Evolving trends in consumption of direct oral anticoagulants in 65 countries/regions from 2008 to 2019

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Key points

- Little is known about the consumption trends and costs of each DOAC at the global level.
- Consumption and cost of individual DOACs were estimated in 65 countries from Q1-2008 to Q2-2019.
- Consumption of rivaroxaban and apixaban overtook dabigatran in most countries, edoxaban use remains limited to East Asian countries
- The United States, Puerto Rico and Thailand paid higher prices for DOACs than other countries.

Abstract

Background DOACs has been increasingly utilised over warfarin. However, little is known about the relative consumption trends and costs of each DOAC at the global level.

Methods Ecological study using pharmaceutical sales data from IQVIA-MIDAS database to estimate consumption and cost of individual DOACs in 65 countries from 2008 to 2019. Consumption was estimated from the volume of DOACs sold, expressed as defined-daily-dose/1000-inhabitants/day (DDDTID). Compound and absolute annual growth rates were reported to quantify consumption changes over time. Costs were estimated as manufacturer price per day-of-therapy.

Results Global consumption of dabigatran, rivaroxaban, apixaban and edoxaban were 0.31, 1.05, 1.08 and 0.78 DDDTID in Q2-2019, compared to 0.23, 0.54, 0.21 and 0.03 in Q2-2015, with highest consumption in Western Europe, Northern Europe and Oceania (18.2, 14.07, 13.14 DDDTID). In the majority of countries (46/65, 70%), rivaroxaban contributed to most DOAC consumption (35-100%), whereas dabigatran accounted for less than one-third. Edoxaban accounted for <20% of the total in Northern America and Europe but contributed significant proportions in Japan (28.58%) and South Korea (31.37%). Longer median time-to-adoption from FDA approval for apixaban and edoxaban was observed. Costs of all DOACs were ~2-4 times higher in the United States, Puerto Rico and Thailand than other countries.

Conclusions Regional differences exist in consumption pattern and trends of individual DOACs over the past decade. Consumption of rivaroxaban and apixaban overtook dabigatran in most countries, whereas use of edoxaban remains limited except in East Asian countries. The United States pays higher prices for DOACs than other countries.

1. INTRODUCTION

Oral anticoagulants (OACs) including vitamin-K antagonists [VKAs] and direct oral anticoagulants [DOACs] are the mainstay therapy for prevention of stroke and thromboembolism in patients with atrial fibrillation (AF), as well as prophylaxis and treatment of venous thromboembolism (VTE), with the former accounting for the majority of chronic use. DOACs, namely dabigatran, rivaroxaban, apixaban, and edoxaban, were successively introduced in the past decade as an alternative to warfarin for its indications. Large-scale clinical trials have consistently shown noninferior or superior efficacy and safety of each DOAC compared to warfarin in patients with AF.[1–4] Consequently, DOACs have begun to replace VKAs (i.e. warfarin) as the recommended standard of care for various indications. Indeed, the latest American and European clinical practice guidelines recommend DOACs over VKAs as first-line therapy in patients with non-valvular AF or pulmonary embolism.[5–7]

Previous studies reported temporal changes in the prescription patterns of OACs in patients with AF. National trends in the use of OACs had been reported in the United States (US)[8], Canada[9,10], United Kingdom[11], Denmark[12], Netherlands[13], Spain[14], Australia[15], China[16] and Qatar[17]. However, these studies generally only focused on assessing patient-related and clinical factors leading to the choice of prescribing warfarin versus DOACs in individual countries. Also, the cost of different DOACs and its influence on consumption of DOACs across multiple regions have not been fully evaluated. As newer DOACs have been introduced with increasing uptake in recent years, the focus is no longer whether DOACs would replace warfarin in clinical use, but rather how the consumption of individual DOACs evolve over time. Understanding the evolving trends in DOAC consumption and cost on a global level would help identify regional differences and provide evidence for formulating national policies.

No study has investigated consumption trends of individual DOACs in detail, nor compared the use of individual DOACs across multiple geographical regions. Further, previous studies

reported DOAC consumption up to 2017 and did not account for the most recent consumption changes and introduction of edoxaban since 2015. This study aimed to describe the global landscape in consumption and cost of DOACs with comparisons between each DOAC and across geographical regions, as well as to assess dynamic changes in consumption trends over time.

2. METHODS

2.1 Data sources

We conducted a descriptive ecological study using national pharmaceutical sales data from the IQVIA Multinational Integrated Data Analysis System (IQVIA-MIDAS) database. IQVIA-MIDAS captures data on the volume of specific pharmaceutical products sold to retail and hospital pharmacies through national audits in each of the included countries and standardises the data to facilitate global-level analysis. In countries with limited raw data, projections have been applied in IQVIA-MIDAS to represent 100% of the total market sales volume based on knowledge of market share, thus providing a representative estimate of the sales volume in each country. Data from IQVIA-MIDAS were internally validated from alternative sources of sales data demonstrating high data accuracy.[18] Researchers routinely use IQVIA-MIDAS data to evaluate medicine consumption patterns.[19,20] No patient-level data such as patient demographics and medical indications are available, hence this study was exempt from ethics approval by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Population estimates for each country was obtained from the UN World Population Prospects 2019.[21] Data on AF prevalence was obtained from the Global Burden of Disease (GBD) study 2019.[22]

2.2 Data analysis

We included quarterly data from Q1 2008 to Q2 2019 in 65 countries, which were classified into six geographical regions (See Supplementary Table 1, Additional file 1). Included

countries constitute 70.5% of the world population and 86.4% of patients with AF globally as of 2019.[22] Consumption of DOACs was estimated from the volume of DOACs sold and expressed in defined daily dose per 1000 inhabitants per day (DDDTID), which estimates the proportion of population receiving a particular medicine daily in a particular year, accounting for differences in population and medicine dosage. Consumption of DOACs was also expressed in defined daily dose per 1000-AF-patients per day (DDDTPD), to provide another perspective which accounts for the different age structure and AF prevalence in different countries and regions. Both the compound annual growth rate ($CAGR = \left(\sqrt[number\ of\ years]{\frac{Final\ consumption\ (DDDTID)}{Initial\ consumption\ (DDDTID)}} - 1\right) \times 100$) and absolute annual growth (DDDTID/year) were reported to quantify changes in consumption over time. To quantify the time lag between introduction of a DOAC and its adoption in individual countries, we defined time to adoption of a DOAC in a specific country to be the number of quarters elapsed from FDA approval of a DOAC to its adoption in that country, where a DOAC is considered adopted when its consumption reaches an arbitrary threshold of at least 2% of the total OAC consumption. Wilcoxon rank sum test with Holm adjustment for multiple comparisons was used to assess any difference in median time to adoption when all countries were considered as a whole. Cost of DOAC was expressed as the manufacturer price (in international dollar (Int$) and US dollar (USD)) per day-of-therapy, taking into account the twice-daily dosing for dabigatran and apixaban and purchasing power parity of different countries. Conversion factors for purchasing power parity and data on country income level were obtained from the World Bank.[23,24] Data were analysed using the R software (version 4.0.3).

3. RESULTS

3.1 Global landscape of DOAC consumption, Q2 2019

As of Q2 2019, the total consumption of DOACs in the countries studied were 2.57 DDDTID (dabigatran: 0.31; rivaroxaban: 1.05; apixaban: 1.08; edoxaban: 0.78), and 270.48 DDDTPD with respect to the AF patient population (dabigatran: 31.89; rivaroxaban: 110.84; apixaban: 110.49; edoxaban: 52.16). Total consumption of DOACs was highest in Western Europe (18.20 DDDTID, 940.64 DDDTPD), Northern Europe (14.07 DDDTID, 690.64 DDDTPD) and Oceania (13.14 DDDTID, 635.59 DDDTPD), and lowest in Southern Asia (0.06 DDDTID, 10.27 DDDTPD) and South-Eastern Asia (0.21 DDDTID, 29.27 DDDTPD) (Tables 1-2 and Figure 1). In the majority (46 of 65, 70%) of countries, rivaroxaban contributes to the greatest proportion of total DOAC consumption (ranging from 35%–100% of the total), whereas dabigatran accounts for less than one-third of the total (Figure 2). The highest proportion of use of apixaban was observed in Northern and Western Europe, Australia and Northern America. Consumption of edoxaban was only observed in 27 of the 65 included countries, mainly in Northern America, Europe, Brazil, Japan and South Korea, accounting for less than 20% of total DOAC consumption in most countries. Yet, edoxaban accounted for a significant portion of DOAC consumption in Japan (2.43 DDDTID; 28.58%) and South Korea (0.80 DDDTID; 31.37%).

3.2 Regional trends in DOAC consumption

Consumption of each DOAC evolves over time and consumption patterns vary across geographical regions (Tables 1-2 and Figure 3). Yet notably, consumption of rivaroxaban and apixaban overtook that of dabigatran over time in all geographical regions (Figure 3). In Northern America, consumption of dabigatran increased by about 7-fold from Q4 2010 (FDA approval of dabigatran for AF) to Q4 2011 (0.90 DDDTID/year, CAGR: 692.63%), but

decreased by ~10% annually (-0.08 DDDTID/year, CAGR: -10.07%) after Q4 2011 (FDA approval of rivaroxaban for AF). Consumption of rivaroxaban increased at a greater annual rate (0.86 DDDTID/year, CAGR: 157.84%) before Q3 2014 than after (0.34 DDDTID/year, CAGR: 13.00%). Consumption of apixaban increased by 50% annually on average, while consumption of edoxaban was minimal (0.01 DDDTID; 0.14% as of Q2 2019) and decreased over the past three years (-0.004 DDDTID/year, CAGR: -20.30%). In Europe, consumption of individual DOACs had increased steadily at different rates over the past three years (dabigatran: 0.16 DDDTID/year, CAGR: 13.46%; rivaroxaban: 0.56 DDDTID/year, CAGR: 16.07%; apixaban: 0.95 DDDTID/year, CAGR: 44.89%; edoxaban: 0.54 DDDTID/year, CAGR: 147.95%). In Oceania, consumption growth of dabigatran was mainly driven by New Zealand, whereas consumption growth of rivaroxaban and apixaban were mainly driven by Australia. In Asia, consumption of edoxaban approximately doubled every year on average since 2015 (0.22 DDDTID/year, CAGR: 106.72%), registering a greater growth rate than other DOACs over the same period, which was mainly contributed by Japan.

3.3 Time from FDA approval to country-wise adoption of DOAC

The pattern of adoption (defined as reaching 2% total OAC consumption) of each DOAC varied across the countries studied (Figure 4). We also observed a wide distribution of the time taken from approval of each DOAC by the US FDA for AF to country-wise adoption within and across different geographical regions (Figure 5). Considering all countries included as a whole, we observed a longer median time to adoption for apixaban and edoxaban compared to dabigatran or rivaroxaban (Table 3).

3.4 Global patterns in DOAC costs

As of Q2 2019, the costs of all DOACs were the highest in the US, Puerto Rico and Thailand, which were approximately 2-4 times higher than most other geographical regions (Table 4 and Figure 6). Notably in China, the price of apixaban (12.83 Int$/day-of-therapy) was around 2.5 times higher than dabigatran (5.70 Int$/day-of-therapy) and rivaroxaban (4.78 Int$/day-of-therapy). After adjusting for purchasing power parity, consumption of individual DOACs were negatively correlated with manufacturer price except edoxaban (dabigatran: r_s=-0.561, p<.001; rivaroxaban: r_s=-0.526, p<.001; Apixaban: r_s=-0.639, p<.001; edoxaban: r_s=-0.106, p=0.599) (Figure 7). The costs of DOACs expressed in USD/day-of therapy were also reported in Supplementary Table 2, Additional file 2.

3.5 Trends in warfarin consumption

With the introduction of DOACs since 2010 and increasing adoption of DOACs in the past few years, consumption of warfarin in most countries studied has decreased during 2016-2019 (Table 6). Total consumption of warfarin in all countries studied decreased from 1.025 DDDTID in Q2 2016 to 0.809 DDDTID in Q2 2019 (0.07 DDDTID/year, CAGR: -7.57%). Nevertheless, in regions with low DOAC consumption including Southern Asia, South-Eastern Asia, Central America and Central Asia, consumption of warfarin has remained stable or increased during 2016-2019 (Table 6).

4. DISCUSSION

4.1 Changing landscape of global DOAC consumption - comparison with previous studies

To our knowledge, this is the first study to describe the consumption and cost of individual DOACs on a global scale, and to assess the changing trends and time to adoption of individual DOACs across multiple geographical regions. Previous studies reported significant increases

in consumption of DOACs in the earlier period of 2010 up to 2017 in multiple countries, including the US, Canada[9], UK[11], Netherlands[13], Spain[14], Australia[15], China[16] and Qatar.[17] Our findings confirmed that these increasing trends continued in the latest period up to Q2 2019 in most of the included countries. The increasing consumption of DOACs in recent years (especially after 2016) was accompanied with decreasing warfarin consumption observed during the same period in most countries, reflecting that the increase in DOAC consumption was indeed contributed by a shift in choice of oral anticoagulant therapy from warfarin to DOACs, rather than merely an increase in the number of AF patients over time. On the other hand, the pattern in consumption and choice of individual DOACs has changed over the past few years compared to those reported from previous studies. For instance, in North America, previous studies reported that rivaroxaban and dabigatran were the most used agents,[10,25–28] whereas in our study apixaban accounted for the highest proportion of consumption since 2018. Interestingly, the consumption trend of DOACs observed in Northern America were also consistent with general popularity trends of DOACs reported by Lippi et al using Google Trends scores from 2004 to 2017,[29] which likely reflects a general awareness and interest in using DOACs. In the UK, while rivaroxaban and apixaban remained the agents most used, rivaroxaban accounted for the majority of NOAC prescriptions (64.8%) in 2015 compared to apixaban (29.3%) in the primary care setting,[11] whereas in 2019 our study showed that the proportion of use in terms of DDDTID of apixaban (48.3%) had become greater than rivaroxaban (40.2%).

4.2 Factors influencing global DOAC consumption

The incidence and prevalence of AF has increased over the past decade, attributing to raised community surveillance, an aging population, and increasing risk factors for AF.[30,31] The recommendation to use the CHA_2DS_2-VASc score to determine eligibility for oral anticoagulant therapy in both European and US guidelines[32] may have increased the number

of eligible patients with AF for DOAC therapy for stroke prevention although undertreatment remains prevalent in many countries. In addition, results from large-scale RCTs of DOACs in the last decade provided evidence for the safety and effectiveness of DOACs in patients with AF. Subsequent changes in clinical guideline recommendations have significantly changed clinician practice in the choice of oral anticoagulant. Table 4 summarises the approximate dates when each DOAC was approved by the United States (US) Food and Drug Administration (FDA) for use in AF,[33] when landmark RCT for each DOAC was published,[1–4] and when AHA/ESC guidelines revised recommendations on DOACs.[5,6,32,34] These changes to clinical guidelines and evidence likely contributed to the global increase in the use of DOACs observed in our study. Nevertheless, our results show that the extent and progress of this change in practice varies significantly across geographical regions, with the growth in DOAC use significantly lower in less developed regions of the world, which could be attributed to the younger population age structure and relatively less affordability of DOACs in less developed countries. The change in guidelines were not immediately reflected in DOAC consumption but as a gradual change over the past decade.

