Affordability of direct oral anticoagulants

Global access to affordable direct oral anticoagulants

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(Submitted: 9 September 2020 – Revised version received: 28 April 2021 – Accepted: 3 May 2021 – Published online: 1 June 2021)

Abstract

Poor control of cardiovascular disease accounts for a substantial proportion of the disease burden in developing countries but often essential anticoagulant medicines for preventing strokes and embolisms are not widely available. In 2019, direct oral anticoagulants were added to the World Health Organization’s WHO Model list of essential medicines. The aims of this paper were to summarize the benefits of direct oral anticoagulants for patients with cardiovascular disease and to discuss ways of increasing their usage internationally. Although the cost of direct oral anticoagulants has provoked debate, the affordability of introducing these drugs into clinical practice could be increased by: price negotiation; pooled procurement; competitive tendering; the use of patent pools; and expanded use of generics. In 2017, only 14 of 137 countries that had adopted national essential medicines lists included a direct oral anticoagulant on their lists. This number could increase rapidly if problems with availability and affordability can be tackled. Once the types of patient likely to benefit from direct oral anticoagulants have been clearly defined in clinical practice guidelines, coverage can be more accurately determined and associated costs can be better managed. Government action is required to ensure that direct oral anticoagulants are covered by national budgets because the absence of reimbursement remains an impediment to achieving universal coverage. Tackling cardiovascular disease with the aid of direct oral anticoagulants is an essential component of efforts to achieve WHO’s target of reducing premature deaths due to noncommunicable disease by 25% by 2025.
Introduction

In April 2019, the World Health Organization’s (WHO’s) Expert Committee on the Selection and Use of Essential Medicines recommended that dabigatran – a direct oral anticoagulant – should be added to the core list of essential medicines.\(^1\) Dabigatran was listed with a square box symbol, which indicates that specified alternatives (e.g. apixaban, edoxaban and rivaroxaban) have full therapeutic equivalence at all approved doses. The decision was based on two independent applications for direct oral anticoagulants: (i) one for their use in individuals with atrial fibrillation;\(^2\) and (ii) the other for their use in individuals with atrial fibrillation or venous thromboembolism.\(^3\) This was the second time an application for the inclusion of direct oral anticoagulants had been considered.\(^4\) In 2015, however, the expert committee rejected the application and commented that further research was required on the unmet need for anticoagulation, particularly in low- and middle-income countries, and that the large cost difference between direct oral anticoagulants and warfarin was disproportionate to the incremental benefit observed.

It is, therefore, timely to reflect upon the arguments presented to WHO’s expert committee on the potential public health impact of including direct oral anticoagulants on national essential medicines lists and to consider how the number of patients who could benefit can be rapidly increased. Listing a medicine as essential is the first step in determining which medicines a country should stock, prescribe and dispense. Moreover, the listing increases the chance that higher-priced essential medicines will be reimbursed by national governments, thereby giving patients easier access to life-saving medicines they cannot afford to buy. At the same time, countries could face disastrous economic consequences without some form of price control.

In 2010, an estimated 33.5 million people worldwide had atrial fibrillation.\(^5\) A study of strokes in 15,400 patients with atrial fibrillation in 47 countries in 2016 found that the annual incidence was greatest in Africa, at 8% (89/1137), compared with 7% (143/2023) in China and 7% (88/1331) in South-East Asia.\(^6\) Venous thromboembolism is also common: in 2014, the incidence ranged from 0.7 to 2.7 per 1000 patient–years in Western Europe, from 1.1 to 2.4 per 1000 patient–years in North America and from 0.2 to 1.6 patient–years in Latin America and Asia.\(^7\)
Anticoagulation therapy has been associated with a 64% reduction in the risk of stroke in people with nonvalvular atrial fibrillation and an 80% reduction in the risk of recurrent venous thromboembolism in those with deep venous thrombosis or pulmonary embolism.\(^8,9\) The narrow therapeutic window (i.e. the safe and effective dose range) of vitamin K antagonists makes it difficult to achieve optimal anticoagulation. In one European study, for example, the proportion of patients with poorly controlled treatment varied from 35% (935/2702) in the United Kingdom of Great Britain and Northern Ireland to 56% (673/1208) in Germany.\(^10\) Among low- and middle-income countries, the proportion of patients with poor anticoagulation has been reported to be as high as 78% (461/588) in Latin America and 83% (1581/1899) in Asia.\(^11\) As could be expected, poor anticoagulation is associated with worse outcomes and higher overall mortality.\(^11\)

