Dabigatran

Statut de médicament essentiel ✓

Section: 10. Medicines affecting the blood > 10.2. Medicines affecting coagulation

Codes ATC: B01AE07

Indication	Venous thromboembolism Code ICD11: BD72
INN	Dabigatran
Type de médicament	Chemical agent
Type de liste	Liste de base
Formulations	Oral > Solid: 110 mg ; 150 mg
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	apixaban (Codes ATC: B01AF02) edoxaban (Codes ATC: B01AF03) rivaroxaban (Codes ATC: B01AF01)
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Dabigatran
DrugBank	Dabigatran (Dabigatran etexilate)

Recommandation du comité d'experts

The Committee recommended the addition of dabigatran with a square box to the core list of the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for treatment of venous thromboembolism based on favourable efficacy and acceptable safety. The square box refers to apixaban, edoxaban and rivaroxaban as therapeutically equivalent alternatives. The Committee noted that the DOACs demonstrated clinical benefits in terms of reduced mortality, reduced risk of stroke or systemic embolism, and were associated with fewer severe/major bleeding episodes compared to well-controlled warfarin in patients with NVAF. In the treatment of patients with venous thromboembolism, DOACs were associated with small reductions in mortality, risk of subsequent/recurrent thromboembolic events and major bleeding compared to low-molecular weight heparin and vitamin K antagonists. The use of DOACs may also have relevant health system benefits related to the infrastructure required for warfarin treatment monitoring, as they do not require laboratory monitoring. The Committee noted that DOACs have higher daily treatment costs than warfarin, but have been found to be a cost-effective intervention. It is recommended that countries take all these factors into consideration when selecting anticoagulants to best suit their national and local needs and circumstances. The Committtee recommended that WHO take action to facilitate access to these medicines through the WHO prequalification programme, and through collaboration with partners such as the Medicines Patent Pool.

Contexte

Two applications requested the inclusion of direct oral anticoagulants (DOACs) on the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and for treatment of venous thromboembolism. In 2015, the Committee rejected an application seeking inclusion of dabigatran, rivaroxaban and apixaban as a therapeutic group on the EML for the treatment of nonvalvular atrial fibrillation (NVAF). The Committee considered that although the evidence presented

indicated a favourable overall clinical benefit of DOACs over warfarin, the absolute magnitude of benefit was limited, inconsistent across trials and may be influenced by a number of factors, such as the quality of oral anticoagulation (time in therapeutic range). The Committee considered that in order for countries to maximize use of available resources, further research was necessary to explore the unmet need in terms of anticoagulation in people unable to be stabilized with warfarin and in clinical settings where access to warfarin monitoring is not readily available. The Committee expressed some concern regarding safety of DOACs, noting that there were currently no specific antidotes that would reverse anticoagulant effects in case of emergency. The Committee also acknowledged that the large difference in cost between DOACs and warfarin was not proportional to the observed incremental clinical benefit. Full details are available in the technical report of the 2015 Expert Committee meeting (1).

Pertinence pour la santé publique

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia (2) and a major public health issue affecting 37.6 million individuals globally in 2017 (3). The incidence and prevalence of AF are expected to increase over the next 30 years (4–6). Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% per year if other risk factors are present (7). In a cohort of 15 400 individuals with atrial fibrillation in 47 countries, the highest number of strokes occurred in patients in Africa (incidence 89/1137 (8%) per year), China (incidence 143/2023 (7%) per year), and Southeast Asia (incidence 88/1331 (7%) per year) (8). In low and middle-income countries (LMICs), stroke is associated with an increased mortality and significant disability, particularly in disadvantaged populations (9–11). Additionally, according to a recent WHO survey of 177 countries, provisions for the treatment and rehabilitation of patients with stroke are available in less than a quarter of public health care facilities in LMICs (12). Deep venous thrombosis and pulmonary embolism are major contributors to global disease burden. Their estimated annual incidence ranges from 0.7 to 2.7 per 1000 population in Western Europe, 1.1 to 2.4 per 1000 population in North America and 0.2 to 1.6 per 1000 population in Latin America and Asia (13). Additionally, venous thromboembolism markedly increases with age, with incidences as high as 4.29 to 5.64 per 1000 population in individuals older than 70 years (14, 15). Thus, venous thromboembolism is likely to become an even more prominent problem with aging populations.