To date, no randomised trials have had data on the safety and effectiveness of DOACs in a head-to-head manner. Yet, observational studies and comparison of individual DOACs with warfarin in RCTs suggest that specific DOACs may be associated with specific clinical merits. For instance, dabigatran may be associated with a lower risk of intracerebral haemorrhage than apixaban and rivaroxaban based on a Bayesian network meta-analysis of DOAC trials,[35] whereas apixaban may be associated with a lower incidence of hospital admission for gastrointestinal bleeding than dabigatran and rivaroxaban as shown in a large retrospective cohort study in the US.[36] These could still influence clinician choice despite no current consensus or guidance about the preference for one DOAC versus another in terms of stroke or bleeding risk. Additionally, the choice of DOAC in the general population is contingent on

non-clinical factors, including convenience of administration, potential side effects, cost and availability. For instance, patients may consider the once-daily dosage of rivaroxaban and edoxaban to be more convenient,[37] and dyspepsia due to tartaric acid in the formulation of dabigatran may render it less desirable to certain patients with previous gastrointestinal conditions.[38] As such, it is reasonable that rivaroxaban and apixaban accounted for the highest proportion of use with consistently increasing trends in most countries studied.

The antidote for dabigatran (idarucizumab) was approved by FDA in October 2015, and became available in most of Europe, North America and Oceania by Q4 2016 (Table 7). Dabigatran was the only DOAC with an antidote for emergency reversal of anticoagulation during 2016-2018, until the approval of andexanet alfa (antidote for rivaroxaban and apixaban) in May 2018. However, proportion of use had been reducing for dabigatran and increasing for rivaroxaban and apixaban in countries where idarucizumab was available, reflecting that the availability of an antidote played only a minor role in physicians' and patients' choice of DOAC, compared to other clinical and non-clinical factors.

Furthermore, nationwide policies and regulations could influence patients' and physicians' choice of anticoagulant therapy as well. For instance, some countries authorized using commercials in the media for drugs or drug indications, while in other countries it is forbidden. Future studies could explore and review how these regulations and policies in different countries could influence consumption of DOACs.

In more developed regions such as North America and Europe, we observed significant uptake of dabigatran and rivaroxaban before or within a year after FDA/EMA approval, yet significant uptake of apixaban and edoxaban was relatively delayed, in general, at least one year after FDA approval in most countries. This could be due to a variety of factors at government and institutional levels. At the government level, limited evidence on the marginal cost-benefit of newer DOACs (for instance, apixaban and edoxaban) compared to earlier ones (for instance,

dabigatran and rivaroxaban) in the early years of approval may have led to lower priority for inclusion in the national formulary or medical coverage plans. At the institutional level, the speed of adopting newer drugs could be influenced by clinicians' risk preferences and the specialty or type of institution.[39] Clinicians tend to be conservative in adopting new cardiovascular drugs due to factors including incomplete information on the intermediate or long-term safety and effectiveness, and lack of awareness about their introduction.[40] Considerable variability in time to adoption of individual DOACs across different regions worldwide likely reflects significant differences in country-wise policies for formulary management and approval of new drugs and healthcare system structure. Consumption of edoxaban remains low in Northern America, although uptake in Asia, especially Japan was prompt.

4.3 Variability in cost of DOACs

Our results showed that as of Q2 2019, the costs of all DOACs were approximately 2–4 times higher in the US and Puerto Rico (an unincorporated territory of the United States) compared to the rest of the countries. This finding was also consistent with recent findings from Emanuel et al where they reported a three to five-fold higher total drug spending per capita in the US than Australia, UK and other Northern European countries in 2018.[41] Indeed, the high costs of prescription drugs in general has long been an issue in the United States, and has been attributed to policy factors in the US healthcare system, including granting monopoly rights to manufacturers by patents upon FDA approval, as well as the lack of negotiation mechanisms and objective standards to inform drug prices.[41,42] Kanavos et al observed that the higher spending on prescription drugs in the US may be attributed partly to their fast uptake of new drugs.[43] While this may be true for biologics, our results do not support any correlation between uptake of DOACs and their prices in the US and other countries. Indeed, many Northern and Western Europe countries had a similar time to adoption and consumption as of Q2 2019 than

the US yet the price per day of therapy in these countries were only about 25% of that in the US.

Similar to the US, we observed that the price of DOACs in Thailand were also 2–4 times higher than that of other countries and were as high as in the US when purchasing power parity was accounted for. This implies that DOACs are likely not affordable for most patients in Thailand, yet the reason behind remains unclear. Indeed, a recent cost-effectiveness analysis of DOACs in Thailand suggested that NOACs were unlikely to be cost-effective at current prices.[44] We also observed that the price of apixaban in China was more than double that of dabigatran and rivaroxaban while the proportion of use of apixaban was less than 1% of the total DOAC consumption. This is likely due to the fact that apixaban is only approved in China for VTE prophylaxis in hip replacement surgery while dabigatran and rivaroxaban are also approved for stroke prevention in nonvalvular AF.[45] In contrast, local approvals for DOACs in other countries generally follows the same indications as the FDA/EMA approval.

When purchasing power parity was accounted for, we found that consumption of DOACs appeared to be negatively correlated with manufacturer price. This may imply that the high cost of DOACs in certain countries could have limited the affordability of DOACs and thus hindered their use in such countries. Consistent with a previous study,[46] consumption of DOACs were generally higher in high-income than middle-income countries. Nevertheless, we observed that for some countries such as the UK, costs of different DOACs were similar and consumption of each DOAC was more dependent on clinical factors and patient preferences.

4.4 Limitations

Our analyses are subject to some limitations. The consumption of DOACs reported were based on national sales data, which may not perfectly correlate with actual medicine use by patients due to non-adherence. Nevertheless, the same potential limitation exists when estimating consumption using prescriptions or claims data. In the absence of global surveillance data, sales

data such as those collected by IQVIA remains a standardised, geographically and temporally comprehensive source of information for evaluating global DOAC consumption and cross-country analyses. Since patient-level data such as demographics and medication indications were not available, we could not differentiate consumption of DOACs for AF versus VTE, nor compare the use of DOACs among patients with different risk of stroke or bleeds. Existing and future studies based on large-scale multicentre patient cohorts would be useful to identify factors influencing the choice of individual DOACs in specific patient populations. Furthermore, the cost of DOACs reported were based on manufacturer-level price, which does not account for discounts or subsidies and does not reflect the price of DOACs at patient-level. Nevertheless, manufacturer-level pricing is a good indicator of overall expenditure and economic burden of DOAC therapy, regardless of whether the cost was eventually borne by patients, insurers or the government, and thus provide a useful perspective for policy setting.

5. CONCLUSIONS

In this study, we observed that the consumption of DOACs especially in more developed countries have been increasing over the past decade, accompanied with a decrease in warfarin consumption recently. Regional differences in consumption pattern and trends of individual DOACs were observed, where the consumption of rivaroxaban and apixaban overtook dabigatran in most countries, yet use of edoxaban remains limited except in East Asian countries. The costs of all DOACs were approximately 2–4 times higher in the United States compared to other countries studied.

DECLARATION

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Conflict of interests

ICKW reports personal fees and non-financial support from IQVIA, outside the submitted work. EWC has received honorarium from the Hospital Authority, research grants from Narcotics Division of the Security Bureau of HKSAR, National Health and Medical Research Council (NHMRC, Australia), National Natural Science Foundation of China (NSFC), Research Fund Secretariat of the Food and Health Bureau (HMRF, HKSAR), Research Grants Council (RGC, HKSAR), Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, RGA and Takeda outside the submitted work. All other authors declare no competing interests.

Authors' contributions

EWC, ICKW, and VKCY conceptualised the study. EWC and IWCK provided resources, supervised the study, and acquired the data. VKCY conducted the formal analysis and wrote the original draft. All authors read and approved the final manuscript.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Ethics approval

This study was exempt from ethics approval by the Institutional Review Board of The University of Hong Kong and the Hong Kong West Cluster of the Hospital Authority.

Data Availability

Source data was obtained under license from IQVIA: IQVIA-MIDAS monthly sales data, 2008–2018; all rights reserved. The aggregated datasets generated and analysed during the current study will be available from the corresponding author upon request.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561

2. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638

3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907

5. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. 2019;140(2):e125-e151.

6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. Published online 2020.

7. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405

8. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. *Pharmacotherapy*. 2018;38(9):907-920. doi:10.1002/phar.2158

9. Perreault S, Denus S de, White-Guay B, et al. Oral anticoagulant prescription trends, profile use, and determinants of adherence in patients with atrial fibrillation. *Pharmacotherapy*. 2020;40(1):40-54. doi:10.1002/phar.2350

10. Weitz JI, Semchuk W, Turpie AG, et al. Trends in prescribing oral anticoagulants in Canada, 2008-2014. *Clin Ther*. 2015;37(11):2506-2514.e4. doi:10.1016/j.clinthera.2015.09.008

11. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol*. 2017;83(9):2096-2106. doi:10.1111/bcp.13299

12. Staerk L, Fosbøl EL, Gadsbøll K, et al. Non-vitamin k antagonist oral anticoagulation usage according to age among patients with atrial fibrillation: Temporal trends 2011-2015 in Denmark. *Sci Rep*. 2016;6:31477. doi:10.1038/srep31477

13. Hanemaaijer S, Sodihardjo F, Horikx A, et al. Trends in antithrombotic drug use and adherence to non-vitamin k oral anticoagulants in the Netherlands. *Int J Clin Pharm*. 2015;37(6):1128-1135. doi:10.1007/s11096-015-0174-4

14. Rodríguez-Bernal CL, Hurtado I, García-Sempere A, Peiró S, Sanfélix-Gimeno G. Oral anticoagulants initiation in patients with atrial fibrillation: Real-world data from a population-based cohort. *Front Pharmacol*. 2017;8:63. doi:10.3389/fphar.2017.00063

15. Baker D, Wilsmore B, Narasimhan S. Adoption of direct oral anticoagulants for stroke prevention in atrial fibrillation. *Intern Med J*. 2016;46(7):792-797. doi:10.1111/imj.13088

16. Yu Z, Yu L, Shan C. Trends of ambulatory oral anticoagulant prescription in five major cities of china, 2012-2017. *BMC Health Serv Res*. 2020;20(1):209. doi:10.1186/s12913-020-5072-3

17. Elewa H, Alhaddad A, Al-Rawi S, Nounou A, Mahmoud H, Singh R. Trends in oral anticoagulant use in Qatar: A 5-year experience. *J Thromb Thrombolysis*. 2017;43(3):411-416. doi:10.1007/s11239-017-1474-4

18. IQVIA. ACTS: IQVIA quality assurance. Published online 2018. Accessed November 1, 2020. https://www.iqvia.com/landing/acts

19. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. *Lancet Infect Dis*. 2019;19(1):67-75. doi:10.1016/S1473-3099(18)30547-4

20. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *Lancet Infect Dis*. 2014;14(8):742-750. doi:10.1016/S1473-3099(14)70780-7

21. United Nations. World population prospects 2019. Published online 2019. Accessed November 1, 2020. https://population.un.org/wpp/

22. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) results. Published online 2020. Accessed November 1, 2020. http://ghdx.healthdata.org/gbd-results-tool

23. World Bank. World Bank Open Data. Published online 2019. Accessed November 1, 2020. https://data.worldbank.org/

24. World Bank. World Bank Country and Lending Groups. Published online 2018. Accessed November 1, 2020. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

25. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128(12):1300-5.e2. doi:10.1016/j.amjmed.2015.05.044

26. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *Am J Med*. 2014;127(11):1075-1082.e1. doi:10.1016/j.amjmed.2014.05.013

27. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the united states. *Am J Cardiol*. 2015;115(8):1095-1101. doi:10.1016/j.amjcard.2015.01.539

28. Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario,

Canada: A population-based descriptive analysis. *CMAJ open*. 2013;1(3):E115-9. doi:10.9778/cmajo.20130032

29. Lippi G, Mattiuzzi C, Cervellin G, Favaloro EJ. Direct oral anticoagulants: Analysis of worldwide use and popularity using google trends. *Ann Transl Med*. 2017;5(16):322-322. doi:10.21037/atm.2017.06.65

30. Conen D. Epidemiology of atrial fibrillation. *European heart journal*. 2018;39(16):1323-1324. doi:10.1093/eurheartj/ehy171

31. Schnabel RB, Yin X, Gona P, et al. 50-year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham heart study: A cohort study. *Lancet*. 2015;386(9989):154-162. doi:10.1016/s0140-6736(14)61774-8

32. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2014;130(23):e199-e267. doi:doi:10.1161/CIR.0000000000000041

33. Drug Administration USF &. Drugs@FDA: FDA-approved drugs. Published online 2020. Accessed November 1, 2020. https://www.accessdata.fda.gov/scripts/cder/daf/

34. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). *Circulation*. 2011;123(10):1144-1150. doi:doi:10.1161/CIR.0b013e31820f14c0

35. Wolfe Z, Khan SU, Nasir F, Raghu Subramanian C, Lash B. A systematic review and Bayesian network meta-analysis of risk of intracranial hemorrhage with direct oral anticoagulants. *J Thromb Haemost*. 2018;16(7):1296-1306. doi:10.1111/jth.14131

36. Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA*. 2018;320(21):2221-2230. doi:10.1001/jama.2018.17242

37. Laliberté F, Bookhart BK, Nelson WW, et al. Impact of once-daily versus twice-daily dosing frequency on adherence to chronic medications among patients with venous thromboembolism. *Patient*. 2013;6(3):213-224. doi:10.1007/s40271-013-0020-5

38. Blommel ML, Blommel AL. Dabigatran etexilate: A novel oral direct thrombin inhibitor. *Am J Health Syst Pharm*. 2011;68(16):1506-1519. doi:10.2146/ajhp100348

39. Zhang Y, Méndez SJ, Scott A. Factors affecting general practitioners' decisions to adopt new prescription drugs - cohort analyses using Australian longitudinal physician survey data. *BMC Health Serv Res*. 2019;19(1):94. doi:10.1186/s12913-019-3889-4

40. Son K-B. The speed of adoption of new drugs and prescription volume after the amendments in reimbursement coverage: The case of non-vitamin k antagonist oral anticoagulants in South Korea. *BMC Public Health*. 2020;20(1):797. doi:10.1186/s12889-020-08929-6

41. Emanuel EJ, Zhang C, Glickman A, Gudbranson E, DiMagno SSP, Urwin JW. Drug reimbursement regulation in 6 peer countries. *JAMA Intern Med*. Published online 2020. doi:10.1001/jamainternmed.2020.4793

42. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: Origins and prospects for reform. *JAMA*. 2016;316(8):858-871. doi:10.1001/jama.2016.11237

43. Kanavos P, Ferrario A, Vandoros S, Anderson GF. Higher US branded drug prices and spending compared to other countries may stem partly from quick uptake of new drugs. *Health Aff (Millwood)*. 2013;32(4):753-761. doi:10.1377/hlthaff.2012.0920

44. Ng SS, Nathisuwan S, Phrommintikul A, Chaiyakunapruk N. Cost-effectiveness of warfarin care bundles and novel oral anticoagulants for stroke prevention in patients with atrial fibrillation in Thailand. *Thromb Res*. 2020;185:63-71. doi:10.1016/j.thromres.2019.11.012

45. Government of the People's Republic of China. National basic medical insurance, work injury insurance and maternity insurance drug list (2020). Published online 2020. http://www.mohrss.gov.cn/xxgk2020/fdzdgknr/shbx_4216/gsbx/202101/t20210112_407492.html

46. Yan VKC, Blais JE, Li X, et al. Trends in cardiovascular medicine use in 65 middle- and high-income countries. *J Am Coll Cardiol*. 2020; 77(7): 1021–1023. doi: 10.1016/j.jacc.2020.12.025.

