Committee has identified medicines as offering relevant public health benefits over the next best treatment but considered that they were not cost-effective compared to treatments that are already on the EML at current prices. For these medicines, availability at lower costs would change the cost-effectiveness balance, potentially tipping it in favour of addition to the EML in the future.

In this case study, we review a class of medicines termed novel oral anticoagulants (NOACs)[j], which are used in preventing blood clots. In 2015, the WHO Expert Committee reviewed an application for the inclusion of NOACs in the EML and considered that "the evidence indicates a favourable, overall clinical benefit of the NOACs over warfarin" but that "the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit".[2] While NOACs offer advantages over the next best therapy (warfarin), and are the guideline-recommended first-line treatment in the US and Europe, they are rarely used in LMICs. The advantages of using NOACs include that they do not require regular monitoring, have fewer drug and food interactions, and emerging evidence suggests that they are safer than warfarin.

In the context of the MPP's role in contributing to reducing the prices of medicines in LMICs, this case study seeks to understand the public health need for NOACs in LMICs, the potential for their introduction and what the public health and economic impact could be if the MPP secured licences on NOACs to facilitate affordable access in LMICs.

More generally, the case study seeks to understand whether there could be a role for the MPP in relation to medicines, such as the NOACs, assessed by the EML Expert Committee as offering clinical benefits but not meeting the comparative cost-effectiveness criterion at current prices.

NOACs have two approved uses that are discussed in this analysis: they are used prophylactically in patients with a heart rhythm disturbance termed non-valvular atrial fibrillation (NVAF), to prevent the common complications of stroke and other blood clots (stroke and systemic embolism; SSE), and in patients who have had a blood clot in a vein (venous thromboembolism (VTE)) to treat the acute phase of the disease and to prevent another one from occurring. A third use, for the prevention of blood clots in patients that have had hip or knee surgery, is not discussed in this chapter.

[j] Also referred to as non-vitamin K antagonist oral anticoagulants or direct-acting oral anticoagulants.

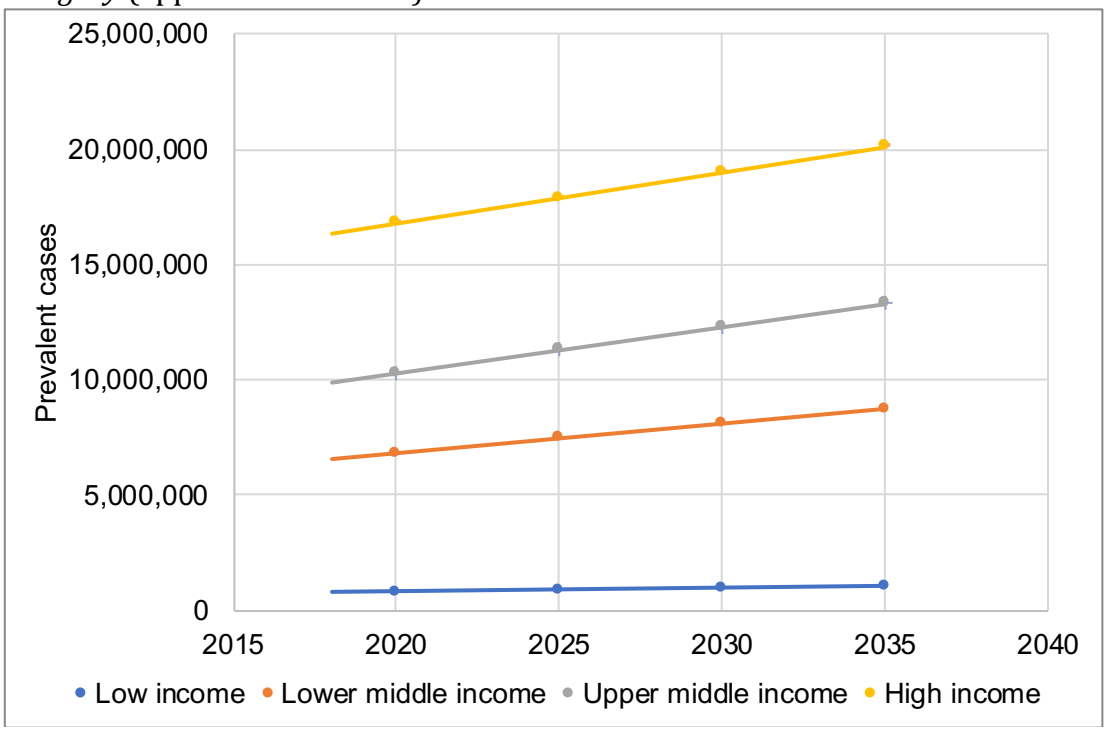
5.2 Burden of Disease in Low- and Middle-Income Countries