Bénéfices

Application 1 - NVAF: This application presented the results of a meta-analysis that updated a published meta-analysis of four randomized controlled trials (RCTs) by Ruff et al (16) with data from the J-ROCKET AF trial (17) involving a total of 59 819 participants. Compared with warfarin, DOACs were associated with a significantly reduced risk of stroke and systemic embolism in patients with NVAF (risk ratio (RR) 0.80, 95%CI 0.71 to 0.91, P=0.003; absolute effect: 8 fewer events per 1000 (95%CI 3 fewer to 11 fewer). The quality of evidence was rated as high using GRADE. This application also presented the results of a systematic literature review of observational studies reporting real-world data for DOACs versus vitamin K antagonists for the primary efficacy outcome of stroke and systemic embolism. Of 23 studies included in the quantitative data synthesis, 12 studies provided data for the primary efficacy outcome of stroke and systemic embolism (18–29). In these studies, NOACs were associated with a reduced risk of stroke and systemic embolism compared with warfarin in patients with NVAF (Risk ratio (RR) 0.79, 95%CI 0.71 to 0.89, p<0.001; absolute effect: 5 fewer events per 1000 (95%CI 3 fewer to 7 fewer). The quality of evidence was rated as very low using GRADE, due to the evidence being based on observational studies with heterogenous findings. When compared individually with warfarin, dabigatran, rivaroxaban and apixaban were each associated with a lower risk of stroke and systemic embolism than warfarin. No real-world data were available for edoxaban. Application 2 - NVAF: This application conducted a meta-analysis of eight systematic reviews (30–37) and 13 randomized trials involving a total of 75 543 participants with AF and one or two additional risk factors for stroke (17, 38–49). Participants were randomized to a DOAC or warfarin (target international normalized ratio 2.0 to 3.0) and were followed for two to three years. Individuals with estimated creatinine clearance of less than 30 mL per minute or a high risk of bleeding were excluded. Use of DOACs instead of vitamin K antagonists in individuals with NVAF was associated with decreased mortality (RR 0.90, 95%CI 0.85 to 0.94, high certainty evidence) and decreased risk of stroke (RR 0.83, 95%CI 0.72 to 0.96; absolute effect: 7 fewer events per 1000 (95%CI 11 fewer to 4 fewer), high certainty evidence). Also, DOACs were found to probably decrease the risk of systemic embolism (RR 0.74, 95%CI 0.48 to 1.13; absolute effect: 1 fewer event per 1000 (95%CI 1 fewer to 0 fewer), moderate certainty evidence) and major bleeding (RR 0.81, 95%CI 0.66 to 0.98; absolute effect: 11 fewer events per 1000 (95%CI 20 fewer to 1 fewer), moderate certainty evidence). Application 2 – venous thromboembolism: This application conducted a meta-analysis of 24 systematic reviews (50–73) and 12 randomized trials involving 28 876 participants with an objectively confirmed symptomatic proximal deep venous thrombosis or pulmonary embolism (74–85). Participants were randomized to a DOAC or to an initial treatment with low molecular weight heparin (five to ten days) followed by dose-adjusted

warfarin (target international normalized ratio 2.0 to 3.0). Dabigatran was also administered after an initial treatment of five to ten days with low molecular weight heparin, while rivaroxaban, apixaban and edoxaban were administered without initial parenteral anticoagulants. The length of the anticoagulation varied across trials from three to twelve months. Individuals with estimated creatinine clearance of less than 30 mL per minute or a high risk of bleeding were excluded. The analysis showed that the use of DOACs instead of vitamin K antagonists in individuals with deep venous thrombosis or pulmonary embolism likely has a small effect on mortality (RR 0.99, 95%CI 0.85 to 1.15; absolute effect: 0 fewer events per 1000 (95%CI 6 fewer to 6 more), moderate certainty evidence) and the risk of subsequent pulmonary embolism (RR 0.97, 95%CI 0.77 to 1.23; absolute effect: 1 fewer event per 1000 (95%CI 5 fewer to 5 more), moderate certainty evidence). DOACs probably decrease the risk of a recurrent deep venous thrombosis (RR 0.80, 95%CI 0.59 to 1.09; absolute effect: 5 fewer events per 1000 (95%CI 11 fewer to 2 more), moderate certainty evidence) and major bleeding (RR 0.63, 95%CI 0.47 to 0.84; absolute effect: 6 fewer events per 1000 (95%CI 9 fewer to 3 fewer), high certainty evidence).