Figure 1: Total consumption of DOACs in 65 countries, Q2 2019.

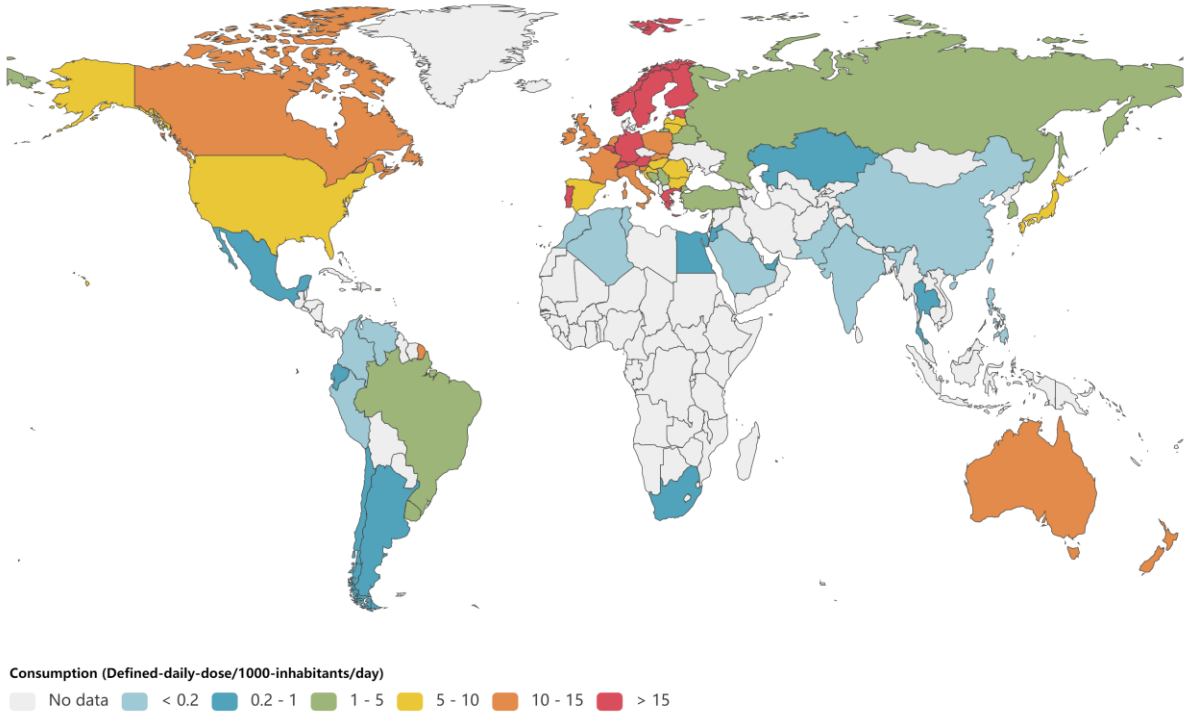


Figure 2: Proportion of use of each DOAC by country, Q2 2019.

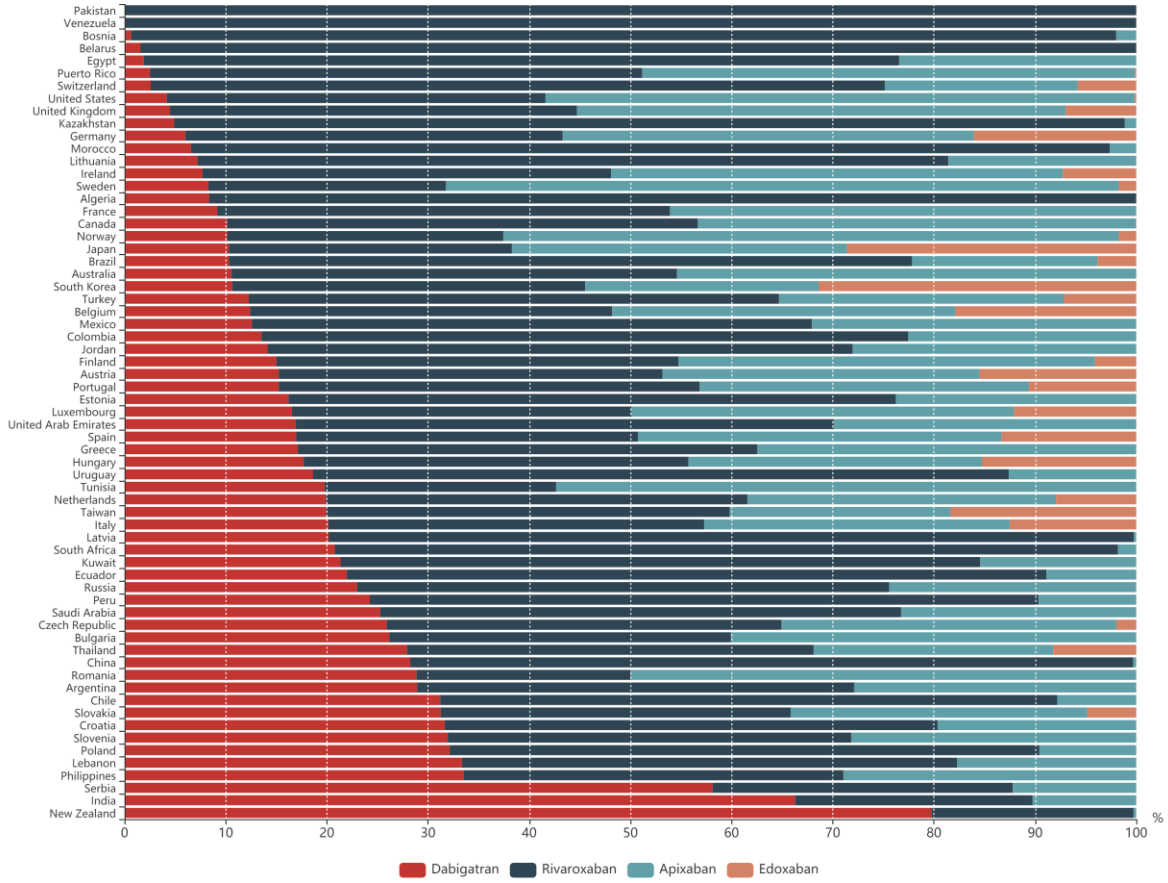
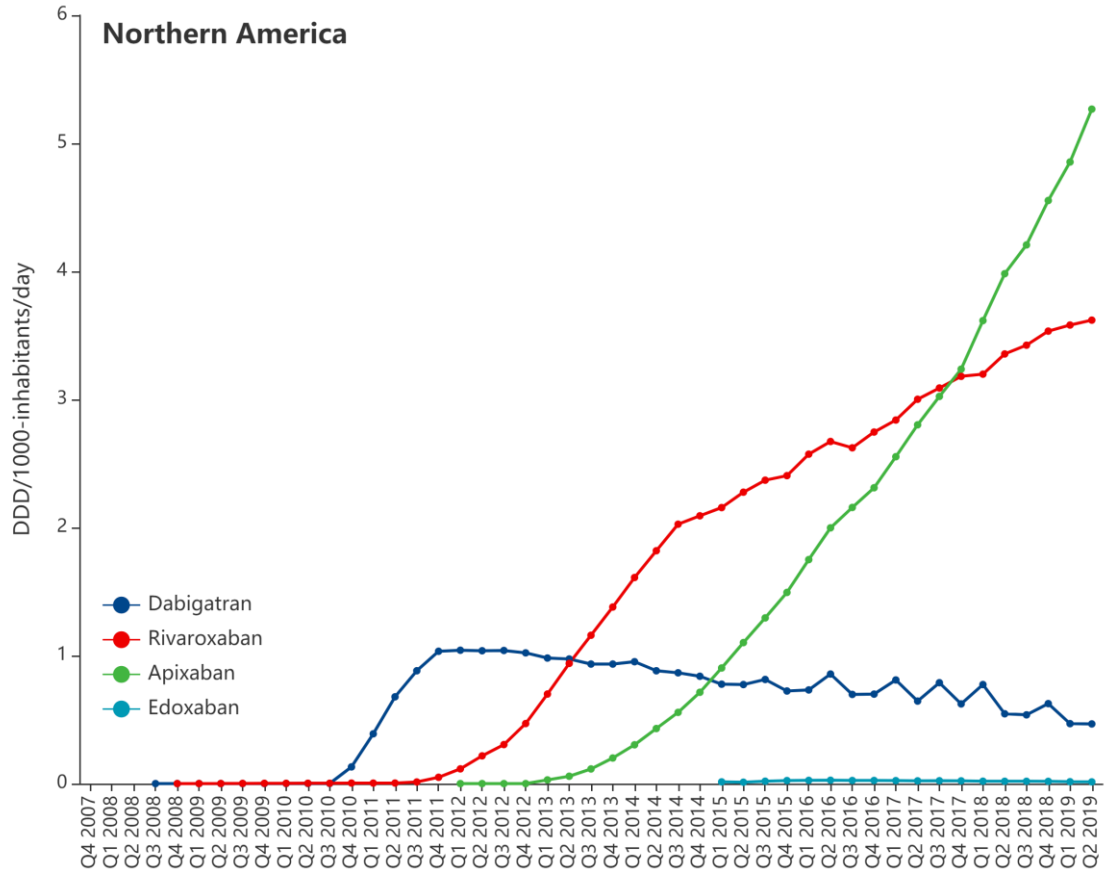
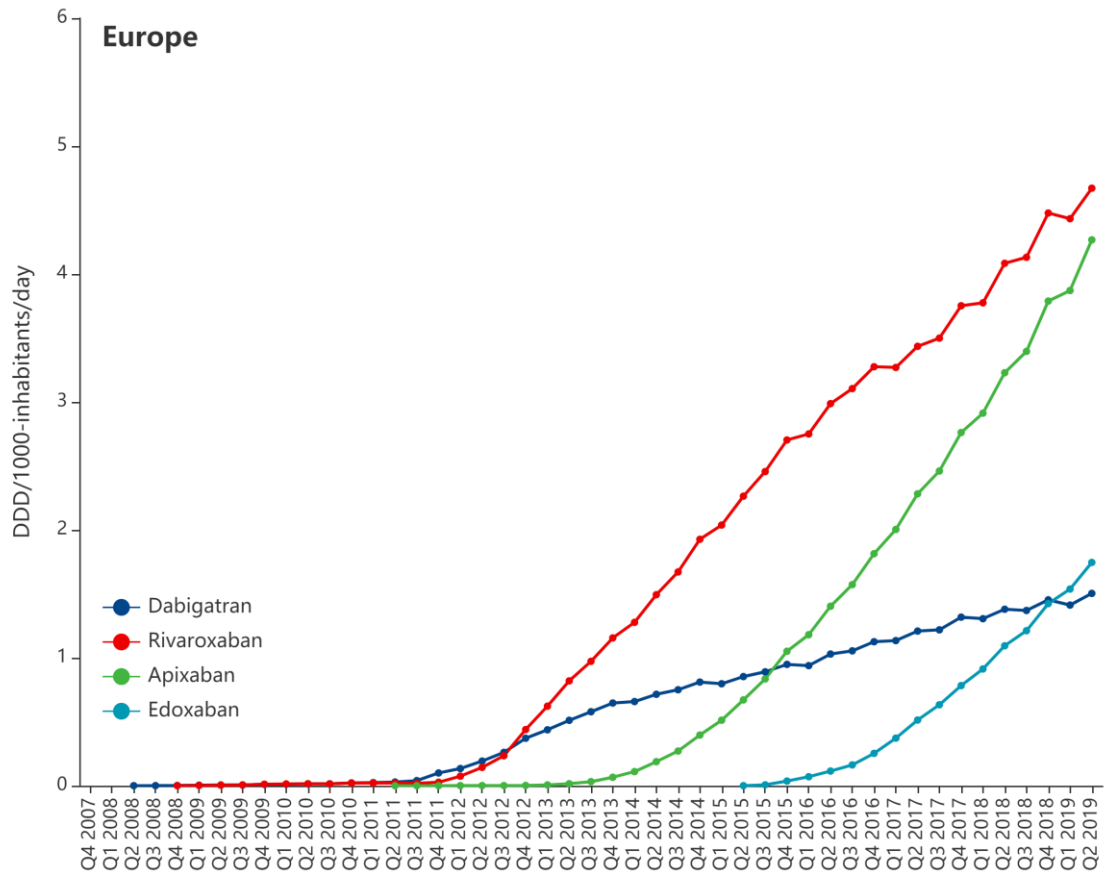
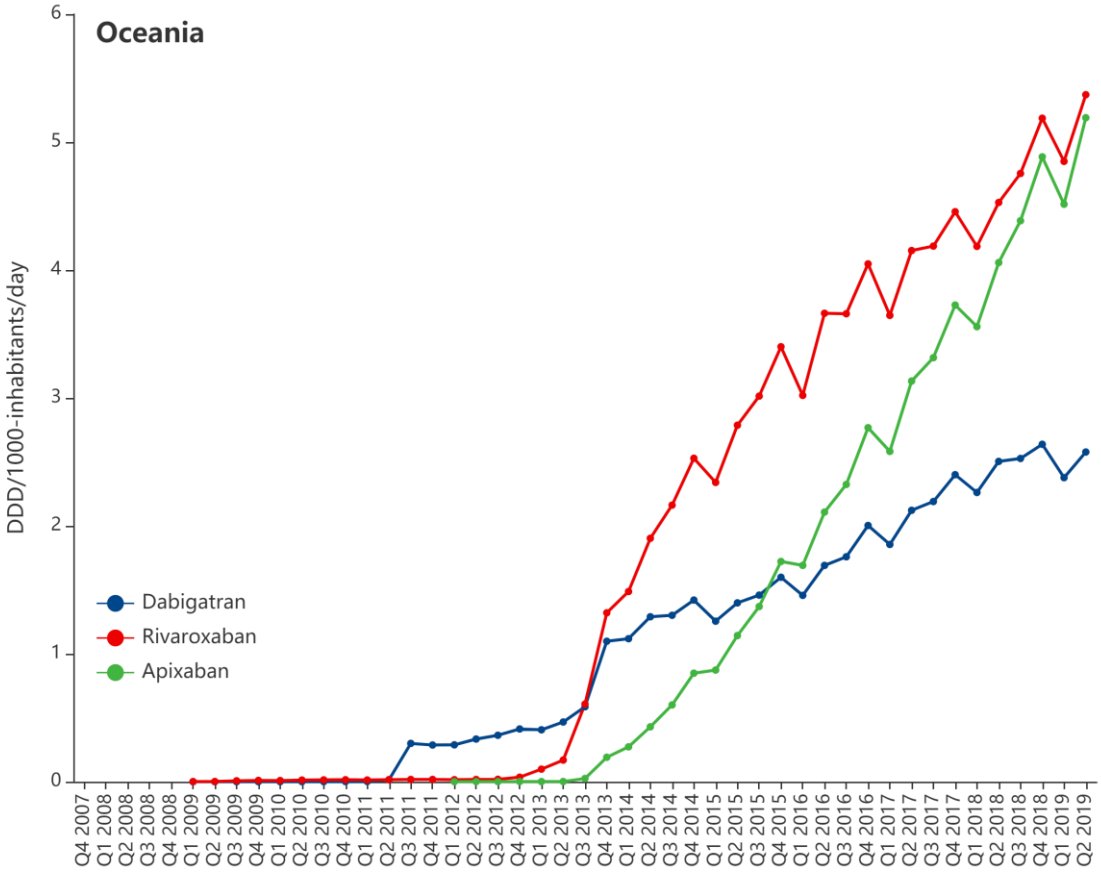


