Dabigatran

Essential medicine status ✓

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

ATC codes: B01AE07

Indication	Other specified atrial fibrillation ICD11 code: BC81.3Y
INN	Dabigatran
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 110 mg ; 150 mg
EML status history	Application rejected in 2015 (TRS 994) Added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	apixaban (ATC codes: B01AF02) edoxaban (ATC codes: B01AF03) rivaroxaban (ATC codes: B01AF01)
Patent information	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 Read more about patents.
Wikipedia	Dabigatran
DrugBank	Dabigatran (Dabigatran etexilate)

Expert Committee recommendation

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.

Background

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).

Public health relevance

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.

Benefits

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).

Harms

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).

Cost / cost effectiveness

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.

WHO guidelines

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.

Availability

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.

Other considerations

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.

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