Torts

Application 1: From the updated meta-analysis of five RCTs (16, 17), DOACs were found to be associated with a significantly lower risk of major bleeding compared with warfarin (RR 0.86, 95%CI 0.74 to 0.99, p=0.04; absolute effect: 8 fewer events per 1000 (95%CI 1 fewer to 16 fewer). The quality of the evidence was rated as moderate using GRADE, downgraded due to inconsistency. This application also presented the results of a systematic literature review of observational studies reporting real-world data for DOACs versus vitamin K antagonists for the primary safety outcome of major bleeding. Of 23 studies included in the quantitative data synthesis, 17 studies provided data for the primary safety outcome (18, 20, 22–29, 86–92). In these studies, DOACs were associated with a lower risk of bleeding compared with warfarin in NVAF patients (RR 0.72, 95%CI 0.64 to 0.80. p<0.001; absolute effect 9 fewer events per 1000 (95%CI 6 fewer to 11 fewer). The quality of evidence was rated as very low using GRADE, due to the evidence being based on observational studies with heterogenous findings. When compared individually with warfarin, dabigatran, rivaroxaban apixaban and edoxaban were each associated with a lower risk of major bleeding than warfarin. No real-world data were available for edoxaban. Application 2: As reported above, randomized trial evidence suggests that DOACs are probably associated with a lower risk of major bleeding than vitamin K antagonists in the treatment of NVAF (RR 0.81, 95%CI 0.66 to 0.98; absolute effect: 11 fewer events per 1000 (95%CI 20 fewer to 1 fewer), moderate certainty evidence) and venous thromboembolism (RR 0.63, 95%CI 0.47 to 0.84; absolute effects 6 fewer events per 1000 (95%CI 9 fewer to 3 fewer), high certainty evidence). Large observational studies on real-world populations suggest that the risk of bleeding with DOACs may be equivalent to or lower than the risk with vitamin K antagonists. • A large cohort of 156 005 adults with atrial fibrillation and venous thromboembolism in the United Kingdom suggested a lower risk of bleeding with apixaban in comparison with warfarin (HR 0.69, 95%CI 0.54 to 0.79 in individuals with atrial fibrillation; HR 0.60, 95%CI 0.46 to 0.79 in individuals without atrial fibrillation). Also, investigators observed no significant differences in the risk of bleeding for the comparisons of rivaroxaban vs warfarin (HR 1.12, 95%CI 0.99 to 1.26 in individuals with atrial fibrillation; HR 0.95, 95%CI 0.82 to 1.10 in individuals without atrial fibrillation) and dabigatran vs warfarin (HR 0.87, 95%CI 0.72 to 1.04 in individuals with atrial fibrillation; HR 0.98, 95%CI 0.71 to 1.35 in individuals without atrial fibrillation) (25). • A propensity-matched analysis of 76 940 individuals with non-valvular atrial fibrillation of an administrative database from the United States suggested a lower risk of bleeding with apixaban in comparison to warfarin (HR: 0.60, 95%CI: 0.54 to 0.65) (29). • A community based population study of 59 525 adults with venous thromboembolism in Canada and the United States showed a similar risk of bleeding with DOAC and VKA (HR 0.99, 95%CI 0.84 to 1.16) (93). • A propensity score matched analysis of 45 361 patients with non-valvular atrial fibrillation of an administrative database from the United States, showed a lower risk of bleeding with dabigatran (HR 0.69m 95%CI 0.50 to 0.96) and apixaban (HR 0.53, 95%CI 0.39 to 0.71) in comparison to warfarin. In patients using rivaroxaban, investigators observed a similar risk of bleeding in comparison to warfarin (HR 0.98, 95%CI 0.83 to 1.17) (94). • A propensity-matched cohort of 29 963 adults with venous thromboembolism in Denmark, also suggested a similar risk of bleeding with DOAC and VKA (HR 1.19, 95%CI 0.66 to 2.13) (95). The application also reported data from recent and ongoing trials involving specific antidotes for emergency reversal of anticoagulation in patients receiving DOACs. Idarucizumab is a monoclonal antibody fragment that has been investigated for use in reversing the anticoagulant effect of dabigatran in the RE-VERSE AD trial in 503 patients with life-threatening bleeding or about to undergo an urgent procedure (96). Following administration of 5 g of IV idarucizumab, anticoagulation was completely reversed in 98% of patients within four hours. Andexanet alfa has recently been approved as an antidote for rivaroxaban and apixaban based on results of two open label randomized trials of rivaroxaban or apixaban compared to placebo (ANNEXA-R and ANNEXA-A). The primary outcome of both trials was anti-factor Xa activity measured with a chromogenic assay. The results showed a reduction of

anti-factor Xa activity of 92±11% with andexanet vs 18±15% with placebo in the rivaroxaban study and a reduction of 94±2% with adexanet vs 21±9% with placebo in the apixaban study (97). There is an ongoing open-label, non-randomized trial (ANNEXA-4) evaluating the effects of andexanet on clinical endpoints in patients with acute bleeding under treatment with rivaroxaban or apixaban. In an interim report of this study, of the 47 patients available for analysis, 37 were judged as having good haemostasis by an independent adjudication committee (98).