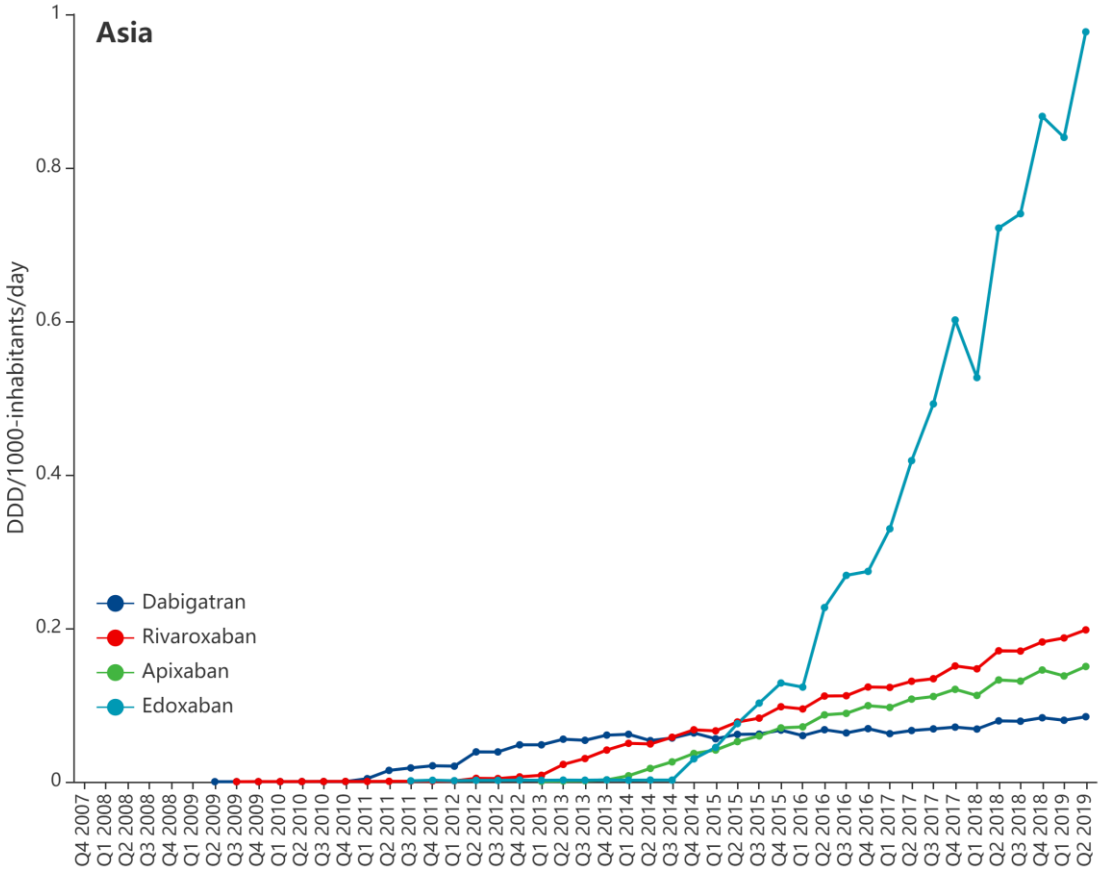
Figure 3: Trends in consumption of each DOAC by geographical region, 2008-2019.



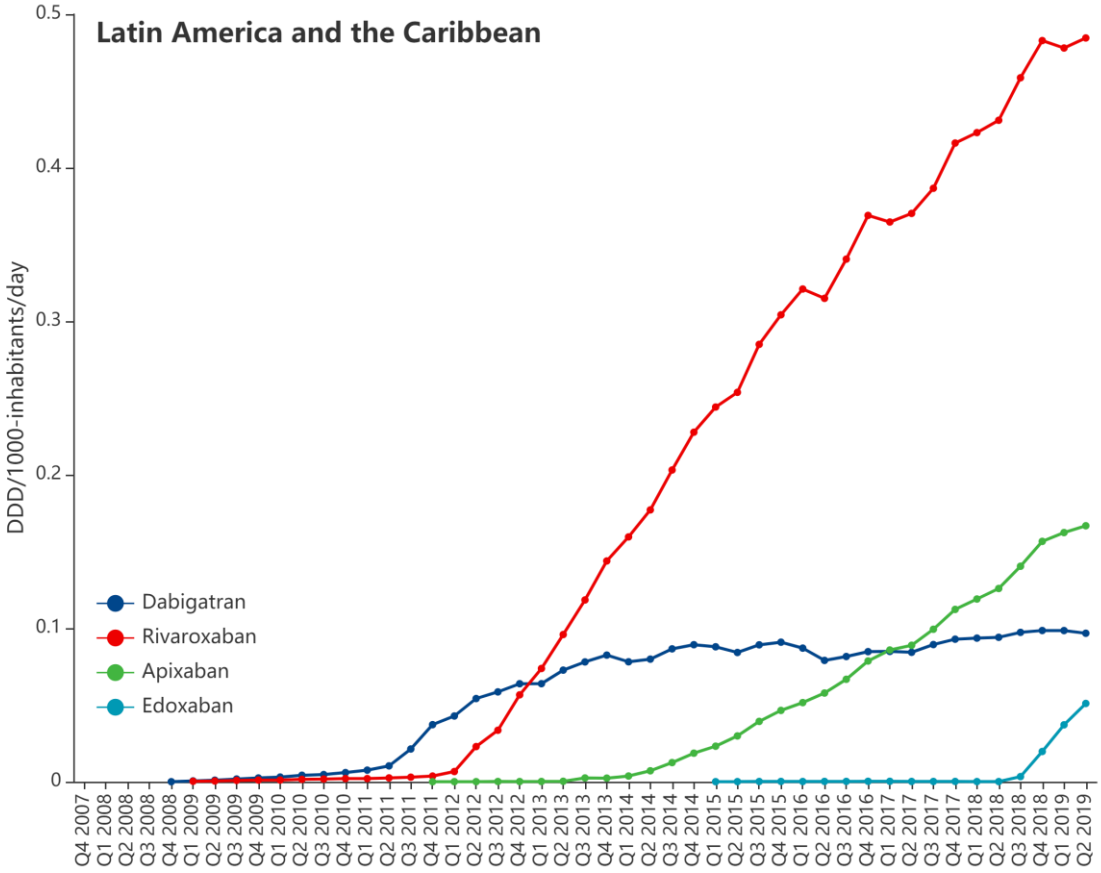



Oceania
DDD/1000-inhabitants/day
0
1
2
3
4
5
6
Dabigatran
Rivaroxaban
Apixaban
Q4 2007
Q1 2008
Q2 2008
Q3 2008
Q4 2008
Q1 2009
Q2 2009
Q3 2009
Q4 2009
Q1 2010
Q2 2010
Q3 2010
Q4 2010
Q1 2011
Q2 2011
Q3 2011
Q4 2011
Q1 2012
Q2 2012
Q3 2012
Q4 2012
Q1 2013
Q2 2013
Q3 2013
Q4 2013
Q1 2014
Q2 2014
Q3 2014
Q4 2014
Q1 2015
Q2 2015
Q3 2015
Q4 2015
Q1 2016
Q2 2016
Q3 2016
Q4 2016
Q1 2017
Q2 2017
Q3 2017
Q4 2017
Q1 2018
Q2 2018
Q3 2018
Q4 2018
Q1 2019
Q2 2019

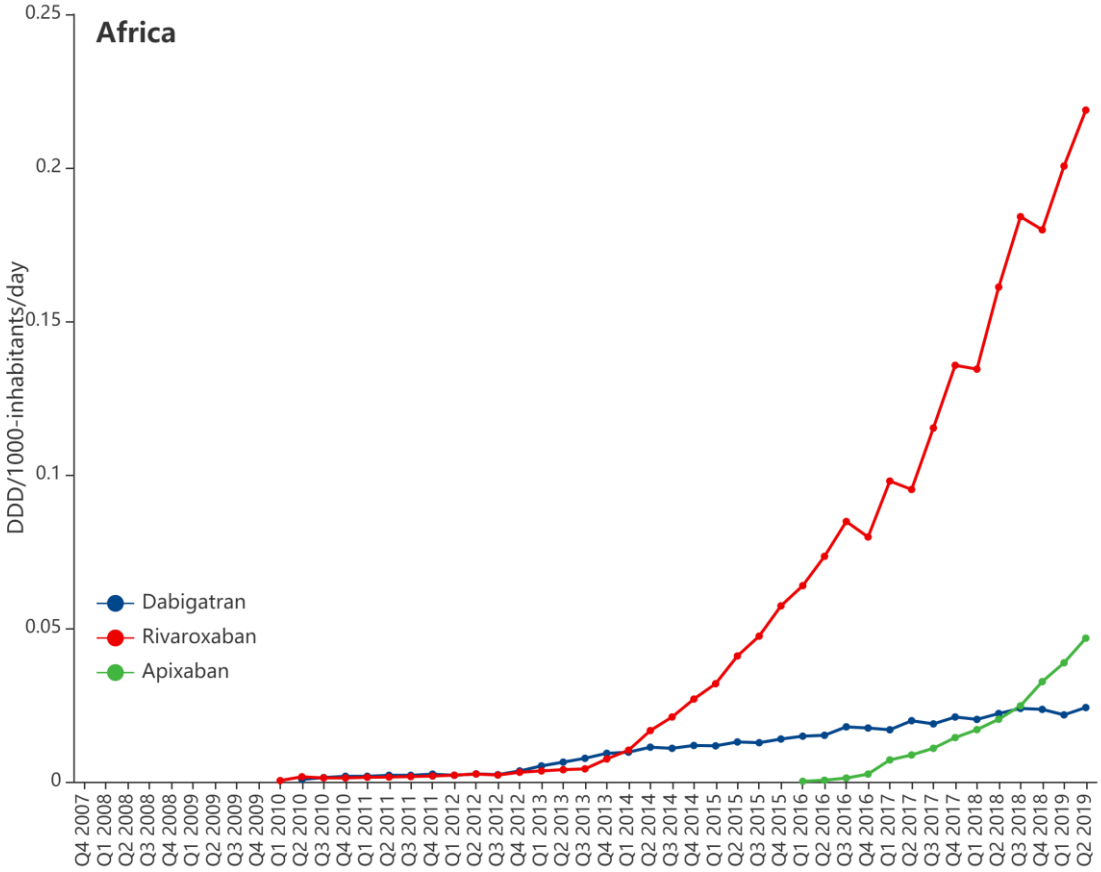
1


Asia
DDD/1000-inhabitants/day
0
0.2
0.4
0.6
0.8
1
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Q4 2007
Q1 2008
Q2 2008
Q3 2008
Q4 2008
Q1 2009
Q2 2009
Q3 2009
Q4 2009
Q1 2010
Q2 2010
Q3 2010
Q4 2010
Q1 2011
Q2 2011
Q3 2011
Q4 2011
Q1 2012
Q2 2012
Q3 2012
Q4 2012
Q1 2013
Q2 2013
Q3 2013
Q4 2013
Q1 2014
Q2 2014
Q3 2014
Q4 2014
Q1 2015
Q2 2015
Q3 2015
Q4 2015
Q1 2016
Q2 2016
Q3 2016
Q4 2016
Q1 2017
Q2 2017
Q3 2017
Q4 2017
Q1 2018
Q2 2018
Q3 2018
Q4 2018
Q1 2019
Q2 2019

2


Latin America and the Caribbean
DDD/1000-inhabitants/day
0.5
0.4
0.3
0.2
0.1
0
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Q4 2007
Q1 2008
Q2 2008
Q3 2008
Q4 2008
Q1 2009
Q2 2009
Q3 2009
Q4 2009
Q1 2010
Q2 2010
Q3 2010
Q4 2010
Q1 2011
Q2 2011
Q3 2011
Q4 2011
Q1 2012
Q2 2012
Q3 2012
Q4 2012
Q1 2013
Q2 2013
Q3 2013
Q4 2013
Q1 2014
Q2 2014
Q3 2014
Q4 2014
Q1 2015
Q2 2015
Q3 2015
Q4 2015
Q1 2016
Q2 2016
Q3 2016
Q4 2016
Q1 2017
Q2 2017
Q3 2017
Q4 2017
Q1 2018
Q2 2018
Q3 2018
Q4 2018
Q1 2019
Q2 2019