**Merits of direct oral anticoagulants**

A new medicine is rarely found to be both more effective and safer than a highly effective comparator and that the level of supporting evidence is good. However, direct oral anticoagulants are one example. These drugs can be used as alternatives to vitamin K antagonists in individuals with atrial fibrillation and an intermediate or high risk of stroke, as well as in patients with venous thromboembolism. Data from large randomized trials indicate that direct oral anticoagulants have a better safety profile than vitamin K antagonists and that they are equally effective, though there is probably little difference between the two in absolute mortality. Table 1 and Table 2 summarize data from comprehensive evidence syntheses from randomized trials that compared direct oral anticoagulants with vitamin K antagonists.\(^3,12\) Table 1 shows clinical outcomes in patients with nonvalvular atrial fibrillation and Table 2 shows outcomes in those with a deep vein thrombosis or pulmonary embolism. Several other systematic reviews have reached similar quantitative and qualitative conclusions.\(^13\)–\(^15\)

As vitamin K antagonists have a narrow therapeutic window and highly variable pharmacokinetics, their use requires strict medical follow-up and dose-monitoring, as well as lifestyle and dietary changes. In contrast, direct oral anticoagulants have more predictable pharmacokinetics and can be administered without dose-monitoring. Although the causes of, and potential solutions for, medication nonadherence are complex, direct oral anticoagulants have the advantage that their use is simple for patients, prescribers and the health-care system. Moreover, these drugs are increasingly used for bridging anticoagulation therapy in patients undergoing
surgery or other invasive procedures and have replaced low-molecular-weight heparin during the perioperative period.\textsuperscript{16}

In 2015, WHO’s expert committee on essential medicines was reluctant to include direct oral anticoagulants on the list of essential medicines, partly because an antidote was unavailable. Recently, however, idarucizumab and andexanet alfa have been approved as reversal agents for dabigatran, rivaroxaban and apixaban,\textsuperscript{17–19} though their efficacy and cost–effectiveness remain uncertain in some settings and patient populations.\textsuperscript{20} Fortunately, bleeding is rare. For instance, in the ROCKET trial,\textsuperscript{21} the rate of life-threatening bleeding in patients with atrial fibrillation was 0.8 and 1.2 per 100 patient–years in the rivaroxaban and warfarin groups, respectively. Current guidelines recommend cessation of the direct oral anticoagulant and supportive care in such cases but do not recommend the routine use of reversal agents.\textsuperscript{22}

Even in highly controlled settings, such as direct oral anticoagulant experimental trials, where patients are properly monitored and those on vitamin K antagonist are maintained in optimal anticoagulation, study participants were in the therapeutic international ratio range for only 60 to 70\% of the time.\textsuperscript{23} Given the difficulty of achieving optimal anticoagulation with vitamin K antagonists in routine clinical practice, then, the medium-term effects of introducing direct oral anticoagulants may be greater than observed in current trials. Data from observational studies seem to confirm this possibility and, in addition, indicate that direct oral anticoagulants also perform better than vitamin K antagonists in older, and more severely ill, patients treated outside of clinical trials.\textsuperscript{2}

**Patients’ preferences**

A systematic review of patients’ preferences for direct oral anticoagulants or warfarin, which were determined using either a survey or the discrete choice method, found that patients preferred direct oral anticoagulants because they were convenient to use and involved less life-style modification.\textsuperscript{24} This preference can also be observed in the progressive increase in direct oral anticoagulant uptake over the years and the accompanying reduction in vitamin K antagonist use. For example, data from the GARFIELD registry,\textsuperscript{25} which was a longitudinal study of individuals from 50 countries with newly diagnosed, nonvalvular atrial fibrillation, show that the proportion of anticoagulant therapy involving direct oral anticoagulants increased from 4\% (224/5500) to 37\% (4065/11 046) between 2010 and 2015 and that the proportion involving vitamin K
antagonists decreased from 53% (2815/5311) to 34% (3714/10 923). Nevertheless, in general patients who were well controlled on vitamin K antagonists and who had no complications preferred to remain on these compounds rather than to switch to direct oral anticoagulants.