Rapport coût/efficacité

Reported monthly costs of DOACs in the two applications indicate that the costs for DOACs range widely between countries: from US$ 20–50 per month in Latin American countries, to US$ 90 per month in the United Kingdom, to up to US$ 600 per month in the United States and Canada. Application 1: A 2016 systematic review of 54 studies from 21 countries reporting cost-effectiveness analyses of DOACs (103) concluded that DOACs are cost-effective in several countries, independent of their health system, direct costs of DOACs and vitamin K antagonists, and costs of diseases. The authors defined a drug as cost-effective when the incremental cost-effectiveness ratio was below the willingness to pay value. Most studies used a conventional Markov decision analysis model, and the rate of events was gathered from the RCTs of DOACs. This application updated the systematic review, including 64 cost-effectiveness analyses from 28 high- and middle-income countries. Most of them used same criteria, but newer cost-effectiveness analyses from the United States included costs from health care resource use and real-world data from health systems to determine rate of stroke and bleeding rather than data solely from randomized trials. All studies to date demonstrated that DOACs were a cost-effective strategy. The studies included in the updated systematic review are referenced in the application. Application 2 - NVAF: The application identified two systematic reviews of economic evaluation of any DOAC versus vitamin K antagonists in patients with AF. The first article identified was a systematic review of cost-utility analyses of dabigatran, rivaroxaban or apixaban versus warfarin. This review included 18 primary studies conducted in North America and Europe. All but one used a Markov model to extrapolate long-term data basing the calculation on the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer. Thirteen models compared dabigatran versus warfarin, four rivaroxaban versus warfarin and four apixaban versus warfarin. Although there was some inconsistency among the conclusions of the individual models, the large majority showed that DOACs were cost-effective with ICERs below the willingness-to-pay thresholds and sometimes dominant over warfarin (104). The second article identified was a systematic review of cost-utility analyses of apixaban versus warfarin. This review identified 26 primary studies conducted in North America, Latin America and Europe. All the studies except of one used a Markov model to extrapolate long-term data with the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer with a lifetime horizon. The results showed that apixaban was cost-effective with incremental cost effectiveness ratios (ICERs) below the willingness-to-pay thresholds (105). Application 2 – venous thromboembolism: The application identified five cost comparisons between DOACs and VKA for patients with venous thromboembolism. Four reports suggested that DOACs are cost-saving compared with warfarin (106–109) and one study found an equivalent cost between DOACs and vitamin K antagonists (110). In addition, the application identified 14 economic evaluations that compared the cost and effectiveness of DOACs versus vitamin K antagonists (107, 111–123). All suggested that DOACs are cost-effective compared to warfarin.

Directives de l'OMS

There are no WHO guidelines currently available for the treatment of NVAF or venous thromboembolism. Oral anticoagulation with warfarin or DOACs (apixaban, dabigatran, rivaroxaban) in patients with atrial fibrillation (AF) at high risk of stroke based on a CHA2DS2-VASc score of 2 or more is recommended in multiple international guidelines (99–102). For management of venous thromboembolism, recent, yet to be published, American and Latin American guidelines are reported to support short-term anticoagulation in individuals at low risk of recurrence and indefinite anticoagulation in individuals at high risk (e.g. unprovoked events). DOACs are the preferred alternative over warfarin.

Disponibilité

Dabigatran, manufactured by Boehringer Ingelheim, apixaban, manufactured by Bristol-Myers Squibb, and rivaroxaban, manufactured by Bayer, all have wide global regulatory approval. Edoxaban, manufactured by Daiichi Sanyko Company, has regulatory approval from regulatory authorities in the United States, Europe, Japan, Canada and Nigeria.