1


Africa
DDD/1000-inhabitants/day
0.25
0.2
0.15
0.1
0.05
0
Dabigatran
Rivaroxaban
Apixaban
Q4 2007
Q1 2008
Q2 2008
Q3 2008
Q4 2008
Q1 2009
Q2 2009
Q3 2009
Q4 2009
Q1 2010
Q2 2010
Q3 2010
Q4 2010
Q1 2011
Q2 2011
Q3 2011
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Q4 2013
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Q2 2014
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Q4 2014
Q1 2015
Q2 2015
Q3 2015
Q4 2015
Q1 2016
Q2 2016
Q3 2016
Q4 2016
Q1 2017
Q2 2017
Q3 2017
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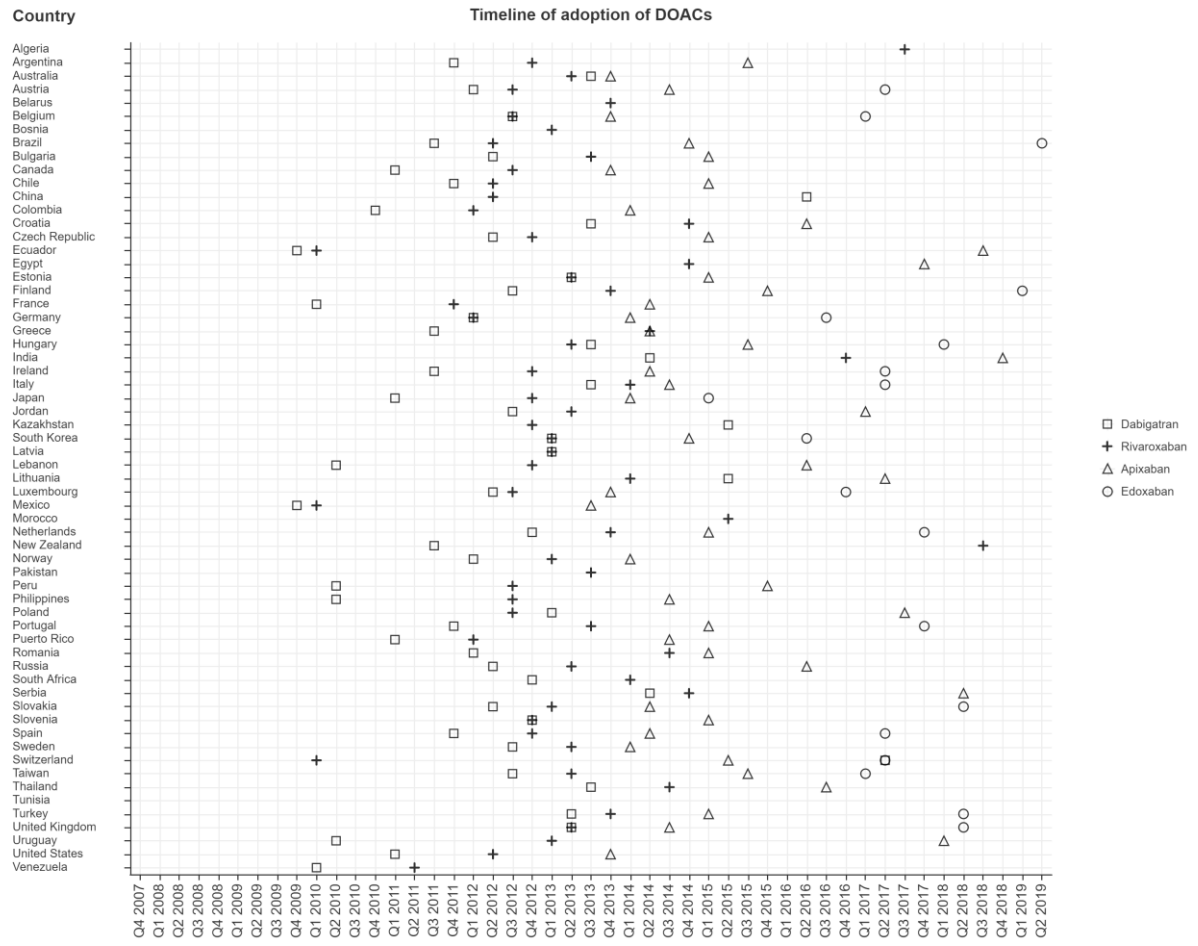
Q1 2018
Q2 2018
Q3 2018
Q4 2018
Q1 2019
Q2 2019

2

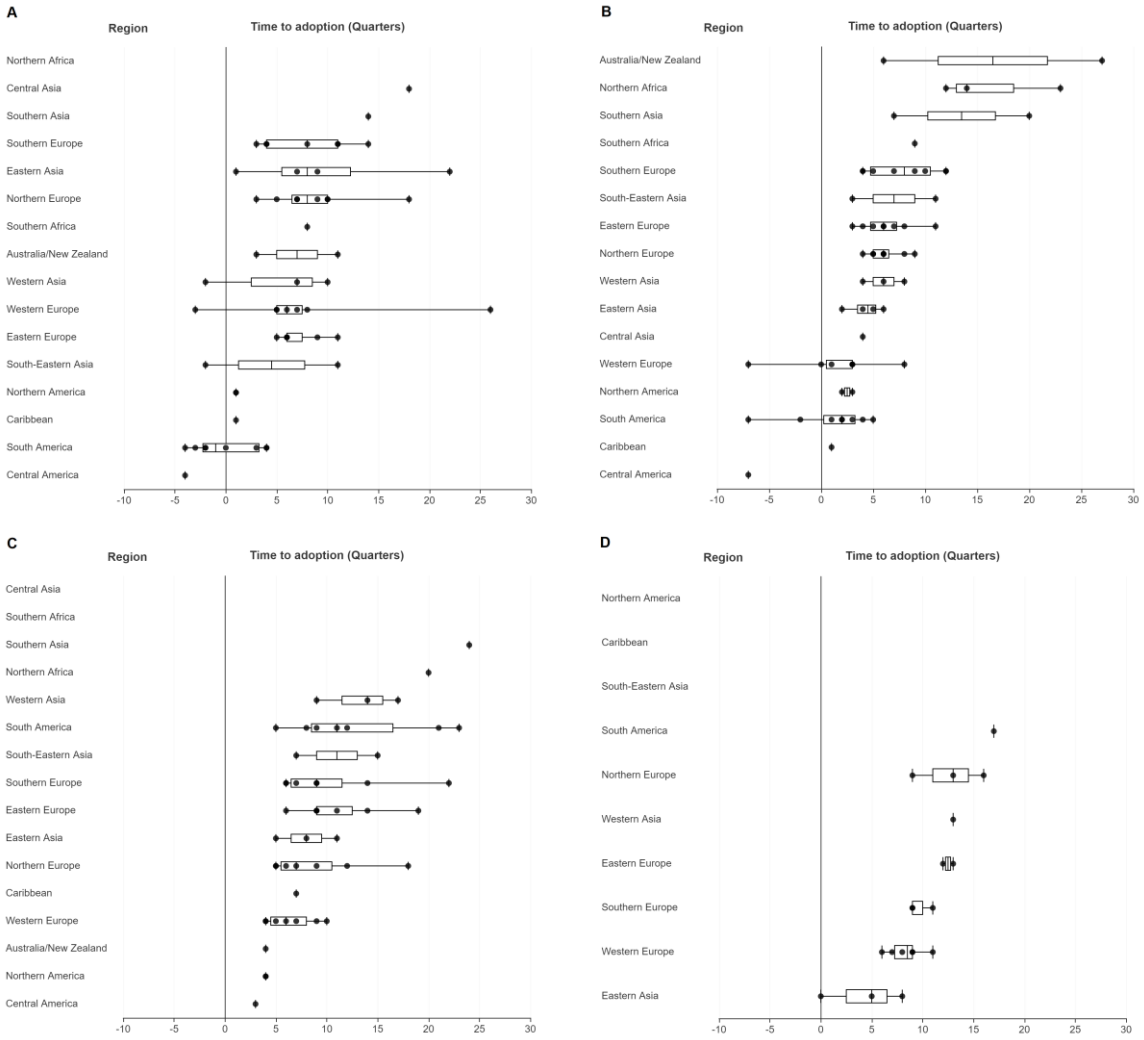
3

Figure 4: Timeline of DOAC adoption by country



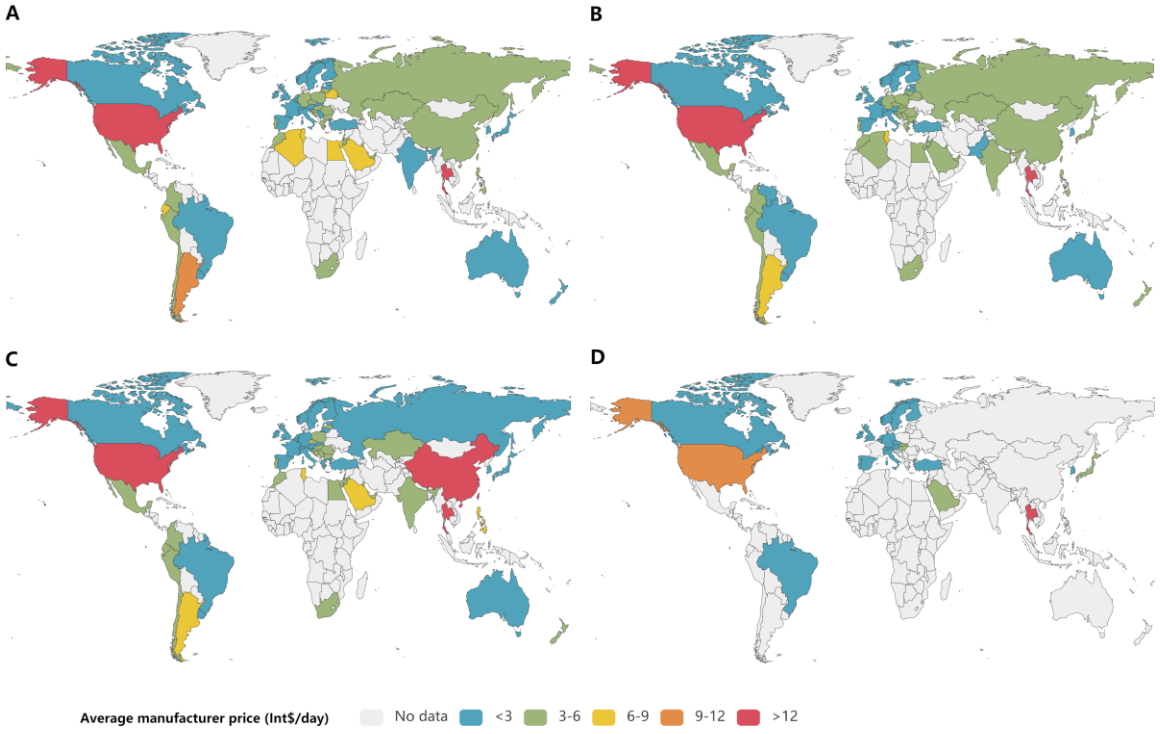
A DOAC is considered adopted when its consumption reaches an arbitrary threshold of at least 2% of the total OAC consumption. Only countries with coverage >=50% were included in this analysis.

Figure 5: Time to adoption from FDA approval by geographical region



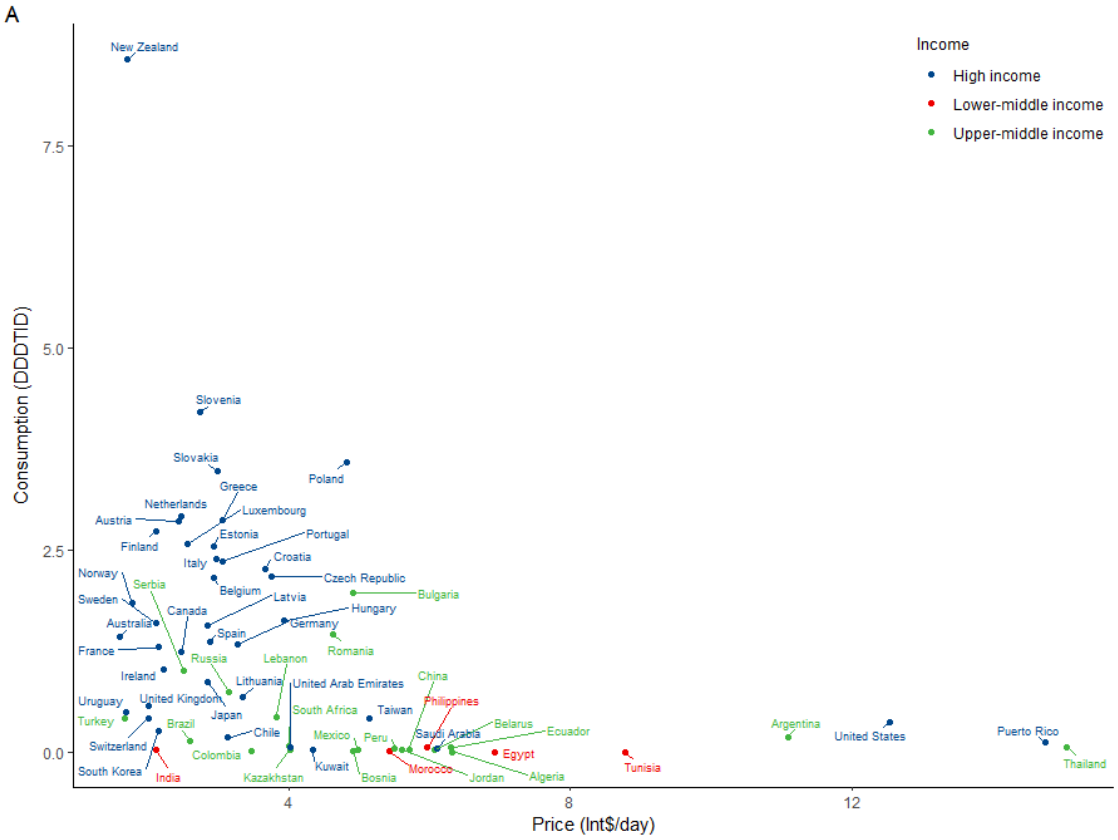
(A) Dabigatran (B) Rivaroxaban (C) Apixaban (D) Edoxaban

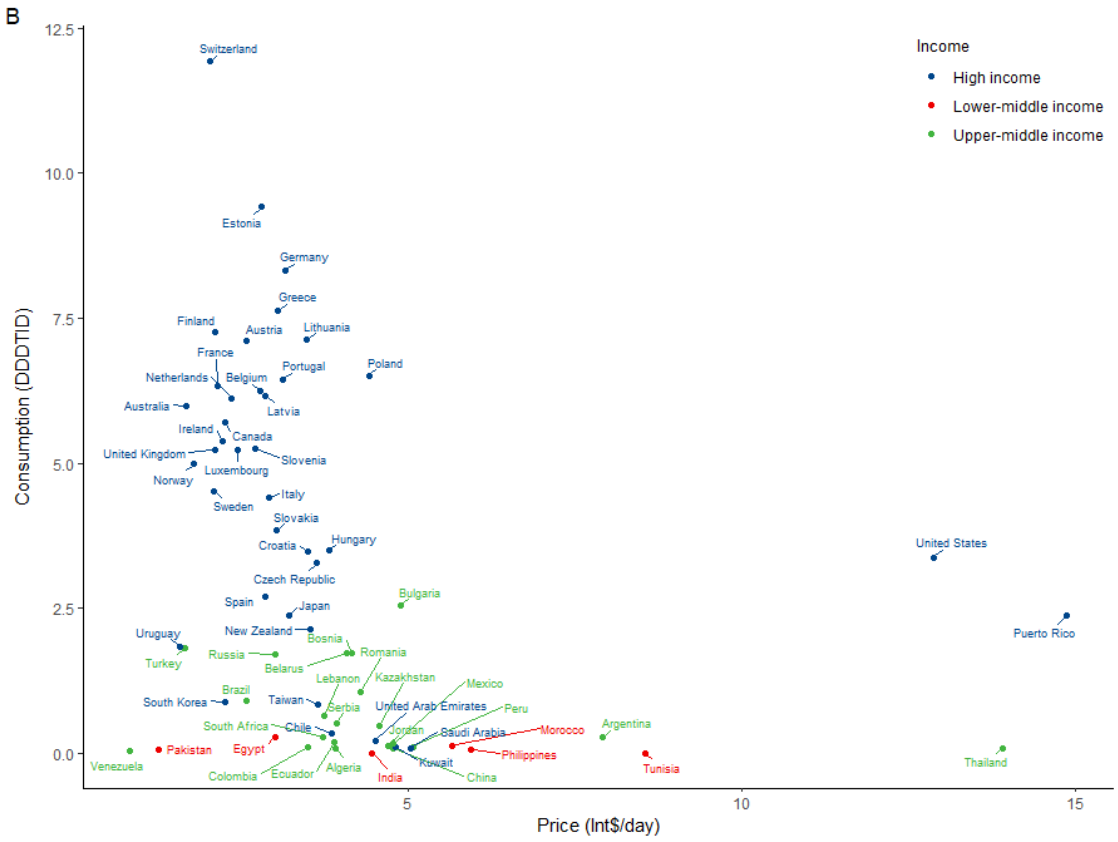
Figure 6: Manufacturer price (international dollars per day-of therapy) of each DOAC in 65 countries, Q2 2019.