5.2.1 The global burden of atrial fibrillation, stroke, and systemic embolism.

Atrial fibrillation (AF) is the most common type of rhythm disturbance of the heart: in Europeans over the age of forty, the lifetime risk for developing AF is one in four.[3,4] Acutely, AF is usually asymptomatic or causes only mild symptoms. However, chronically, it confers significant risk of blood clots in the brain, causing stroke, or elsewhere in the circulation, causing injury to tissue or organs.

By 2020, it is estimated that there will be 17.8 million people with non-valvular AF in LMICs (Figure 1).[5] AF causes significant long-term morbidity and mortality, increasing, among other things, the risk of heart failure by a factor of two–three and stroke by a factor of four–five.[3] In addition, stroke has been observed to be more closely associated with AF as a risk factor in LMICs than in high-income countries.[6,7]

Figure 1. Projected prevalence of non-valvular atrial fibrillation by country income category (appendix for details)



Linear projections based on GBD data.[5]

Stroke is a significant cause of death in LMICs. The proportion of deaths that are caused by stroke is in decline in high-income countries, but increasing in most other world regions.[8] Stroke is associated with a significantly higher fatality rate in LMICs, with, for example, 41% of stroke patients in Kolkata, India, and 57% of stroke patients in the Gambia, dying within 30 days.[9–11] In survivors, stroke is associated with significant disability, with 50% experiencing one-sided weakness, 46% experiencing cognitive deficits, 35% experiencing depression, 31% unable to walk without assistance, 22% incontinent of urine, 20% losing vision on one side, and 19% losing the ability to converse.[12]

This disability is particularly catastrophic in developing countries. In a recent WHO survey of 177 countries, the majority of low- and lower-middle-income countries reported that provisions for the treatment of acute stroke and stroke rehabilitation were available in less than a quarter of public healthcare facilities.[13] It was reported that in China, 37% of households that suffered a stroke were pushed below the poverty line.[14] Studies found that only 17% of stroke survivors in Nigeria returned to work,[15] and 65% of survivors in Tanzania permanently retired.[16]

Anticoagulation therapy is a crucial tool for the prevention of stroke, reducing incidents in patients with risk factors by approximately 66%.[17]

Limited data are available on the annual risk of stroke conferred by AF outside of North America and Europe.[18] In a recent analysis of 15,400 patients presenting to emergency departments in 47 countries with a primary or secondary diagnosis of AF, a stroke occurred within one year in 4% of all patients, 1% of patients in India, 3% in the Middle East, 7% in South-East Asia, and 8% in Africa.[19]

5.2.2 The global burden of venous thromboembolism.

Venous thromboembolism is an event in which a blood clot forms in veins. The main locations where this occurs are in the lower limbs, termed a deep venous thrombosis (DVT), and in the lungs, termed a pulmonary embolism (PE). Pulmonary embolisms carry a high risk of death, with about 40% of those affected dying within a year.[20] DVTs in most cases do not result in lasting damage to the leg. However, the clot in the leg can travel to the lungs, causing a PE, which poses a significant risk to life.

In addition to the high risk of death, VTE also causes substantial disability.[21] For example, following DVT, 10-20% of patients develop severe post-thrombotic syndrome, which affects the ability to walk.[22]

While there are limited data on the global epidemiology of VTE, the broadest available study estimated the annual incidence of VTE in low- and middle-income countries at 6 million, among hospital inpatients alone. Based on this study, we estimated the annual incidence of VTE in countries previously included in MPP licences to be 3.6 million (appendix).[22,23] As projections for future trends in VTE burden are not, to our knowledge, available, we assume that this incidence would remain constant over the next few years for the purposes of estimating MPP impact. This is likely to be a conservative assumption as VTE burden is expected to rise.[22] In addition, this captures only VTEs in hospital inpatients.