Autres considérations

Comments on the applications were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of DOACs to the complementary list of the EML as they are effective medicines for which EML listing may improve equity by making them more accessible to patients, and driving costs down.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. J Geriatr Cardiol. 2017;14(3):195–203.
3. Global Burden of Disease compare data visualization. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2016. Available from https://vizhub.Healthdata.Org/gbd-compare/, accessed 29 September 2019.
4. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European heart journal. 2013;34(35):2746–51.
5. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest. 2012;142(6):1489–98.
6. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.
7. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e531S–e75S.
8. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet. 2016;388(10050):1161–9.
9. Joubert J, Prentice LF, Moulin T, Liaw ST, Joubert LB, Preux PM et al. Stroke in rural areas and small communities. Stroke. 2008;39(6):1920–8.
10. Lloyd-Sherlock P. Stroke in Developing Countries: Epidemiology, Impact and Policy Implications. Development Policy Review. 2010;28(6):693–709.
11. Pandian JD, Srikanth V, Read SJ, Thrift AG. Poverty and stroke in India: a time to act. Stroke. 2007;38(11):3063–9.
12. Assessing national capacity for the prevention and control of noncommunicable diseases. Geneva: World Health Organization; 2016.
13. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363–71.
14. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158(6):585–93.
15. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232(2):155–60.
16. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.
17. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J. 2012;76(9):2104–11.
18. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016;353:i3189.
19. Maura G, Blotiere PO, Bouillon K, Billionnet C, Ricordeau P, Alla F et al. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study. Circulation. 2015;132(13):1252–60.
20. Kohsaka S, Katada J, Saito K, Terayama Y. Safety and effectiveness of apixaban in comparison to warfarin in patients with nonvalvular atrial fibrillation: a propensity-matched analysis from Japanese administrative claims data. Curr Med Res Opin. 2018;34(9):1627–34.
21. Yoshimura S, Koga M, Sato S, Todo K, Yamagami H, Kumamoto M et al. Two-Year Outcomes of Anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation- SAMURAI-NVAF Study. Circ J. 2018;82(7):1935–42.
22. Sjogren V, Bystrom B, Renlund H, Svensson PJ, Oldgren J, Norrving B et al. Non-vitamin K oral anticoagulants are non-inferior for stroke prevention but cause fewer major bleedings than well-managed warfarin: A retrospective register study. PloS one. 2017;12(7):e0181000.
23. Lee HF, Chan YH, Tu HT, Kuo CT, Yeh YH, Chang SH et al. The effectiveness and safety of low-dose rivaroxaban in Asians with non-valvular atrial fibrillation. Int J Cardiol. 2018;261:78–83.
24. Chan YH, Kuo CT, Yeh YH, Chang SH, Wu LS, Lee HF et al. Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation. J Am Coll Cardiol. 2016;68(13):1389–401.
25. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505.
26. Laliberte F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. CurrMed Res Opin. 2014;30(7):1317–25.
27. Seeger JD, Bykov K, Bartels DB, Huybrechts K, Zint K, Schneeweiss S. Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation. Thromb Haemost. 2015;114(6):1277–89.
28. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND et al. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2016;5(6).
29. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost. 2017;117(6):1072–82.
30. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017;39(7):1456-78.e36.
31. Bajaj NS, Kalra R, Patel N, Hashim T, Godara H, Ather S et al. Comparison of Approaches for Stroke Prophylaxis in Patients with Non-Valvular Atrial Fibrillation: Network Meta-Analyses of Randomized Controlled Trials. PloS one. 2016;11(10):e0163608.
32. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database Syst Rev. 2018;3:CD008980.
33. Cohen AT, Hill NR, Luo X, Masseria C, Abariga SA, Ashaye AO. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: A comparison of efficacy and safety following treatment with direct oral anticoagulants. Int J Cardiol. 2018;269:174–81.
34. Lowenstern A, Al-Khatib SM, Sharan L, Chatterjee R, LaPointe NMA, Shah B et al. Interventions for Preventing Thromboembolic E