In making its recommendation, WHO’s expert committee on essential medicines noted that the underlying philosophy of anticoagulation therapy was to offer a choice of options that included, in particular, treatments that do not depend on frequent laboratory testing. Moreover, as the provision of several anticoagulant therapies involves an opportunity cost for health services, the committee was particularly careful in making its decision. The committee requested that all evidence available in 2015 and afterwards should be reviewed before coming to a final decision in 2019 when it became clear that patients were being deprived of a beneficial treatment.

**Increasing access**

Despite the global burden of death and disability linked to heart disease, access to the medicines essential for preventing and treating cardiac syndromes remains challenging. There are substantial barriers to anti-coagulation therapies, especially in low-resource settings. For instance, adherence to long-term therapy is often poor and tends to decrease over time in patients with non- or pauci-symptomatic conditions. Governments play a central role in improving access to essential medicines for circulatory diseases and in ensuring that all patients in need receive safe and effective treatment. In addition, the widespread use of direct oral anticoagulants in the future, as part of universal health coverage, will depend on developing a competitive market.

**Price**

Since direct oral anticoagulants first entered the market, they have been priced substantially higher than vitamin K antagonists. However, although this price differential may impact out-of-pocket expenditure, it could have a smaller effect on overall costs. Patients receiving vitamin K antagonists require dose-monitoring and frequent visits to anticoagulation clinics. From the payer’s perspective, then, the availability of an anticoagulation monitoring system is a prerequisite for safely providing anticoagulation with vitamin K antagonists. In contrast, direct oral anticoagulants do not require dose-monitoring and the frequency of follow-ups is dictated by the patient’s health rather than by the need for dose adjustments. Hence, when the cost of running anticoagulation clinics or their equivalents is considered, the direct costs of vitamin K antagonists and direct oral anticoagulants are likely to be similar.
Recent systematic reviews of economic evaluations have moved from assessing willingness to pay from a fixed-budget perspective and have adopted a payer’s perspective. As a result, reviews now indicate that it is cheaper to anticoagulate patients with nonvalvular atrial fibrillation or venous thromboembolism using direct oral anticoagulants than vitamin K antagonists.\textsuperscript{26,27} Furthermore, the pharmaceutical market can change rapidly: once generic alternatives are available, competition and pricing negotiations can reduce the financial burden for countries. Table 3 illustrates how prices for direct oral anticoagulants can vary globally and puts potential target pricing in context. For example, the monthly cost of dabigatran and rivaroxaban in Brazil was as low as 20 United States dollars (US$), which was 50 to 95% below prices in some other countries. Given current price trends, we forecast that the cost of generic direct oral anticoagulants can easily be far less than US$ 1 per day (for two tablets) in most countries.

**Introduction into the health-care system**

In 2017, the cost of direct oral anticoagulants was reimbursed in several high-income countries, whereas only a few low- and middle-income countries recognized their potential advantages and listed them beside vitamin K antagonists in their national essential medicines lists.\textsuperscript{28} In 2019, dabigatran was listed by 14 countries out of 137 investigated: Bahrain, Bulgaria, Croatia, Czechia, Estonia, the Islamic Republic of Iran, Mexico, Poland, Portugal, the Russian Federation, Slovakia, Slovenia, Sri Lanka and Sweden.\textsuperscript{29} Most were European. Ten countries listed another therapeutically equivalent direct oral anticoagulant (e.g. rivaroxaban and apixaban) as an alternative. However, in many places where private and public health-care provision coexist, direct oral anticoagulants have been preferentially introduced in the private sector, thereby increasing gaps in health equity. For example, a recent observational study of prescription patterns in individuals with atrial fibrillation in the United States of America found that the probability of receiving a direct oral anticoagulant instead of a vitamin K antagonist was higher in educated individuals with a high income.\textsuperscript{30}

Health authorities need to develop a strategic model for managing the introduction of direct oral anticoagulants into their health-care systems and for avoiding serious discrepancies in access. Strategies should include extensive prelaunch activities, risk-sharing arrangements, restrictions on prescribing, and monitoring prescribing after direct oral anticoagulants have been
introduced. In the past, several countries experienced difficulties with managing the launch of direct oral anticoagulants: they subsequently withdrew them from reimbursement lists, restricted access or struggled for funding.