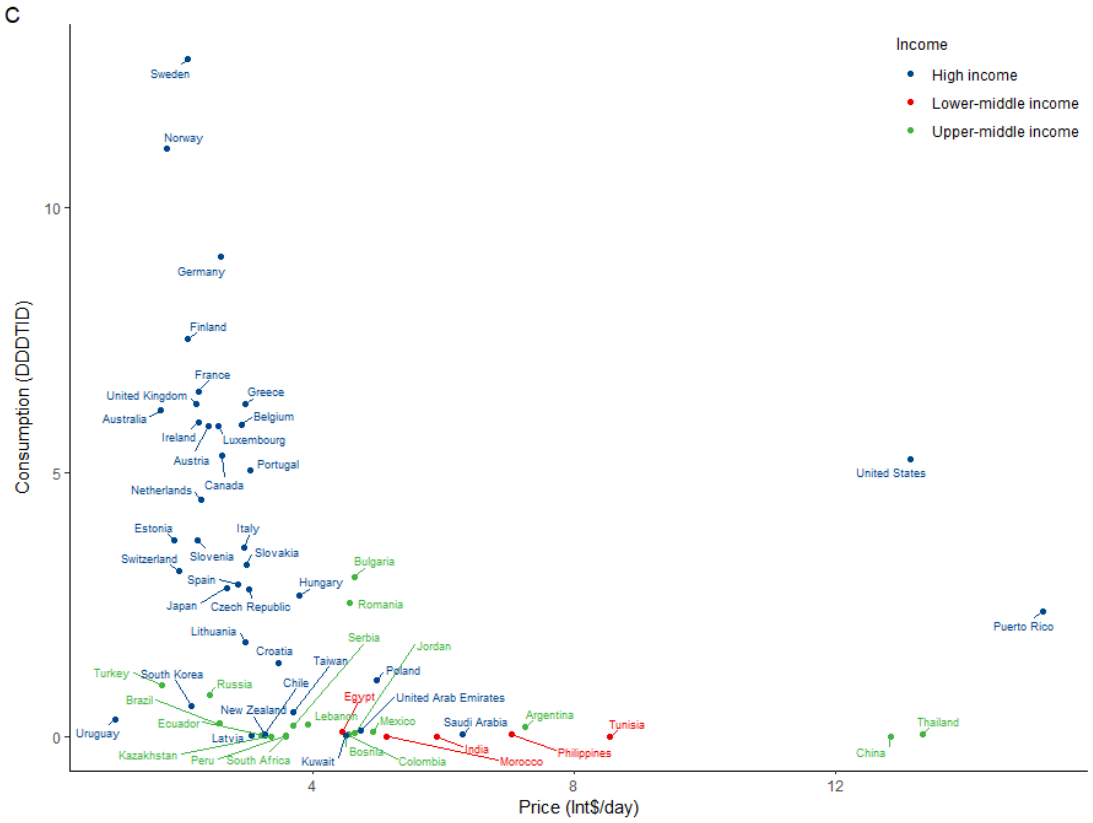


(A) Dabigatran (B) Rivaroxaban (C) Apixaban (D) Edoxaban

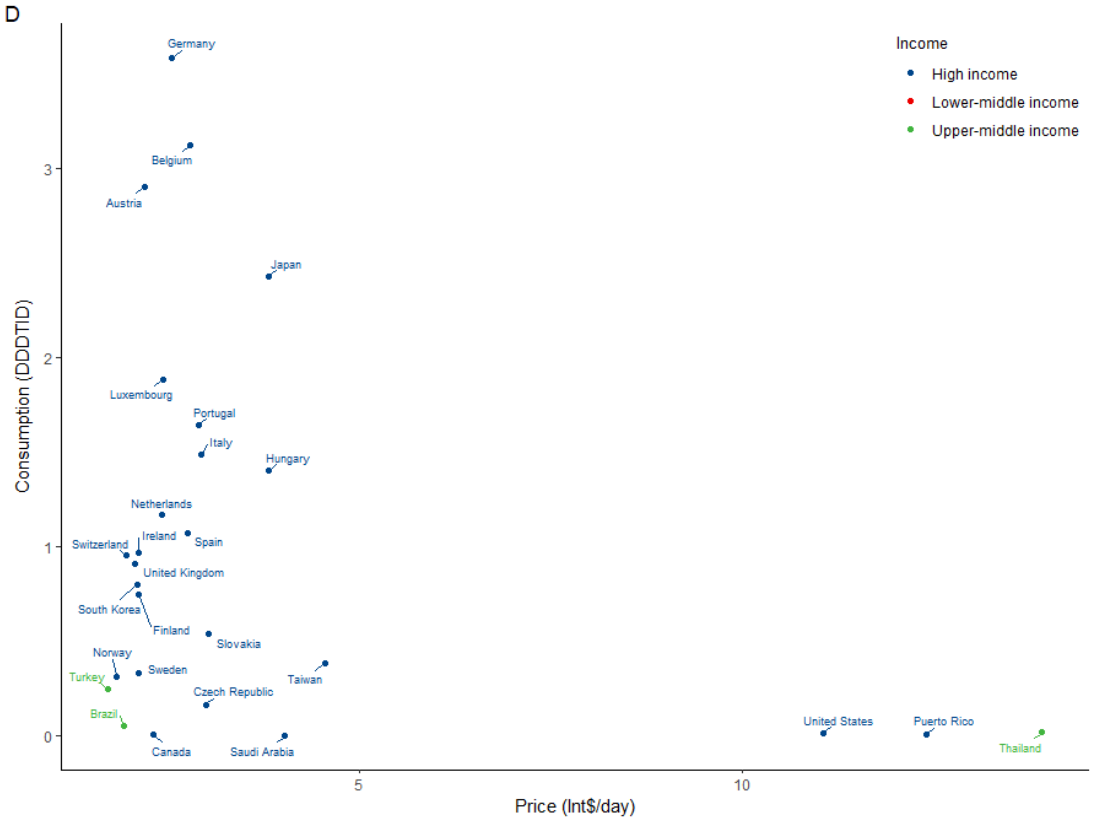
Figure 7: Consumption versus manufacturer price of each DOAC in 65 countries, Q2 2019.







1



2

3 (A) Dabigatran (B) Rivaroxaban (C) Apixaban (D) Edoxaban

4

Table 1: Consumption trends of DOACs from 2008-2019 by geographical region.

Region	Total DOAC consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	**0.000**	**0.001**	**0.005**	**0.064**	**0.166**	**0.380**	**0.647**	**0.965**	**1.352**	**1.687**	**2.134**	**2.566**	**322.864**	**52.604**	**23.815**
Europe	0.000	0.010	0.030	0.050	0.336	1.346	2.392	3.778	5.460	7.167	9.230	11.315	256.646	59.494	27.494
Western Europe	0.001	0.016	0.055	0.082	0.790	3.423	5.135	7.075	9.618	12.269	15.152	18.198	296.010	41.103	23.686
Northern Europe	0.000	0.014	0.037	0.049	0.158	0.719	1.720	3.562	6.190	8.813	11.524	14.074	168.911	104.947	31.493
Eastern Europe	0.000	0.004	0.008	0.015	0.091	0.419	0.994	1.732	2.315	2.892	4.098	5.323	268.739	76.773	31.991
Southern Europe	0.000	0.007	0.031	0.066	0.276	0.612	1.603	3.027	4.769	6.474	8.415	10.298	170.544	98.237	29.248
Africa	0.000	0.000	0.002	0.004	0.005	0.010	0.028	0.054	0.089	0.122	0.200	0.282	63.508	105.293	46.850
Northern Africa	0.000	0.000	0.001	0.001	0.002	0.002	0.011	0.029	0.056	0.082	0.164	0.252	63.455	191.348	64.632
Southern Africa	0.000	0.000	0.008	0.013	0.016	0.036	0.081	0.135	0.194	0.252	0.319	0.379	63.906	75.629	25.071
Asia	0.000	0.000	0.000	0.014	0.041	0.076	0.116	0.193	0.282	0.341	0.449	0.525	505.740	54.976	22.965
Central Asia	-	-	-	0.002	0.004	0.020	0.053	0.082	0.127	0.185	0.274	0.515	-	85.487	59.642
Eastern Asia	0.000	0.000	0.000	0.028	0.083	0.147	0.213	0.345	0.501	0.589	0.756	0.871	592.615	50.569	20.237
South-Eastern Asia	0.000	0.000	0.000	0.017	0.023	0.036	0.049	0.068	0.095	0.117	0.171	0.206	470.653	38.001	29.617
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.003	0.005	0.008	0.012	0.017	0.036	0.056	720.882	66.946	68.358
Western Asia	0.000	0.001	0.003	0.008	0.022	0.095	0.283	0.621	0.953	1.310	1.793	2.092	212.331	115.851	29.942
Latin America and the Caribbean	0.000	0.001	0.006	0.013	0.077	0.169	0.264	0.366	0.448	0.538	0.644	0.759	208.899	38.496	19.195
Caribbean	0.000	0.000	0.000	0.110	0.385	0.827	1.323	1.758	2.166	2.745	3.537	4.869	-	37.860	30.995
Central America	0.000	0.004	0.011	0.019	0.073	0.088	0.120	0.158	0.208	0.256	0.280	0.310	101.553	32.960	14.282
South America	0.000	0.001	0.004	0.010	0.075	0.188	0.298	0.418	0.509	0.609	0.736	0.870	253.777	39.481	19.591
Northern America	0.000	0.001	0.003	0.682	1.254	1.969	3.129	4.161	5.550	6.468	7.900	9.365	731.920	41.261	19.049
Oceania	0.000	0.002	0.013	0.032	0.352	0.637	3.621	5.327	7.460	9.405	11.089	13.138	261.447	127.134	20.762

Region	Dabigatran consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	**0.000**	**0.001**	**0.003**	**0.062**	**0.132**	**0.184**	**0.209**	**0.226**	**0.260**	**0.271**	**0.297**	**0.311**	**316.010**	**12.160**	**6.167**
Europe	0.000	0.006	0.015	0.029	0.193	0.511	0.714	0.853	1.029	1.209	1.379	1.503	227.314	26.277	13.464
Western Europe	0.001	0.007	0.023	0.038	0.345	1.030	1.107	1.156	1.266	1.400	1.498	1.547	257.173	7.108	6.919
Northern Europe	0.000	0.007	0.014	0.025	0.121	0.364	0.530	0.636	0.745	0.848	0.933	0.944	196.047	26.977	8.234
Eastern Europe	0.000	0.004	0.005	0.009	0.064	0.215	0.394	0.587	0.800	1.017	1.234	1.410	243.853	54.865	20.771
Southern Europe	0.000	0.007	0.022	0.050	0.257	0.429	0.862	1.045	1.291	1.518	1.766	1.982	170.580	44.379	15.371
Africa	0.000	0.000	0.001	0.002	0.003	0.006	0.011	0.013	0.015	0.020	0.022	0.024	104.236	33.347	16.910
Northern Africa	0.000	0.000	0.000	0.000	0.000	0.001	0.002	0.003	0.003	0.005	0.006	0.007	-	66.283	38.401
Southern Africa	0.000	0.000	0.003	0.009	0.011	0.025	0.042	0.046	0.055	0.067	0.076	0.079	99.659	30.364	12.866
Asia	0.000	0.000	0.000	0.015	0.039	0.055	0.054	0.062	0.068	0.067	0.079	0.085	658.240	6.947	7.717
Central Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.013	0.016	0.024	0.021	0.025	-	540.776	16.940
Eastern Asia	0.000	0.000	0.000	0.027	0.074	0.101	0.088	0.097	0.103	0.095	0.107	0.111	-	0.666	2.621
South-Eastern Asia	0.000	0.000	0.000	0.017	0.023	0.028	0.028	0.032	0.037	0.041	0.057	0.064	496.842	9.982	20.055
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.002	0.004	0.005	0.006	0.007	0.021	0.035	-	38.093	83.391
Western Asia	0.000	0.001	0.003	0.007	0.020	0.065	0.158	0.228	0.290	0.341	0.344	0.277	177.906	65.066	-1.501
Latin America and the Caribbean	0.000	0.001	0.004	0.010	0.054	0.073	0.080	0.084	0.079	0.084	0.094	0.097	158.620	2.822	6.963
Caribbean	0.000	0.000	0.000	0.110	0.213	0.212	0.216	0.190	0.192	0.179	0.165	0.122	-	-3.360	-13.961
Central America	0.000	0.002	0.008	0.014	0.046	0.040	0.038	0.036	0.038	0.043	0.042	0.039	74.639	-1.959	0.985
South America	0.000	0.001	0.003	0.008	0.055	0.081	0.092	0.098	0.091	0.096	0.110	0.115	193.442	3.728	8.041
Northern America	0.000	0.000	0.001	0.678	1.037	0.973	0.881	0.773	0.855	0.644	0.545	0.466	983.814	-4.202	-18.331
Oceania	0.000	0.000	0.001	0.016	0.333	0.467	1.289	1.398	1.691	2.121	2.504	2.577	873.965	53.595	15.087