5.3 Outline of drugs, drug classes, diagnostic methods, and guidelines.

5.3.1 Diagnosis and management of AF.

AF is relatively simple to diagnose even in resource-limited settings. It can be detected by a clinician by simply taking a patient's pulse and is suspected if the pulse is found to be irregular. The diagnosis is confirmed by electrocardiography. After diagnosis, the clinician must balance the likely benefits and risks of starting anticoagulation as primary prevention of SSE. To decide on appropriate therapy, guidelines recommend

the use of predictive scoring systems that are simple and can be calculated based on medical history alone. In general, no laboratory tests are required before initiating anticoagulation.

National background papers contributed by national experts in Botswana, Nigeria, South Africa and Peru[K] to collect information for this study confirmed that such diagnostic techniques are regularly used in primary care and hospitals and the locally available infrastructure is sufficient for effective AF diagnosis. In India, electrocardiography was reported as often unavailable outside of large urban centres and, while clinical diagnosis is reliable, it has lower sensitivity and many cases are likely missed.

If the scoring system predicts moderate or high risk, a NOAC is the preferred first-line treatment for prevention of SSE in high-income countries. [24] Treatment is continued life-long unless intolerable or dangerous side effects emerge, or a contraindication develops (for example, end-stage kidney disease).

Besides anticoagulation, other medications are commonly used in AF to control the heartrate and, in some cases, to control the heart rhythm.[24] These medicines, such as calcium channel blockers and beta blockers, are generic. A recent WHO survey with results from 177 countries found that calcium channel blockers were generally available in the public health sector in 31%, 64%, and 81% of low-income, lower-middle income and upper-middle income countries, and beta blockers in 38%, 67%, and 86% respectively.[13]

5.3.2 Diagnosis and management of VTE.

DVT is relatively easy to detect clinically, as it presents as acute one-sided leg swelling. PE is more challenging to diagnose as it commonly presents with vague symptoms. A risk-stratification scoring system (Wells score) is available to estimate the likelihood of DVT and PE before the need for laboratory tests or imaging. A relatively simple and affordable blood test exists to further narrow the probability.[25] The diagnosis of DVT is confirmed with an ultrasound of the leg, which can be performed at the bedside. Ultrasound devices are becoming more compact and affordable and availability in LMICs is increasing.[26] They are a priority diagnostic instrument for any hospital, as they are used in many different areas of medicine. National background papers contributed by national experts indicated that ultrasound is routinely used to confirm DVT in Botswana, Nigeria, Peru, South Africa, and large metropolitan centres in India.

In PE, the gold standard diagnostic test uses computer-assisted tomography (CT scan), which is often not available in resource-limited settings.[27] National background papers indicated that CT is routinely used in Botswana, Peru, and large metropolitan centres in India, while in Nigeria, South Africa, and rural India most cases are diagnosed on clinical grounds. However, a combination of the Wells score and the D-dimer blood test can correctly exclude more than 95% of non-cases.[28]

[K] National experts contributing background papers for this Chapter were: Professor Marc Blockman (University of Cape Town/Groote Schuur Hospital, South Africa), Dr Prabhakar Dorairaj (Public Health Foundation India, India), Dr German Malaga (Hospital Cayetano Heredia, Peru), and Dr Anthony Oyekunle (University of Botswana, Botswana).

In both DVT and PE, guidelines in high-income countries recommend therapy with a NOAC generally for 3-6 months[L], and treatment without admission to hospital, or discharge from hospital as early as possible unless the patient is considered high-risk.[29] Guidelines note that the use of some NOACs (apixaban or rivaroxaban) enables treatment without admission or early discharge, as they do not require pre-treatment with heparin, which is needed if using other NOACs or warfarin.[29]

5.3.3 Warfarin.

Warfarin is the most commonly used medicine in the vitamin K antagonist (VKA) class and the most widely used anti-coagulant in LMICs, according to national background papers undertaken by national experts to inform this study. Aspirin and other antiplatelet medications are also widely used in LMICs to prevent stroke in patients with AF, despite being significantly inferior to anticoagulants (VKAs and NOACs) and exclusion from modern guidelines recommendations.[24,29,30] Warfarin is taken orally in tablet form and has been in clinical use as an anticoagulant for decades.[31] When using warfarin in acute VTE, heparin, which is an injectable blood thinner, must be added to the treatment for the first 10 days.[32]

The pharmacokinetics of warfarin are highly variable between patients, and potentially affected by a number of factors such as other medicines and foods. [33-35] As warfarin has a narrow therapeutic window (i.e. a narrow range of blood concentration within which it is safe and effective), the dose of warfarin must be carefully tailored and monitored for each patient. If the levels of warfarin in the blood are too low, the drug will not be effective. If it is too high, there is a substantial risk of bleeding and death.