**Improving usage**

For individual countries, the use of direct oral anticoagulants is usually defined by clinical practice guidelines, which determine who should be prescribed the drugs. Countries with low resources or where direct oral anticoagulants are expensive might restrict their use to high-risk populations. In several countries, these drugs were initially used as non-routine treatment for highly selected patients who were ineligible for vitamin K antagonists. However, active marketing by drug companies encouraged extending their use to patients who might not have been eligible for direct oral anticoagulants according to local guidelines or local medical authorities. In Australia, direct oral anticoagulant-related events sponsored by the pharmaceutical industry reached 90,000 health professionals over a period of 4 years. By favouring expensive alternatives or unnecessary drug use, promotional marketing can undermine the principle behind essential medicines lists, which is the careful selection of safe and effective medicines. Government agencies should promote independent information on direct oral anticoagulants and control the quality of continuous medical education.

Although thresholds for an increased risk of stroke may vary between regions, individuals with atrial fibrillation and one risk factor for stroke are generally considered to have an intermediate risk (estimated annual risk: 3%), whereas those who have had a previous stroke or who have two or more risk factors are defined as high risk (estimated annual risk: 8%). People who have had a venous thromboembolism provoked by a transient risk factor, such as recent surgery, are considered to have a low risk of recurrence (estimated annual risk of a new event: 4%), whereas those who experience an unprovoked event are generally considered at a high risk (estimated annual risk: 7%). Treating high-risk individuals with direct oral anticoagulants is a starting point for achieving the 50% treatment coverage threshold for eligible individuals but policies are needed to extend treatment to those with an intermediate risk. This 50% coverage threshold is a voluntary target of WHO’s global action plan for noncommunicable diseases and is a precondition for reducing premature deaths due to heart attacks and strokes.
Pooled procurement

With pooled procurement, the needs of several buyers are aggregated, which influences price negotiations with manufacturers. In Chile, for example, the public health-care system covers approximately 85% of the population and, although the administration of health-care facilities is decentralized, many medications are purchased centrally. With this mechanism, the cost of dabigatran to the public system is approximately 60% of its price at pharmacies (I Neumann, personal communication, December 2020). However, Chile is a relatively small country. The purchasing power of bigger countries may be larger and could further reduce the cost of direct oral anticoagulants. Overall, countries should avoid low levels of pooled procurement or a high degree of procurement fragmentation. The efficiency of procurement is maximized when demand can be predicted with high confidence and contract payments are reliable. These factors will decrease transaction costs and the market risk for suppliers, thereby encouraging better offers and preferential prices.

In WHO’s *WHO Model list of essential medicines*, direct oral anticoagulants are listed with the square box symbol, without a preferred formulation being specified for individual indications. This indication was done because all approved doses of different formulations are valid alternatives. Moreover, it enables countries or central health-care hubs to choose to purchase a single formulation that covers all doses required or to make selective purchases and limit the use of alternative formulations to common indications, thereby achieving the best tendering prices.

Generic alternatives

Generic direct oral anticoagulants are expected to become more available in the next 5 years. The market exclusivity period has ended for dabigatran, the first direct oral anticoagulants approved by the United States Food and Drug Administration (FDA; October 2010), and generic alternatives have already been introduced in some countries. In 2019, the FDA approved the first generic versions of apixaban and, in 2020, the European Medicines Agency approved generic versions of rivaroxaban. The introduction of generic bioequivalents to market jurisdictions is subject to local legislation and approval from national authorities. Product regulation and market access can be affected by a lack of transparency or by collusion between manufacturing companies and political
or technical bodies.\textsuperscript{41} Although switching from an original drug to its generic is still debated in some countries, the evidence shows that there are no clinically meaningful differences from the reference product in terms of quality, safety or efficacy and that generics should be considered as therapeutically equivalent for procurement purposes.\textsuperscript{37,42} Placing an unnecessary burden and cost on the development and licensing of generics can delay the availability of alternative drugs and affect national competitive pharmaceutical markets. As a result, the level of local competition can vary greatly between countries, as illustrated by the cost differences in direct oral anticoagulants presented in Table 3. Explicit or tacit agreements between companies to set prices above market-clearing rates, thereby leading to a cartelized market, are also possible, particularly when there are few competitors, as is the case for direct oral anticoagulants. Governments are the primary coordinators of efficient tendering processes and should ensure market competition is enforced by expanding the pool of potential suppliers.