Region	Rivaroxaban consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	**0.000**	**0.001**	**0.003**	**0.004**	**0.039**	**0.196**	**0.378**	**0.540**	**0.692**	**0.791**	**0.932**	**1.051**	**324.626**	**52.176**	**14.943**
Europe	0.000	0.004	0.015	0.021	0.143	0.819	1.493	2.263	2.987	3.435	4.084	4.671	278.680	53.892	16.074
Western Europe	0.000	0.010	0.033	0.044	0.444	2.347	3.618	4.624	5.600	6.136	6.794	7.437	316.368	33.623	9.917
Northern Europe	0.000	0.008	0.023	0.024	0.036	0.345	0.982	2.035	3.257	4.122	4.855	5.394	146.842	111.291	18.313
Eastern Europe	0.000	0.000	0.003	0.006	0.027	0.203	0.576	1.054	1.306	1.449	2.054	2.615	305.114	85.903	26.026
Southern Europe	0.000	0.000	0.009	0.015	0.018	0.180	0.595	1.348	2.181	2.728	3.362	3.931	168.687	129.743	21.701
Africa	0.000	0.000	0.002	0.002	0.002	0.004	0.017	0.041	0.073	0.095	0.161	0.219	34.539	165.934	43.899
Northern Africa	0.000	0.000	0.001	0.001	0.002	0.002	0.010	0.026	0.053	0.068	0.136	0.196	47.370	216.682	54.516
Southern Africa	0.000	0.000	0.005	0.004	0.005	0.011	0.039	0.089	0.139	0.185	0.243	0.293	30.012	132.762	28.301
Asia	0.000	0.000	0.000	0.001	0.004	0.022	0.049	0.078	0.112	0.131	0.171	0.198	366.735	70.547	21.022
Central Asia	0.000	0.000	0.000	0.002	0.004	0.020	0.050	0.070	0.109	0.157	0.250	0.484	-	76.609	64.390
Eastern Asia	0.000	0.000	0.000	0.001	0.009	0.044	0.090	0.132	0.185	0.206	0.260	0.297	362.256	61.974	16.988
South-Eastern Asia	0.000	0.000	0.000	0.000	0.001	0.008	0.020	0.027	0.039	0.048	0.066	0.080	404.636	68.882	27.032
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.001	0.002	0.003	0.006	0.009	0.015	0.021	400.989	116.766	53.021
Western Asia	0.000	0.000	0.000	0.000	0.003	0.030	0.125	0.327	0.498	0.685	0.959	1.095	559.681	154.352	30.042
Latin America and the Caribbean	0.000	0.000	0.002	0.002	0.023	0.096	0.177	0.254	0.315	0.370	0.431	0.484	297.610	48.648	15.449
Caribbean	0.000	0.000	0.000	0.000	0.172	0.599	1.041	1.306	1.463	1.686	1.909	2.369	-	34.648	17.421
Central America	0.000	0.002	0.003	0.005	0.027	0.048	0.072	0.097	0.124	0.147	0.160	0.172	145.721	36.934	11.525
South America	0.000	0.000	0.001	0.002	0.020	0.106	0.202	0.293	0.365	0.429	0.505	0.569	370.979	50.992	15.974
Northern America	0.000	0.000	0.003	0.004	0.217	0.939	1.818	2.275	2.671	3.001	3.355	3.619	607.024	41.720	10.648
Oceania	0.000	0.002	0.013	0.016	0.018	0.169	1.903	2.787	3.662	4.152	4.528	5.370	135.209	178.857	13.616

Region	Apixaban consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.007**	**0.071**	**0.213**	**0.405**	**0.601**	**0.835**	**1.085**	**-**	**289.399**	**38.834**
Europe	0.000	0.000	0.000	0.000	0.001	0.015	0.188	0.671	1.403	2.281	3.228	4.267	-	349.786	44.890
Western Europe	0.000	0.000	0.000	0.000	0.002	0.046	0.411	1.294	2.542	3.992	5.513	7.217	-	280.649	41.590
Northern Europe	0.000	0.000	0.000	0.000	0.000	0.010	0.208	0.891	2.176	3.761	5.408	6.978	-	501.603	47.471
Eastern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.025	0.095	0.216	0.440	0.799	1.273	-	856.203	80.510
Southern Europe	0.000	0.000	0.000	0.000	0.002	0.004	0.146	0.634	1.298	1.992	2.634	3.314	-	612.655	36.671
Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.009	0.020	0.047	-	-	361.280
Northern Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.012	0.028	0.062	-	-	354.314
Southern Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.007	-	-	-
Asia	0.000	0.000	0.000	0.000	0.000	0.001	0.017	0.052	0.087	0.108	0.133	0.150	-	352.480	19.909
Central Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.003	0.003	0.006	-	-	46.469
Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.002	0.034	0.098	0.159	0.189	0.224	0.244	-	344.262	15.337
South-Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.010	0.019	0.028	0.044	0.055	-	484.155	43.174
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001	0.002	0.003	0.005	-	146.966	70.588
Western Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.066	0.165	0.284	0.434	0.581	-	2131.861	52.053
Latin America and the Caribbean	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.030	0.058	0.089	0.126	0.167	-	499.201	42.390
Caribbean	0.000	0.000	0.000	0.000	0.000	0.015	0.066	0.258	0.499	0.869	1.457	2.372	-	221.095	68.106
Central America	0.000	0.000	0.000	0.000	0.000	0.000	0.010	0.026	0.046	0.066	0.079	0.100	-	-	29.170
South America	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.029	0.058	0.090	0.131	0.172	-	547.787	44.007
Northern America	0.000	0.000	0.000	0.000	0.000	0.057	0.430	1.101	1.997	2.801	3.981	5.267	-	226.397	38.156
Oceania	0.000	0.000	0.000	0.000	0.001	0.001	0.429	1.142	2.108	3.132	4.058	5.190	-	1116.059	35.045

Region	Edoxaban consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	**0.000**	**0.000**	**0.000**	**0.000**	**0.001**	**0.001**	**0.001**	**0.025**	**0.105**	**0.269**	**0.516**	**0.775**	**-**	**456.105**	**94.755**
Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.114	0.513	1.094	1.745	-	-	147.951
Western Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.315	1.115	2.022	2.995	-	-	111.914
Northern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.013	0.088	0.350	0.806	-	-	292.184
Eastern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.025	0.389	0.708	-	-	-
Southern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.294	0.812	1.333	-	-	-
Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Northern Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Southern Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asia	0.000	0.000	0.000	0.000	0.002	0.002	0.002	0.076	0.227	0.418	0.721	0.977	-	376.583	62.681
Central Asia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eastern Asia	0.000	0.000	0.000	0.000	0.003	0.004	0.004	0.143	0.430	0.798	1.341	1.775	-	379.466	60.398
South-Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.008	0.019	-	-	-
Southern Asia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Western Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.070	0.175	-	-	-
Latin America and the Caribbean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.051	-	-	547.994
Caribbean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.004	0.012	0.011	0.006	0.006	-	-	-20.958
Central America	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
South America	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.052	-	-	-
Northern America	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.011	0.026	0.022	0.018	0.013	-	-	-20.300
Oceania	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2. Consumption trends of DOACs from 2008-2019 by geographical region, with respect to population with atrial fibrillation (AF)

Region	Total DOAC consumption (DDD/1000-AF-patients/day)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	0.005	0.189	0.636	8.011	20.365	45.550	75.808	110.807	151.869	185.150	229.328	270.478	315.207	49.392	21.214
Europe	0.015	0.532	1.623	2.804	18.855	74.746	131.548	205.310	292.763	378.860	486.598	602.436	258.452	57.632	27.193
Western Europe	0.042	0.784	2.602	4.204	40.146	172.050	254.928	347.366	466.318	587.511	739.400	940.642	304.374	39.426	26.352
Northern Europe	0.012	0.782	1.994	2.606	8.291	37.229	87.761	179.511	310.270	439.943	570.709	690.643	165.302	102.747	30.568
Eastern Europe	0.000	0.262	0.509	0.916	5.430	24.761	58.247	100.311	131.923	161.799	226.707	293.102	265.003	74.657	30.487
Southern Europe	0.000	0.420	1.739	4.001	16.801	37.107	96.573	180.574	280.008	374.069	477.632	572.477	177.382	96.143	26.920
Africa	0.000	0.000	0.844	1.272	1.770	3.560	9.547	18.236	29.637	40.105	64.578	89.261	61.593	102.669	44.414
Northern Africa	0.000	0.000	0.189	0.253	0.571	0.793	3.832	9.716	18.865	27.086	52.999	80.130	61.428	187.561	61.949
Southern Africa	0.000	0.000	2.863	4.431	5.515	12.245	27.576	45.241	63.948	81.809	101.790	118.629	62.330	73.496	22.873
Asia	0.000	0.004	0.062	2.541	7.013	12.444	18.431	29.810	42.268	49.585	63.315	71.579	486.434	50.321	19.195
Central Asia	0.000	0.000	0.000	0.249	0.519	2.623	6.985	10.818	16.464	23.700	34.745	64.238	-	84.454	57.431
Eastern Asia	0.000	0.000	0.066	3.982	11.349	19.269	26.856	41.965	58.988	67.190	83.294	92.106	564.622	45.201	16.013
South-Eastern Asia	0.000	0.000	0.036	3.145	4.046	6.114	8.048	10.917	14.681	17.627	24.997	29.273	453.756	33.910	25.865
Southern Asia	0.000	0.000	0.001	0.019	0.032	0.540	1.027	1.586	2.330	3.297	6.740	10.273	698.332	62.790	63.980
Western Asia	0.000	0.182	0.946	2.326	6.696	28.306	83.846	181.673	273.969	368.272	485.887	537.774	210.449	113.112	25.208
Latin America and the Caribbean	0.000	0.376	1.458	3.169	18.647	39.785	60.537	81.995	98.087	115.065	136.785	163.954	201.056	35.093	18.678
Caribbean	0.000	0.000	0.000	17.376	58.661	121.610	186.890	236.695	274.890	326.745	394.183	509.848	-	31.239	22.865
Central America	0.000	1.443	4.083	6.888	26.320	31.098	41.374	53.179	68.324	82.221	87.727	94.821	96.751	30.002	11.543
South America	0.000	0.182	0.986	2.278	16.666	40.335	62.483	85.397	101.399	118.538	142.918	173.336	244.581	35.973	19.569
Northern America	0.000	0.034	0.179	35.204	63.748	98.387	153.952	201.033	261.830	295.397	348.278	398.086	719.278	38.578	14.988
Oceania	0.000	0.088	0.743	1.730	18.911	33.802	189.561	274.935	378.796	468.906	544.283	635.591	257.011	123.779	18.829

Region	Dabigatran consumption (DDD/1000-AF-patients/day)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	0.005	0.112	0.316	7.634	15.778	21.512	23.902	25.290	28.436	28.923	31.040	31.885	308.328	9.747	3.890
Europe	0.015	0.312	0.797	1.614	10.788	28.387	39.286	46.355	55.181	63.896	72.713	80.037	228.971	24.803	13.197
Western Europe	0.042	0.314	1.067	1.965	17.503	51.765	54.932	56.753	61.366	67.028	73.096	79.961	264.718	5.835	9.224
Northern Europe	0.012	0.356	0.756	1.351	6.366	18.834	27.051	32.049	37.330	42.319	46.210	46.340	192.074	25.614	7.473
Eastern Europe	0.000	0.236	0.323	0.556	3.820	12.731	23.067	33.977	45.606	56.914	68.281	77.619	240.370	53.011	19.394
Southern Europe	0.000	0.404	1.217	3.060	15.610	25.989	51.913	62.345	75.765	87.721	100.244	110.173	177.419	42.854	13.292
Africa	0.000	0.000	0.269	0.739	0.894	2.208	3.848	4.378	5.037	6.516	7.165	7.655	101.844	31.642	14.971
Northern Africa	0.000	0.000	0.000	0.000	0.000	0.212	0.542	0.880	0.937	1.741	1.861	2.364	-	64.122	36.146
Southern Africa	0.000	0.000	1.096	3.032	3.685	8.473	14.276	15.464	18.097	21.812	24.207	24.672	97.739	28.782	10.883
Asia	0.000	0.004	0.022	2.518	6.413	8.816	8.236	9.205	9.813	9.379	10.802	11.139	633.327	3.634	4.316
Central Asia	0.000	0.000	0.000	0.020	0.010	0.008	0.345	1.657	2.054	3.128	2.720	3.151	-	537.209	15.320
Eastern Asia	0.000	0.000	0.000	3.841	10.078	13.238	11.117	11.812	12.111	10.818	11.759	11.757	-	-2.922	-0.984
South-Eastern Asia	0.000	0.000	0.024	3.088	3.957	4.727	4.657	5.075	5.746	6.147	8.390	9.104	479.171	6.721	16.579
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.440	0.710	0.962	1.069	1.254	3.696	6.061	-	34.396	78.307
Western Asia	0.000	0.182	0.914	2.229	5.905	19.264	46.669	66.626	83.386	95.859	93.349	71.292	176.231	62.972	-5.089
Latin America and the Caribbean	0.000	0.259	1.070	2.557	13.106	17.131	18.336	18.861	17.283	18.011	19.978	20.876	152.053	0.295	6.500
Caribbean	0.000	0.000	0.000	17.376	32.498	31.220	30.537	25.558	24.309	21.301	18.376	12.775	-	-8.002	-19.302
Central America	0.000	0.792	2.854	5.068	16.515	14.142	13.032	12.092	12.457	13.806	13.048	11.929	70.478	-4.140	-1.435
South America	0.000	0.162	0.750	1.884	12.204	17.506	19.173	20.047	18.101	18.764	21.342	22.815	185.815	1.119	8.021
Northern America	0.000	0.007	0.040	34.982	52.739	48.620	43.343	37.364	40.355	29.423	24.034	19.808	967.345	-6.022	-21.117
Oceania	0.000	0.003	0.028	0.862	17.935	24.774	67.497	72.153	85.851	105.765	122.884	124.680	862.011	51.327	13.244

Region	Rivaroxaban consumption (DDD/1000-AF-patients/day)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	0.000	0.078	0.325	0.479	4.766	23.527	44.363	62.011	77.785	86.845	100.152	110.838	316.938	48.973	12.529
Europe	0.000	0.220	0.826	1.190	8.012	45.515	82.089	123.005	160.139	181.566	215.275	248.673	280.597	52.095	15.801
Western Europe	0.000	0.470	1.535	2.239	22.556	117.968	179.609	227.056	271.539	293.806	331.537	384.426	325.163	32.035	12.286
Northern Europe	0.000	0.426	1.238	1.254	1.901	17.877	50.098	102.540	163.256	205.758	240.427	264.709	143.529	109.022	17.481
Eastern Europe	0.000	0.025	0.186	0.360	1.607	12.016	33.789	61.034	74.461	81.056	113.646	144.004	301.010	83.677	24.590
Southern Europe	0.000	0.016	0.521	0.941	1.081	10.900	35.878	80.417	128.031	157.604	190.843	218.532	175.478	127.315	19.509
Africa	0.000	0.000	0.575	0.533	0.876	1.352	5.700	13.858	24.468	31.223	51.976	69.340	32.964	162.534	41.512
Northern Africa	0.000	0.000	0.189	0.253	0.571	0.581	3.290	8.835	17.755	22.240	44.008	62.351	45.542	212.566	51.998
Southern Africa	0.000	0.000	1.767	1.399	1.830	3.772	13.300	29.776	45.850	59.998	77.583	91.819	28.762	129.936	26.046
Asia	0.000	0.000	0.040	0.095	0.748	3.690	7.799	11.987	16.705	19.037	24.065	26.970	351.860	65.424	17.311
Central Asia	0.000	0.000	0.000	0.228	0.508	2.615	6.640	9.144	14.168	20.217	31.686	60.360	-	75.626	62.112
Eastern Asia	0.000	0.000	0.066	0.141	1.214	5.728	11.346	16.054	21.831	23.483	28.591	31.398	343.574	56.200	12.879
South-Eastern Asia	0.000	0.000	0.012	0.057	0.089	1.371	3.253	4.318	6.032	7.217	9.624	11.322	389.695	63.875	23.354
Southern Asia	0.000	0.000	0.001	0.019	0.032	0.123	0.322	0.568	1.159	1.821	2.777	3.838	387.226	111.369	49.042
Western Asia	0.000	0.000	0.032	0.097	0.792	9.037	37.026	95.781	143.121	192.688	259.995	281.578	555.707	151.125	25.304
Latin America and the Caribbean	0.000	0.118	0.388	0.613	5.535	22.595	40.665	56.835	68.875	79.107	91.516	104.608	287.514	44.995	14.948
Caribbean	0.000	0.000	0.000	0.000	26.163	88.172	147.003	175.889	185.695	200.710	212.687	248.057	-	28.181	10.133
Central America	0.000	0.651	1.229	1.820	9.804	16.955	24.876	32.495	40.693	47.153	49.994	52.485	139.867	33.887	8.853
South America	0.000	0.019	0.236	0.394	4.454	22.786	42.239	59.860	72.669	83.577	97.977	113.289	358.737	47.195	15.953
Northern America	0.000	0.027	0.139	0.221	11.008	46.897	89.456	109.945	126.021	137.053	147.907	153.836	596.280	39.028	6.874
Oceania	0.000	0.086	0.715	0.868	0.945	8.966	99.615	143.827	185.930	207.004	222.229	259.806	132.322	174.738	11.798