Warfarin therapy is monitored using a blood test known as an international normalized ratio (INR) test. Though numerous protocols exist for the initiation of warfarin therapy, in general, multiple INR tests must be done in the first few weeks of warfarin treatment, and thereafter every 1-3 months. Warfarin levels in the blood must be within a certain range at least 65% of the time in order for warfarin to have a significant benefit over other treatments.[36]

Little data have been published on the availability of, and adherence to, INR monitoring in resource-limited settings. A study in South Africa found that four out of five patients on warfarin failed to maintain an average time in therapeutic range that meets the 65% target.[37] In Ethiopia, it was found that 70% of patients on warfarin therapy did not have effective and safe blood levels of warfarin.[38] Small studies undertaken in hospital inpatients in Nigeria and Botswana found that only 39% and 20% of INR tests were in therapeutic range, respectively.[39,40]

Background papers undertaken to inform this analysis in Botswana, India, Nigeria, Peru and South Africa concluded that the convenience of NOACs, reduced need for testing, and reduced drug and food interactions presented major advantages in these countries. Prices of NOACs appeared to be the main barrier to treatments adoption. A national expert in South Africa noted that access to NOACs "in the public sector would be

[L] Unless the patient has cancer, in which case LMWH is preferred over VKA or NOACs.

essential due to lack of INR clinics close to many of our patients, especially the rural areas" (appendix).

Expert analyses of stroke management in LMICs have suggested that in many settings the burden of INR monitoring makes physicians reluctant to prescribe warfarin to patients.[41–43] In addition, INR monitoring comprises a substantial part of the total cost to health systems and patients of using warfarin as an anticoagulant. For example, a study in Mexico found that the cost of warfarin itself represented less than 2% of the total costs of warfarin therapy.[44] Added to these costs is the inconvenience of having to travel to a health facility to undertake monitoring and any dose adjustments.[43]

With all anticoagulants, the risk of bleeding increases, and in situations of acute bleeding the anti-coagulation may need to be 'reversed'. For example, if a patient taking warfarin suffers trauma, they are likely to bleed more than someone who is not taking warfarin, and their bleeding is likely to be harder to stop. Another scenario in which warfarin may need to be reversed is if emergency surgery is needed in order to minimise the likelihood of excessive blood loss during surgery. In the context of emergencies like these, warfarin can be reversed by using prothrombin complex concentrate (a product that is extracted from donated blood) and/or vitamin K.[45] However, full reversal can take more than 24 hours.[46]

5.3.4 Novel oral anticoagulants.

Novel oral anticoagulants (NOACs) are also known as non-vitamin K antagonist oral anticoagulants. There are four medicines in this class: dabigatran, rivaroxaban, apixaban, and edoxaban. Though NOACs became available less than a decade ago, they are now the most commonly prescribed antithrombotic treatment in Europe and US, prescribed more often than warfarin by a wide margin, in line with guidelines.[47]

NOACs is indicated for non-valvular AF and not for valvular AF, such as rheumatic heart disease – a syndrome in which an autoimmune reaction to a bacterial throat infection causes damage to the heart.[18,48] Rheumatic heart disease causes a significant proportion of AF in LMICs.[18] In such cases, warfarin can still be used. An ongoing clinical trial is investigating the use of rivaroxaban in patients with rheumatic heart disease.[49]

The major advantages of NOACs compared to warfarin are:

- No requirement for monitoring due to significantly more consistent and predictable pharmacokinetics. This may be particularly important in LMICs where access to INR monitoring is may be limited.
- Significantly lesser restrictions on foods and interactions with other medications.
- A meta-analysis found that NOACs were safer and more effective in Asians and significantly reduced the risk of SSE and major bleeding compared to warfarin.[50]
- For rivaroxaban and apixaban, no requirement for lead-in coadministration of an injectable anticoagulant (heparin) in acute VTE treatment.[29]
- Some meta-analyses have found that NOACs have superior efficacy to warfarin.[51,52]