vents in Patients With Atrial Fibrillation: A Systematic Review. Ann Intern Med. 2018;169(11):774–787
35. Ntaios G PV, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with at rial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized con trolled trials. Stroke. 2017;12(6):589–96.
36. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN et al. Oral anticoagulants for primary prevention, treatm ent and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review , network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017;21(9):1–386.
37. Tawfik A, Bielecki JM, Krahn M, Dorian P, Hoch JS, Boon H et al. Systematic review and network meta-analysis of stroke preventi on treatments in patients with atrial fibrillation. Clin Pharmacol. 2016;8:93–107.
38. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost. 2011;105(3):535–44.
39. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibr illation. N Engl J Med. 2009;361(12):1139–51.
40. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007;100(9):1419 –26.
41. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fib rillation. N Engl J Med. 2013;369(22):2093–104.
42. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fib rillation. N Engl J Med. 2011;365(11):981–92.
43. NCT00973245. BAY59-7939 in Atrial Fibrillation Once Daily (OD). 2014. Available from https://clinicaltrials.gov/ct2/show/NC T00973245, accessed 30 October 2019.
44. NCT00973323. BAY59-7939 Japanese in Atrial Fibrillation (2nd). 2014. Available from https://clinicaltrials.gov/ct2/show/NCT 00973323, accessed 30 October 2019.
45. NCT01136408. A Dose Response Study of Dabigatran Etexilate(BIBR 1048) in Pharmacodynamics and Safety in Patients With Non-valvular Atrial Fibrillation in Comparison to Warfarin. 2014. Available from https://clinicaltrials.gov/ct2/show/NCT01136408, accessed 30 October 2019.
46. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non -valvular atrial fibrillation. -The ARISTOTLE-J study. Circ J. 2011;75(8):1852–9.
47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
48. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Throm b Haemost. 2010;104(3):633–41.
49. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circ J. 2012;76(8):1840–7.
50. Adam SS, McDuffie JR, Ortel TL, Williams Jr JW. Comparative effectiveness of warfarin and new oral anticoagulants for the mana gement of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157(11):796–807.
51. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral A nticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-Analyses. Clin Ther. 2017;39(7): 1456–78.
52. Canadian Agency for D, Technologies in H. Rivaroxaban (Xarelto): Treatment of Venous Thromboembolic Events (Deep Vein Thro mbosis [DVT], Pulmonary Embolism [PE]) and Prevention of Recurrent DVT and PE2015 2015/08/None. Available from https://www .ncbi.nlm.nih.gov/books/NBK344331/, accessed 30 October 2019.
53. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA. 2014;312(11):1122–35.
54. Cohen AT, Hamilton M, Mitchell SA, Phatak H, Liu X, Bird A et al. Comparison of the Novel Oral Anticoagulants Apixaban, Dabigat ran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Re view and Network Meta-Analysis. PloS one. 2015;10(12):e0144856.
55. Dentali F, Di Minno MN, Gianni M, Ambrosino P, Squizzato A, Ageno W. Non-vitamin K oral anticoagulants in patients with pulmo nary embolism: a systematic review and meta-analysis of the literature. Intern Emerg Med. 2015;10(4):507–14.
56. Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Dentali F. Direct oral anticoagulants for the treatment of unprovoked venous th romboembolism: a meta-analysis of randomised controlled trials. Blood Transfus. 2015;13(3):391–5.
57. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute v enous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. BMJ. 2012;345(7884):e7498.
58. Ganji R, Ala S, Aarabi M, Baghery B, Salehifar E. Comparison of Dabigatran vs. Warfarin in Acute Vnous Thromboemboly: Systema tic Review. Iran J Pharm Res. 2016;15(2):611–7.
59. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct oral anticoagulants in the trea tment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review. Vasc Health Risk Manag. 2014;10:627–39.
60. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, Suárez-Gea ML, Vargas-Castrillón E. Direct oral anticoagulants in the trea tment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014;134(4):774–82.
61. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism - a systematic review with indir ect comparisons. VASA Zeitschrift für Gefässkrankheiten. 2014;43(5):353–64.
62. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxab an, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Met a-analysis of Phase III Trials. Eur J Vasc Endovasc Surg. 2014;48(5):565–75.
63. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembol ism. Thromb Res. 2014;133(6):1145–51.
64. Loffredo L, Perri L, Del Ben M, Angelico F, Violi F. New oral anticoagulants for the treatment of acute venous thromboembolism: a re they safer than vitamin K antagonists? A meta-analysis of the interventional trials. Intern Emerg Med. 2015;10(4):499–506.
65. Mumoli N, Cei M, Pesavento R, Campanini M, Dentali F. Are direct oral anticoagulants equally effective in reducing deep vein thro mbosis and pulmonary embolism? Int J Cardiol. 2015;187:645–7.
66. Petrov VI, Shatalova OV, Gorbatenko VS, Smuseva ON, Maslakov AS. Efficacy and safety of the new oral anticoagulants in the tre atment of venous thromboembolic complications: meta-analysis. Rational Pharmacotherapy in Cardiology. 2016;12(1):31–9.
67. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein t hrombosis. Cochrane Database Syst Rev. 2015;6(6):CD010956.
68. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev. 2015;12(12):CD010957.
69. Senoo K, Kondo Y, Miyazawa K, Isogai T, Chun YH, Kobayashi Y. Safety and efficacy of direct oral anticoagulants over warfarin in J apanese patients with acute venous thromboembolism: A meta-analysis. J Cardiol. 2017;69(5):763–8.
70. Tahir F, Riaz H, Riaz T, Badshah MB, Riaz IB, Hamza A et al. The new oral anti-coagulants and the phase 3 clinical trials - a system atic review of the literature. Thromb J. 2013;11(1):18.
71. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulan ts as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review an d meta-analysis. J Thromb Haemost. 2014;12(3):320–8.
72. Van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for a