**Patent pools and prequalification**

Improving access to novel medicines requires new strategies. One emerging approach is the use of patent pools, which enable third parties to acquire nonexclusive licences for the intellectual property needed to market medicines. These pools can help address some of the barriers to access for low- and middle-income countries. The Medicines Patent Pool is a public health organization backed by the United Nations that negotiates medicine licences with patent holders. Historically, negotiations have concerned the treatment of communicable diseases (e.g. human immunodeficiency virus infection). In 2018, the Medicines Patent Pool extended its mandate to include other patented essential medicines.\textsuperscript{43} One product category that could potentially be licensed through the patent pool was identified by analysing the epidemiology, treatment landscape, market size and pricing of direct oral anticoagulants in low- and middle-income countries. The Medicines Patent Pool estimated that, in 2018, public health licensing of direct oral anticoagulants could facilitate up to 1.9 million patient–years of treatment for nonatrial fibrillation and venous thromboembolism.\textsuperscript{44} In addition, patent pools could generate substantial savings for national health systems because direct expenditure on medicines would be calibrated to local budgets by recognized international organizations. Potential savings are in the order of hundreds of millions of US$. Important information on patented small molecule medicines, including dabigatran, apixaban and edoxaban, can be found in MedsPaL,\textsuperscript{45} a free database on the
intellectual property status of patented medicines included in *WHO Model list of essential medicines* for low- and middle-income countries.

Another important contributor to the increased availability and affordability of essential medicines is WHO’s prequalification programme. This service helps local authorities in low- and middle-income countries manufacture, regulate and monitor the quality of medicines considered important for public health.46 High-quality generic versions of dabigatran have already been produced and it is possible that the launch of large programmes against noncommunicable diseases could encourage competitive manufacturers to develop other generic direct oral anticoagulants. Where resources are limited, prequalification of a generic should be regarded as a precondition for its selection as an essential medicine. Prequalification could occur simultaneously with public health licensing (with appropriate royalties), thereby creating profitable conditions for medicines to be marketed at a low cost.47

**Conclusions**

Tackling cardiovascular disease is essential for achieving WHO’s target of reducing premature deaths due to noncommunicable diseases by 25% by 2025.48 One step in this process will involve developing strategies to introduce direct oral anticoagulants and other interventions, identifying those patients most likely to benefit in individual countries and increasing the drugs’ affordability, thus mitigating scepticism by potential adopters. Currently the price of direct oral anticoagulants is a major obstacle for health-care systems. However, this obstacle could be removed through multiple actions, including price negotiations, pooled procurement, competitive tendering, patent pools and expanded use of generics. Including direct oral anticoagulants in national essential medicines lists can help increase the proportion of patients who receive optimal anticoagulation and reduce their risk of premature death.

**Acknowledgments**

NM was secretary of WHO’s Expert Committee on the Selection and Use of Essential Medicines between 2015 and 2020. LB and GC are former chairs of the Expert Committee.

**Competing interests:**

IN and HJS were involved in preparing applications for the inclusion of direct oral anticoagulants in WHO’s Model List of Essential Medicines.
References


Table 1. **Treatment outcomes with direct oral anticoagulants versus vitamin K antagonists in patients with nonvalvular atrial fibrillation, meta-analysis, 2019**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trial participants followed up&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Evidence quality&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Relative risk (95% CI) of outcome with direct oral anticoagulants versus vitamin K antagonists</th>
<th>Incidence of outcome in first year of treatment</th>
<th>Difference between direct oral anticoagulants and vitamin K antagonists, per 1000 patients (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>73,641</td>
<td>High</td>
<td>0.90 (0.85 to 0.94)</td>
<td>75</td>
<td>−7 (−11 to −4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>75,543</td>
<td>High&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.83 (0.72 to 0.96)</td>
<td>33</td>
<td>−6 (−9 to −1)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>75,018</td>
<td>Moderate&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>0.74 (0.48 to 1.13)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3</td>
<td>−1 (−1 to 0)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>75,490</td>
<td>Moderate&lt;sup&gt;g&lt;/sup&gt;</td>
<td>0.81 (0.66 to 0.98)</td>
<td>59</td>
<td>−11 (−20 to −1)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

<sup>a</sup> The meta-analysis included participants in 13 randomized controlled trials.