Real-world evidence is also emerging to show that some NOACs may have additional benefits over VKAs than those described above. A study of 61,678 patients in a Danish database found a lower risk of bleeding and death with apixaban and dabigatran compared to warfarin.[53] A study of 15,390–32,350 patients in the US mirrored this, finding that apixaban and dabigatran conferred a lower risk of major bleeding than warfarin.[54] Meta-analyses of the main randomised controlled trials for NOACs found that NOACs as a class conferred significantly greater reduction in strokes, all-cause mortality, and intracranial haemorrhage compared to warfarin, but increased the risk of gastrointestinal bleeding.[51,52] Other meta-analyses, however, have not confirmed the significance of these findings for individual NOACs.[55,56]

The main disadvantage of NOACs compared to warfarin is the absence of reversal agents for all but one NOAC. While warfarin can be reversed relatively easily, the only NOAC for which a reversal agent exists is dabigatran, for which a biological reversal agent has been developed (idarucizumab). Reversal agents for the others are in development and may enter the market in 2018,[57] but in most cases of bleeding, discontinuation and supportive care are likely to be sufficient, in large part owing to the NOACs' short half-lives.[58,59]

NOACs are in general well-tolerated. Among the side effects, dabigatran is associated with significantly increased rates of dyspepsia (indigestion), with 5–10% of patients experiencing this side effect.[60,61] Use of dabigatran is also contraindicated in renal impairment. NOACs are contraindicated in pregnancy. Analyses from the US suggest that adherence to rivaroxaban and apixaban is higher than for dabigatran or warfarin[M].[62–65]

5.3.5 Relative differences between individual NOACs

Significant differences in efficacy between the different NOACs are yet to be conclusively demonstrated.[55,66,67] However, there appear to be important differences in safety and practical terms.

Recent meta-analyses have found that apixaban appears to be safer, in terms of bleeding risk, than warfarin and the other NOACs.[66,67] Both apixaban and rivaroxaban are associated with a lower rate of side effects and discontinuations compared to dabigatran.[62,63,68,69] In addition, in the treatment of VTE, dabigatran and edoxaban require at least five days (average 10 days)[35] of lead-in treatment with another injectable anticoagulant (heparin), requiring an extended hospital stay, while apixaban and rivaroxaban do not have this requirement.[29] This would add costs and inconvenience to the patient. A 10-day treatment course with heparin, needed as a lead-in overlapping treatment if using warfarin, dabigatran and edoxaban, costs US$26–69 at lowest available prices (see appendix), plus the costs of longer hospitalisation.

In the US, recent data show that apixaban is now the most widely prescribed NOAC, with rivaroxaban as a close second. Dabigatran use is significantly lower, and edoxaban use is negligible.[70]

[M] Edoxaban had not become available within the timeframe of the cited studies.

In addition, generic apixaban, rivaroxaban, and edoxaban have the potential for being cheaper than dabigatran in view of their considerably lower dosage and active pharmaceutical ingredient (API) requirement (Table 1). The cost of API can be a central determinant of generic prices, accounting for 65–90% of the price of antiretroviral medicines in competitive generic markets, and medicines with lower dosage can often have a significant price advantage over generic medicines that have higher API cost requirements.[71] Therefore, the significantly lower dosing of apixaban (10mg daily), rivaroxaban (20mg daily) and edoxaban (60mg daily) compared to dabigatran (300mg daily) may mean potential for lower generic prices in the long term.

Table 1. Dosage and treatment protocol for NOACs.