Region	Apixaban consumption (DDD/1000-AF-patients/day)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	0.000	0.000	0.000	0.000	0.017	0.797	8.017	23.639	44.059	63.841	86.756	110.488	-	281.001	35.861
Europe	0.000	0.000	0.000	0.000	0.054	0.856	10.312	36.432	75.181	120.544	170.109	227.162	-	344.526	44.569
Western Europe	0.000	0.000	0.000	0.000	0.088	2.317	20.387	63.533	123.269	191.164	269.035	373.023	-	276.126	44.642
Northern Europe	0.000	0.000	0.000	0.000	0.023	0.517	10.611	44.921	109.057	187.746	267.822	342.431	-	495.143	46.433
Eastern Europe	0.000	0.000	0.000	0.000	0.003	0.015	1.448	5.519	12.343	24.649	44.253	70.159	-	844.690	78.463
Southern Europe	0.000	0.000	0.000	0.000	0.110	0.217	8.782	37.813	76.211	115.104	149.523	184.233	-	605.127	34.209
Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.161	2.895	6.662	15.046		-	354.078
Northern Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.227	4.083	9.394	20.343		-	347.569
Southern Africa	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	2.137			-
Asia	0.000	0.000	0.000	0.000	0.000	0.150	2.659	7.795	12.612	15.138	18.068	19.748	-	338.461	16.123
Central Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.016	0.241	0.355	0.339	0.727		-	44.440
Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.238	4.328	11.920	18.706	21.546	24.629	25.780	-	328.423	11.285
South-Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.016	0.138	1.523	2.903	4.245	6.513	7.802	-	466.835	39.029
Southern Asia	0.000	0.000	0.000	0.000	0.000	0.015	0.059	0.148	0.205	0.353	0.613	0.936	-	140.354	65.859
Western Asia	0.000	0.000	0.000	0.000	0.000	0.004	0.151	19.266	47.462	79.725	117.626	149.274	-	2103.541	46.514
Latin America and the Caribbean	0.000	0.000	0.000	0.000	0.007	0.062	1.596	6.540	12.383	18.645	26.315	35.549	-	484.973	42.123
Caribbean	0.000	0.000	0.000	0.000	0.000	2.219	9.350	34.749	63.370	103.419	162.426	248.399	-	205.673	57.672
Central America	0.000	0.000	0.000	0.000	0.000	0.000	3.466	8.592	15.173	21.263	24.685	30.407		-	26.075
South America	0.000	0.000	0.000	0.000	0.008	0.044	1.121	5.750	11.138	16.978	24.771	33.584	-	532.161	44.469
Northern America	0.000	0.000	0.000	0.000	0.001	2.870	21.152	53.199	94.214	127.935	175.532	223.877	-	220.197	33.444
Oceania	0.000	0.000	0.000	0.000	0.031	0.062	22.448	58.955	107.015	156.137	199.171	251.105	-	1098.097	32.883

Region	Edoxaban consumption (DDD/1000-AF-patients/day)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	0.000	0.000	0.000	0.000	0.039	0.045	0.047	1.809	7.422	18.609	35.057	52.157	-	446.905	91.540
Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.013	5.703	25.280	54.279	89.212	-	-	150.096
Western Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.032	14.031	49.118	92.068	149.016	-	-	119.811
Northern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.673	4.420	17.425	39.818	-	-	289.621
Eastern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.112	17.589	33.550	-	-	-
Southern Europe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	16.789	45.643	73.694	-	-	-
Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Northern Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Southern Africa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asia	0.000	0.000	0.000	0.000	0.312	0.358	0.364	12.323	36.089	64.766	106.627	134.959	-	365.482	55.217
Central Asia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eastern Asia	0.000	0.000	0.000	0.000	0.548	0.634	0.650	22.138	65.313	117.882	187.176	226.602	-	368.715	51.387
South-Eastern Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.031	0.797	1.773	-	-	-
Southern Asia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Western Asia	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	17.292	41.269	-	-	-
Latin America and the Caribbean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.010	0.031	0.026	0.014	8.691	-	-	557.988
Caribbean	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.499	1.516	1.314	0.695	0.618	-	-	-25.864
Central America	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
South America	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	8.875	-	-	-
Northern America	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.525	1.240	0.984	0.804	0.566	-	-	-23.019
Oceania	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Time to adoption of each DOAC, considering all included countries as a whole

(A)	Time to adoption in quarters [median (IQR)]
Dabigatran	6.00 (3.00 - 9.50)
Rivaroxaban	5.00 (3.00 - 8.00)
Apixaban	9.00 (6.00 - 12.00)
Edoxaban	9.00 (8.00 - 12.50)

(B)	Apixaban	Dabigatran	Edoxaban
Dabigatran	0.00763	-	-
Edoxaban	0.982	0.013	-
Rivaroxaban	0.000138	0.982	0.00131

(A) Median (IQR) time to adoption in quarters (B) Results of pairwise comparisons using Wilcoxon rank sum test with Holm adjustment

Table 4: Manufacturer price (Int$ per day-of therapy) of each DOAC in 65 countries, Q2 2019.

Country	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Algeria	6.32	3.92		
Argentina	11.1	7.91	7.25	
Australia	1.59	1.68	1.68	
Austria	2.42	2.59	2.42	2.19
Belarus	6.07	4.07		
Belgium	2.92	2.79	2.92	2.78
Bosnia	4.91	4.16	4.52	
Brazil	2.58	2.58	2.58	1.91
Bulgaria	4.91	4.89	4.64	
Canada	2.46	2.27	2.61	2.3
Chile	3.13	3.85	3.27	
China	5.7	4.78	12.8	
Colombia	3.47	3.5	4.55	
Croatia	3.66	3.49	3.48	
Czech Republic	3.74	3.64	3.04	2.98
Ecuador	6.3	3.9	3.23	
Egypt	6.92	3.01	4.45	
Estonia	2.92	2.81	1.89	
Finland	2.11	2.1	2.11	2.11
France	2.14	2.14	2.26	
Germany	3.26	3.17	2.6	2.54
Greece	3.04	3.06	2.98	
Hungary	3.92	3.81	3.81	3.81
India	2.1	4.46	5.9	
Ireland	2.21	2.23	2.27	2.1
Italy	2.97	2.93	2.97	2.92
Japan	2.83	3.22	2.69	3.81
Jordan	5.61	4.7	4.65	
Kazakhstan	4.01	4.58	3.37	
South Korea	2.13	2.26	2.15	2.09
Kuwait	4.33	4.82	4.51	
Latvia	2.83	2.87	3.07	
Lebanon	3.82	3.75	3.94	
Lithuania	3.33	3.49	2.98	
Luxembourg	2.55	2.45	2.56	2.43
Mexico	4.97	4.78	4.94	
Morocco	5.42	5.66	5.12	
Netherlands	2.45	2.36	2.3	2.42
New Zealand	1.69	3.53	3.27	
Norway	1.76	1.8	1.78	1.82
Pakistan		1.27		
Peru	5.5	5.08	3.6	
Philippines	5.96	5.93	7.04	
Poland	4.82	4.41	4.99	
Portugal	3.05	3.13	3.05	2.9
Puerto Rico	14.8	14.9	15.2	12.4

Romania	4.61	4.29	4.57	
Russia	3.14	3.01	2.43	
South Africa	3.99	3.73	3.59	
Saudi Arabia	6.1	5.04	6.29	4.02
Serbia	2.49	3.94	3.72	
Slovakia	2.98	3.03	2.99	3.02
Slovenia	2.72	2.72	2.24	
Spain	2.87	2.86	2.87	2.75
Sweden	2.11	2.09	2.11	2.11
Switzerland	2	2.04	1.96	1.95
Taiwan	5.13	3.65	3.71	4.54
Thailand	15.1	13.9	13.3	13.9
Tunisia	8.78	8.55	8.55	
Turkey	1.66	1.65	1.71	1.7
United Arab Emirates	4.01	4.51	4.74	
United Kingdom	2	2.11	2.23	2.06
Uruguay	1.67	1.58	0.996	
United States	12.6	12.9	13.1	11.1
Venezuela		0.83		

Table 5: Key dates of DOAC FDA approval for AF and AF guideline changes.

DOAC	FDA approval for use in AF	First major RCT published	First recommendation by guideline
Dabigatran	Oct 2010	Sep 2009 (RE-LY)	Feb 2011 (ACC/AHA) Aug 2012 (ESC)
Rivaroxaban	Nov 2011	Sep 2011 (ROCKET-AF)	Mar 2014 (ACC/AHA) Aug 2012 (ESC)
Apixaban	Dec 2012	Mar 2011 (AVERROES) Sep 2011 (ARISTOTLE)	Mar 2014 (ACC/AHA) Aug 2012 (ESC)
Edoxaban	Jan 2015	Nov 2013 (ENGAGE-TIMI-48)	Jan 2019 (ACC/AHA) Aug 2016 (ESC)

Table 6: Consumption trends of warfarin from 2008-2019 by geographical region.

Region	Total warfarin consumption (DDDTID)												Compound annual growth rate (%)		
	Q2 2008	Q2 2009	Q2 2010	Q2 2011	Q2 2012	Q2 2013	Q2 2014	Q2 2015	Q2 2016	Q2 2017	Q2 2018	Q2 2019	2010-13	2013-16	2016-19
All regions	1.022	1.054	1.061	1.104	1.099	1.193	1.194	1.079	1.025	0.937	0.889	0.809	3.973	-4.925	-7.568
Europe	2.276	2.418	2.623	2.840	3.032	3.208	3.296	3.314	3.221	3.016	2.769	2.537	6.945	0.136	-7.650
Western Europe	0.415	0.469	0.534	0.629	0.723	0.714	0.769	0.796	0.795	0.753	0.698	0.712	10.148	3.647	-3.619
Northern Europe	7.305	7.441	7.615	8.193	8.615	9.117	9.242	9.024	8.516	7.518	6.387	5.390	6.184	-2.250	-14.142
Eastern Europe	0.912	1.081	1.449	1.684	1.814	2.037	2.166	2.300	2.387	2.434	2.483	2.415	12.028	5.439	0.383
Southern Europe	3.163	3.331	3.432	3.431	3.658	3.740	3.767	3.753	3.562	3.328	3.022	2.789	2.902	-1.613	-7.826
Africa	0.726	0.725	0.894	0.735	0.781	0.913	1.164	0.832	1.231	0.817	1.054	1.087	0.717	10.455	-4.049
Northern Africa	0.837	0.819	1.072	0.807	0.879	1.096	1.509	0.990	1.576	0.957	1.340	1.347	0.752	12.864	-5.098
Southern Africa	0.547	0.575	0.607	0.619	0.620	0.613	0.591	0.570	0.652	0.581	0.567	0.643	0.313	2.067	-0.458
Asia	0.209	0.223	0.254	0.272	0.306	0.318	0.319	0.327	0.314	0.304	0.301	0.286	7.752	-0.469	-3.018
Central Asia	-	-	-	0.090	0.198	0.411	0.602	0.456	0.514	0.506	0.768	0.606		7.729	5.606
Eastern Asia	0.313	0.344	0.386	0.403	0.464	0.463	0.454	0.455	0.439	0.421	0.400	0.376	6.189	-1.758	-4.989
South-Eastern Asia	0.032	0.048	0.174	0.207	0.226	0.253	0.324	0.338	0.328	0.343	0.355	0.400	13.278	9.026	6.888
Southern Asia	0.042	0.045	0.055	0.061	0.062	0.070	0.079	0.098	0.091	0.094	0.105	0.102	8.570	9.071	3.757
Western Asia	0.935	0.858	0.987	1.185	1.270	1.443	1.375	1.338	1.285	1.222	1.206	1.115	13.499	-3.795	-4.628
Latin America and the Caribbean	0.256	0.274	0.280	0.309	0.337	0.318	0.293	0.282	0.280	0.290	0.274	0.274	4.355	-4.137	-0.740
Caribbean	2.099	2.267	2.503	2.640	2.691	2.572	2.482	2.170	2.224	2.250	2.073	1.813	0.906	-4.731	-6.575
Central America	0.032	0.030	0.036	0.039	0.034	0.033	0.028	0.019	0.011	0.016	0.014	0.015	-3.303	-30.838	11.126
South America	0.306	0.329	0.333	0.369	0.408	0.385	0.356	0.347	0.348	0.360	0.342	0.344	5.013	-3.363	-0.354
Northern America	7.140	7.219	6.766	6.831	6.079	7.006	6.902	5.376	4.803	4.219	3.984	3.426	1.173	-11.824	-10.657
Oceania	6.672	6.431	6.512	6.676	6.545	6.528	5.600	5.131	4.606	4.016	3.451	3.000	0.080	-10.975	-13.311

Table 7: Time since when idarucizumab (antidote of dabigatran) were first available and sold by country.

Time (quarter)	Countries
Q4 2015	Finland, Netherlands, Slovenia, Sweden, United Kingdom, United States
Q1 2016	Austria, Croatia, Czech Republic, France, Germany, Latvia, Norway, Poland, Puerto Rico
Q2 2016	Belgium, Canada, Hungary, Italy, New Zealand, Romania
Q3 2016	Australia, Portugal, Slovakia, Spain
Q4 2016	Ireland, Japan, South Africa, Switzerland, Taiwan
Q2 2017	Ecuador, Serbia
Q3 2017	India, Mexico, Philippines
Q4 2017	Lebanon, Thailand
Q2 2018	Kuwait, Peru
Q3 2018	Saudi Arabia, United Arab Emirates
Q1 2019	China, Turkey
Q2 2019	Lithuania, Russia