<sup>b</sup> Evidence quality was assessed using the grading of recommendations assessment, development and evaluation (GRADE) approach.

<sup>c</sup> Although some heterogeneity was observed ($I^2 = 47\%$), we did not downgrade the level of evidence because of inconsistency.

<sup>d</sup> Although some heterogeneity was observed ($I^2 = 31\%$), we did not downgrade the level of evidence because of inconsistency.

<sup>e</sup> The level of evidence was downgraded because of imprecision (i.e. studies included few patients and few events and, therefore, the confidence interval for the effect was large).

<sup>f</sup> As the confidence interval probably crosses decision thresholds, the possibility of either benefit or harm cannot be excluded.

<sup>g</sup> Significant heterogeneity was observed ($I^2 = 77\%$).

### Table 2. Treatment outcomes with direct oral anticoagulants versus vitamin K antagonists in patients with deep vein thromboses or pulmonary embolisms, meta-analysis, 2020

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trial participants followed up(^a)</th>
<th>Evidence quality(^b)</th>
<th>Relative risk (95% CI) of outcome with direct oral anticoagulants versus vitamin K antagonists</th>
<th>Incidence of outcome in first year of treatment with vitamin K antagonists, per 1000 patients</th>
<th>Difference between direct oral anticoagulants and vitamin K antagonists, per 1000 patients (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>28,778</td>
<td>Moderate(^c)</td>
<td>0.99 (0.85 to 1.15)(^d)</td>
<td>39</td>
<td>0 (−6 to 6)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>28,571</td>
<td>Moderate(^c)</td>
<td>0.97 (0.77 to 1.23)(^d)</td>
<td>20</td>
<td>−1 (−5 to 5)</td>
</tr>
<tr>
<td>Proximal deep vein thrombosis</td>
<td>28,668</td>
<td>Moderate(^c)</td>
<td>0.80 (0.59 to 1.09)(^d)</td>
<td>26</td>
<td>−5 (−11 to 2)</td>
</tr>
<tr>
<td>Major bleeding(^e)</td>
<td>28,876</td>
<td>High</td>
<td>0.63 (0.47 to 0.84)</td>
<td>17</td>
<td>−6 (−9 to −3)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

\(^a\) The meta-analysis included participants in 12 randomized controlled trials.

\(^b\) Evidence quality was assessed using the grading of recommendations assessment, development and evaluation (GRADE) approach.

\(^c\) The level of evidence was downgraded because of imprecision (i.e. studies included few patients and few events and, therefore, the confidence interval for the effect was large).

\(^d\) As the confidence interval probably crosses decision thresholds, the possibility of either benefit or harm cannot be excluded.

\(^e\) At 6 months.

Data source: Ortel et al., 2019.\(^12\)

### Table 3. Estimated cost of direct oral anticoagulants, by region and country, 2019

<table>
<thead>
<tr>
<th>Region and country</th>
<th>Approximate monthly cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td><strong>Americas</strong></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>50</td>
</tr>
<tr>
<td>Brazil</td>
<td>20</td>
</tr>
<tr>
<td>Chile</td>
<td>30</td>
</tr>
<tr>
<td>Canada and United States</td>
<td>300 to 601</td>
</tr>
<tr>
<td>Colombia</td>
<td>30</td>
</tr>
<tr>
<td><strong>European</strong></td>
<td></td>
</tr>
<tr>
<td>United Kingdom(^a)</td>
<td>90</td>
</tr>
<tr>
<td><strong>South-East Asia</strong></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>61</td>
</tr>
<tr>
<td><strong>Western Pacific</strong></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>65</td>
</tr>
<tr>
<td>China</td>
<td>222</td>
</tr>
</tbody>
</table>

ND: not determined; US$: United States dollar.

\(^a\) In the United Kingdom, edoxaban also cost approximately 90 United States dollars per month.