cute venous thromboembolism: Evidence from phase 3 trials. Blood. 2014;124(12):1968–75.
73. Vedovati MC, Becattini C, Germini F, Agnelli G. Efficacy and safety of direct oral anticoagulants after pulmonary embolism: a meta-analysis. Int J Cardiol. 2014;177(2):601–3.
74. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799–808.
75. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation. 2007;116(2):180–7.
76. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–510.
77. Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost. 2008;6(8):1313–8.
78. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406–15.
79. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS et al. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood. 2008;112(6):2242–7.
80. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.
81. Nakamura M, Nishikawa M, Komuro I, Kitajima I, Uetsuka Y, Yamagami T et al. Apixaban for the Treatment of Japanese Subjects With Acute Venous Thromboembolism (AMPLIFY-J Study). Circ J. 2015;79(6):1230–6.
82. Piazza G MV, Grosso M, et al. A randomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy versus low-molecular weight heparin/warfarin in patients with symptomatic deep vein thrombosis—edoxaban thrombus reduction imaging study (eTRIS) [abstract]. Circulation. 2014;130:A12074.
83. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764–72.
84. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342–52.
85. Yamada N, Hirayama A, Maeda H, Sakagami S, Shikata H, Prins MH, et al. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE program. Thromb J. 2015;13:2.
86. Lamberts M, Staerk L, Olesen JB, Fosbol EL, Hansen ML, Harboe L et al. Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. J Am Heart Assoc. 2017;6(2).
87. Ramagopalan S, Allan V, Saragoni S, Esposti LD, Alessandrini D, Perrone V et al. Patient characteristics and bleeding events in nonvalvular atrial fibrillation patients treated with apixaban or vitamin K antagonists: real-world evidence from Italian administrative databases. J Comp Eff Res. 2018;7(11):1063–71.
88. Kohsaka S, Murata T, Izumi N, Katada J, Wang F, Terayama Y. Bleeding risk of apixaban, dabigatran, and low-dose rivaroxaban compared with warfarin in Japanese patients with non-valvular atrial fibrillation: a propensity matched analysis of administrative claims data. Current medical research and opinion. 2017;33(11):1955–63.
89. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian Patients With Atrial Fibrillation: Effectiveness and Safety. J Am Coll Cardiol. 2018;72(8):838–53.
90. Yap LB, Eng DT, Sivalingam L, Rusani BI, Umadevan D, Muhammad Z et al. A Comparison of Dabigatran With Warfarin for Stroke Prevention in Atrial Fibrillation in an Asian Population. Clin Appl Thromb Hemost. 2016;22(8):792–7.
91. Halvorsen S, Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O et al. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. Eur Heart J Cardiovasc Pharmacother. 2017;3(1):28–36.
92. Chan YH, Yen KC, See LC, Chang SH, Wu LS, Lee HF et al. Cardiovascular, Bleeding, and Mortality Risks of Dabigatran in Asians With Nonvalvular Atrial Fibrillation. Stroke. 2016;47(2):441–9.
93. Jun M, Lix LM, Durand M, Dahl M, Paterson JM, Dormuth CR et al. Comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism: multicentre, population based, observational study. BMJ. 2017;359:j4323.
94. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost. 2016;116(5):975–86.
95. Larsen TB, Skjoth F, Kjaeldgaard JN, Lip GYH, Nielsen PB, Sogaard M. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. Lancet Haematol. 2017;4(5):e237–e44.
96. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431–41.
97. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015;373(25):2413–24.
98. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131–41.
99. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr. et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):2071–104.
100. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2016;32(10):1170–85.
101. Atrial fibrillation: management. Clinical guidline [CG180]. London: National Institute for Health and Care Excellence; 2014. Available from https://www.nice.org.uk/guidance/cg180, accessed 30 October 2019.
102. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ. 2018;27(10):1209–66.
103. Liberato NL, Marchetti M. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a systematic and qualitative review. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):221–35.
104. Limone BL, Baker WL, Kluger J, Coleman CI. Novel anticoagulants for stroke prevention in atrial fibrillation: a systematic review of cost-effectiveness models. PloS one. 2013;8(4):e62183.
105. Pinyol C, Cepeda JM, Roldan I, Roldan V, Jimenez S, Gonzalez P et al. A Systematic Literature Review on the Cost-Effectiveness of Apixaban for Stroke Prevention in Non-valvular Atrial Fibrillation. Cardiol Ther. 2016;5(2):171–86.
106. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Real-World Medical Cost Avoidance When New Oral Anticoagulants are Used Versus Warfarin for Venous Thromboembolism in the United States. Clin Appl Thromb Hemost. 2016;22(1):5–11.
107. Amin A, Jing Y, Trocio J, Lin J, Lingohr-Smith M, Graham J. Evaluation of medical costs associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients. J Med Econ. 2014;17(11):763–70.
108. Margolis JM, Deitelzweig S, Kline J, Tran O, Smith DM, Crivera C, et al. Pulmonary Embolism Inpatients Treated With Rivaroxaban Had Shorter Hospital Stays and Lower Costs Compared With Warfarin. Clin Ther. 2016;38(11):2496–503.
109. Weeda ER, Kohn CG, Peacock WF, Fermann GJ, Crivera C, Schein JR et al. Rivaroxaban versus Heparin Bridging to Warfarin Therapy: Impact on Hospital Length of Stay and Treatment Costs for Low-Risk Patients with Pulmonary Embolism. Pharmacotherapy. 2016;36(10):1109–15.
110. Courtney W, Groarke E, Conway J, Conway E, Bourke D, Saunders J et al. A Direct Oral Anticoagulant as a Cost Effective Altern