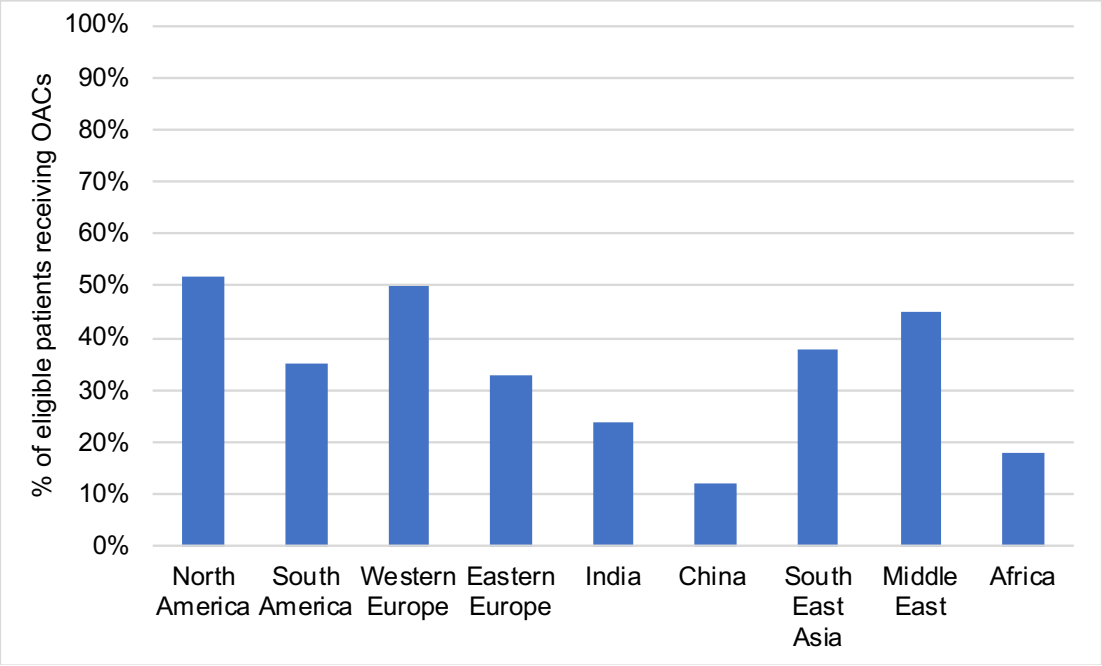
Medicine	NVAF treatment	VTE treatment
Dabigatran	150mg twice daily	150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days
Rivaroxaban	20mg once daily	15mg twice daily for the first three weeks, then 20 mg once daily
Apixaban	5mg twice daily	10mg twice daily for first week, then 5mg twice daily
Edoxaban	60mg once daily	60mg once daily following treatment with a parenteral anticoagulant for at least 5 days

5.3.6 Availability and affordability of medicines for anticoagulation in AF and VTE.

Before the emergence of NOACs, the preferred first-line medicines used in primary prevention of stroke in AF were warfarin, aspirin, and clopidogrel, with warfarin being, , the most effective medicine out of the three by a significant margin..[30] Although there is a lack of published data on the availability and affordability of these medicines, background papers on Botswana, India, Nigeria, Peru, and South Africa undertaken to inform this feasibility study uniformly noted that warfarin and aspirin are widely available at low cost. A recent study of 45 hospitals and 100 private pharmacies in Uganda found 65% availability of warfarin.[72]

An analysis of 15,400 patients presenting to emergency departments in 46 countries found that, among patients for whom oral anticoagulants were clinically indicated, the percentage of patients that were on oral anticoagulants was less than 40% in Southeast Asia and South America, less than 30% in India, less than 20% in Africa, and only slightly above 10% in China (Figure 2).[73] These figures may be overestimates of the proportion of people for whom oral anticoagulants are guideline-indicated that actually receives these medicines (appendix).[30,55,73]

Figure 2. Percentage of clinically eligible patients receiving oral anticoaugulants, by country/region.



Data from Oldgren et al.[73] OACs – oral anticoagulants. Graph shows OAC use among patients who had non-rheumatic AF and a CHADS2 score of 2 or above.

There is little information available on NOAC registration, availability, or use in LMICs, although the costs of NOACs have been noted as prohibitive in sub-Saharan Africa,[74] India,[75] Asia,[76] and South America.[77] Background papers confirmed that NOACs have very limited availability, with lack of reimbursement by healthcare systems and price being some of the barriers to wider use. In South Africa, access to NOACs is essentially confined to a small proportion of patients in the private sector. In Botswana, "[m]ost experts point to the cost of the NOACs as being the major stumbling block to unfettered prescription and use of the NOACs." In Nigeria, the experts consulted identified two significant barriers, namely the comparatively higher cost of NOACs and the lack of awareness of NOACs locally and reluctance of most physicians to prescribe them. In India, physicians often do not prescribe warfarin because INR monitoring is poor, making the treatment ineffective. In Peru, NOACs are not in the formularies of the public healthcare system, and their availability is limited to the private system or a minimal proportion of patients from the public system that can support costs.

5.4 Anticoagulants and the EML Expert Committee.

NOACs were submitted for inclusion in the WHO EML in 2015. The Expert Committee's report noted the favourable overall clinical benefits of NOACs and some of the advantages over warfarin in terms of monitoring and dietary requirements. It also noted, however, that "the prices of novel oral anticoagulants (NOACs) in most countries are still several times higher than those of older oral anticoagulants such as warfarin, even taking into account of the cost of monitoring warfarin dose and response" and that "the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit".