ative to Warfarin for Treatment of Provoked Venous Thrombosis. Ir Med J. 2016;109(9):466.
111. Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R. Cost-effectiveness analysis of treatment of venous thromboemb olism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. Thromb J. 2015;13:20.
112. Jimenez D, Jimenez S, Martinez-Lopez I, Monreal M, Vicente V, Perez-Alcantara F et al. Cost-effectiveness of rivaroxaban in the treatment of venous thromboembolism in Spain. Pharmacoeconomics. 2015;12(4):147–56.
113. Jugrin AV, Ustyugova A, Urbich M, Lamotte M, Sunderland T. The cost-utility of dabigatran etexilate compared with warfarin in treatment and extended anticoagulation of acute VTE in the UK. Thromb Haemost. 2015;114(4):778–92.
114. Lanitis T, Leipold R, Hamilton M, Rublee D, Quon P, Browne C et al. Cost-effectiveness of Apixaban Versus Other Oral Anticoag ulants for the Initial Treatment of Venous Thromboembolism and Prevention of Recurrence. Clin Ther. 2016;38(3):478-93.e1–16.
115. Law S, Ghag D, Grafstein E, Stenstrom R, Harris D. A pharmacoeconomic study of traditional anticoagulation versus direct oral a nticoagulation for the treatment of venous thromboembolism in the emergency department. CJEM. 2016;18(5):340–8.
116. Lefebvre P, Coleman C, Bookhart B, Wang S, Mody S, Tran K et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. J Med Econ. 2014; 17(1):52–64.
117. Maervoet J, Verhamme P, Hainaut P, McLeod E, Bamber L, Raf P et al. Cost effectiveness of Rivaroxaban versus low molecular weight heparin and vitamin K antagonists for the treatment of deep-vein thrombosis in the Belgian healthcare setting. Eur J Cardiov asc Med. 2015;3(1):452–61.
118. Preblick R, Kwong WJ, White RH, Goldhaber SZ. Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study. Hosp Pract (1995). 2015;43(5):249–57.
119. Quon P, Le HH, Raymond V, Mtibaa M, Moshyk A. Clinical and economic benefits of extended treatment with apixaban for the tr eatment and prevention of recurrent venous thromboembolism in Canada. J Med Econ. 2016;19(6):557–67.
120. Rudakova AV. Cost-effectiveness of new oral anticoagulants in the treatment and secondary prevention of venous thromboemb olism. Rational Pharmacotherapy in Cardiology. 2015;11(5):496–503.
121. Santos IF, Pereira S, McLeod E, Guillermin AL, Chatzitheofilou I. Economic analysis of rivaroxaban for the treatment and long-te rm prevention of venous thromboembolism in Portugal. Acta Med Port. 2014;27(5):615–24.
122. Seaman CD, Smith KJ, Ragni MV. Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurr ent venous thromboembolism: a U.S. perspective. Thromb Res. 2013;132(6):647–51.
123. Stevanovic J, De Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the treatment and secondary pre vention of venous thromboembolism; a cost-effectiveness analysis for the Netherlands. PLoS One. 2016;11 (10) (no pagination)(e01 63550).