The EML committee therefore considered that "despite some cost-effectiveness analyses suggesting that the NOACs are "cost-effective", replacing warfarin with a NOAC will require significant investment of a country's healthcare funds, which might be better spent on alternative treatments for other diseases or healthcare facilities."

The failure in the comparative cost-effectiveness criterion appears to have been a significant factor in the Expert Committee's rejection, along with concerns about the lack of the NOACs' reversibility and of data supporting improved outcomes. In recent years, some evidence suggested that NOACs may be superior to warfarin in efficacy and safety, both in meta-analyses of the trials and in real-world settings (see *5.3.4. and 5.3.5.*, above*)*. The concern over lack of reversal agents may also be overcome in the near future, through new reversal agents (adexanet alpha and ciraparantag) that are currently in late stae development. In addition, the concern about reversibility may not be as significant, as bleeding in patients taking NOACs can usually be managed without a reversal agent (see *5.3.4.*, above).

5.5 Inclusion in national essential medicines lists (NEMLs).

We found that NOACs were included in seven of the 25 LMIC NEMLs that we were able to review. One or more NOACs were included in the NEML of Romania, Russia, Serbia, Jamaica, and Panama, and the reimbursement list of Mexico. In the context of consultations with a select number of governments, high prices for NOACs were noted as one of the reasons for non-inclusion in national EMLs.

5.6 Patent landscape for NOACs.

The primary patent for dabigatran has expired in LMICs in 2018, although there are secondary patents until 2024/5 that may delay access to generics in countries where those patents are granted. The expiry dates for the primary patent of the other NOACs in LMICs are 2020, 2022, and 2023 for rivaroxaban, apixaban, and edoxaban respectively. There are also secondary patents on these medicines that may provide exclusivity until 2026-2031 and could potentially play a role in keeping generics out of the market. As shown in Table 2 below, there are patents filed or granted in key countries of generic manufacture such as India, China, and South Africa.

With the expiry of the primary patent on dabigatran, it is likely that generic manufacturers may be able to sell the treatment in countries without blocking secondary patents. Nevertheless, even if a generic version of dabigatran were to become available in some LMICs, there could be significant benefit in enabling generic entry of other NOACs, both from a clinical perspective as well as in terms of price. These were described above.

The need for access to more affordable generic medications was highlighted in the World Heart Federation's 2017 'Roadmap for Nonvalvular Atrial Fibrillation', which noted 'strategies for improving the affordability of [cardiovascular] medications', including '[promoting] the use of high-quality, safe, and efficacious generic medications by overcoming legal barriers relating to patents and licenses in LMICs'.[43]

Table 2. Patent status of NOACs in selected LMICs

NOACS	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM
Apixaban															
Apixaban product generically	2019	.	F	G	G	.	.	G	.	.	G	.	.	G	.
Apixaban product	2022	.	G	G	.	.	G	G	.	.	G	F	G	G	G
Crystalline apixaban composition	2031	.	F	F	.	.	.	F	.	.	.	.	.	G	G
Dabigatran															
Dabigatran product and its etexilate	2018	.	G	G	G	.	G	G	.	.	G	G	G	G	G
Blister packaging for Dabigatran formulation	2025	.	G	R	G**	.	G	G	.	.	G	.	G	G	G
Polymorphic Modification II of Dabigatran Etexilate Mesylate	2024	.	F	G	G**	.	G	G	.	.	G	F	.	G	G
Rivaroxaban															
Rivaroxaban Product	2020	.	G	G	.	G	G	G	G	.	G	F	G	G	.
Process of preparing tablets	2024	.	G	G	G*	G	G	G	G	.	G	G	G	G	.
Method of treating a thromboembolic disorder	2026	.	F	R	.	.	G	A	G	.	G	.	G	G	.
Edoxaban															
Edoxaban and its salts	2022	.	G	G	.*	.	G	G	.	.	G	G	.	G	.
For III crystals of edoxaban	2031	.	F	G	.	.	.	G	.	.	.	.	.	.	.
Edoxaban tablet composition	2028	.	G	G	.*	.	G	G	.	.	G	.	.	G	G

** Patent granted in RU. ** Patent terminated in AM, AZ, KZ, KG, KZ, MD, TJ and TM.*
ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organization Africaine de la Propriete Intellectuelle

5.7 Estimated public health impact.

We estimated that MPP licence could facilitate 0.5–1.6 million additional patient-years of treatment for patients with NVAF, preventing 10,000–31,000 cases of SSE across countries in sub-Saharan Africa, low-income countries, and lower-middle-income countries. For the VTE indication, we estimated that 234,000–702,000 additional patients could be treated, preventing 94,000–281,000 VTE events (further details in the appendix).

Table 2. Estimated public health impact for NVAF/SEE

Assumed duration of MPP impact	4 years
Absolute risk reduction for SSE, per year	2%
Cumulative number of patient-years treated to prevent SSE in NVAF	522,000–1,566,000
Cumulative cases of SSE averted	10,000–31,000

Table 3. Estimated public health impact for VTE

Assumed duration of MPP impact	4 years
Absolute risk reduction for VTE per year	40%
Cumulative number of patients treated for VTE	234,000–702,000
Cumulative cases of VTE averted	94,000–281,000

5.8 Estimated economic impact.

We estimated the potential economic impact of MPP licensing of NOACs in terms of combined savings for SSE and VTE indications, taking into account the potential cost advantages of NOACs for which there are no generics currently on the market. The assumed quantity purchased, per year, was based on projected disease burden and conservative assumptions regarding rate of diagnosis, access to healthcare, and market penetration.

We estimated that MPP licensing could enable savings of US$82–332 million, depending on the medicine licensed and market penetration. We were unable to find pricing information for edoxaban in India (used as the reference country in our analysis).

5.9 Relevant market analysis.

The global market for anticoagulants is expected to grow by 44% in value between 2016 and 2021.[78] Originator NOACs are currently priced US$69–70 per month in the Indian private market. As noted earlier, several generic versions of dabigatran entered the Indian private market in early 2018, with the lowest priced version costing US$26 per month.[79] Cost of production modelling, based on the current market price of raw materials, suggested that NOACs could be profitably manufactured at fairly low cost and could become available at lower prices as volumes increase and the market expands (see appendix). The lowest available price for warfarin is around $1 per month, but there are significant healthcare system costs linked to its use, particularly in connection to the monitoring requirements.[80] Over time, it is expected that total costs of using generic NOACs would be lower than warfarin therapy.

5.10 Conclusions.

There is a substantial burden of atrial fibrillation and venous thromboembolism in LMICs. It is estimated that there will be 17.9 million people NVAF in LMICs by 2020, each with a 1-8% yearly risk of stroke.[19] In addition, there are at least 6 million cases of VTE annually in LMICs.[21] Compounding this significant burden, LMICs are faced with multiple challenges in treating and preventing stroke and VTE, such as limited facilities to treat and rehabilitate those with stroke.[13]

The recommended first-line therapy for these indications in high-income countries is with NOACs,[3,29,60] owing to disadvantages of the next best therapy – warfarin – such as the need for monitoring, and food and drug interactions. In resource-poor settings, attending regular clinic appointments for warfarin monitoring can be challenging for patients and health systems, and physicians in resource-poor settings are often reluctant to prescribe warfarin to patients for this reason. NOACs, however, are unavailable to most patients in LMICs. The recent entry of generic versions of dabigatran to the Indian market can be expected to lead to increased access. [81]

There may be certain economic and clinical advantages for using other NOACs instead of dabigatran. These include possible superior safety of apixaban, the advantage of not needing to coadminister an injectable anticoagulant in the treatment of VTE when using

apixaban or rivaroxaban, and the likely lower generic prices that could be achieved for other NOACs, owing to their significantly lower dosages compared to dabigatran.

We estimated that MPP licensing could facilitate up to 1.9 million patient-years of treatment for both NVAF and VTE. Licensing could also lead to savings for developing county health systems. The economic impact was estimated only for savings in direct expenditure on medicines; other aspects potentially conferring economic gains such as reduction in disability were not included. Similarly, we did not include potential savings from averting additional costs associated with warfarin use, such as monitoring and time spent in hospital.

In view of the limited current use of NOACs in many LMICs and the limited commercial originator markets in such countries, there may be opportunities for win-win agreements that could benefit all stakeholders, through appropriate royalties.

NOACs therefore represent an interesting example of medicines with strong potential for improving public health outcomes in LMICs, that were not included in the WHO EML partly due to affordability concerns. Early MPP licensing in such cases could contribute to making such medicines available sooner to more people in LMICs, where otherwise their use remains limited. Given the lower monitoring requirements of NOACs over alternatives, this could enable more people to access anticoagulation therapy, therefore reducing the risk of strokes and other sometimes fatal complications in LMICs.

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