ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 December 26; 13(12): 650-757

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 13 Number 12 December 26, 2021

EDITORIAL

650 Improving the heart team: An interdisciplinary team and integrated practice unit

Veronese ET, Pomerantzeff PMA, Jatene FB

REVIEW

654 Chagas heart disease: An overview of diagnosis, manifestations, treatment, and care

Saraiva RM, Mediano MFF, Mendes FS, Sperandio da Silva GM, Veloso HH, Sangenis LHC, Silva PSD, Mazzoli-Rocha F, Sousa AS, Holanda MT, Hasslocher-Moreno AM

676 Cardiovascular benefits from SGLT2 inhibition in type 2 diabetes mellitus patients is not impaired with phosphate flux related to pharmacotherapy

Nashawi M, Ahmed MS, Amin T, Abualfoul M, Chilton R

695 Current role and future perspectives of cardiac rehabilitation in coronary heart disease

Vilela EM, Ladeiras-Lopes R, Joao A, Braga J, Torres S, Viamonte S, Ribeiro J, Teixeira M, Nunes JP, Fontes-Carvalho R

MINIREVIEWS

710 Dabigatran in cardiovascular disease management: A comprehensive review

Javed A, Ajmal M, Wolfson A

720 Pulmonary artery catheterization in acute myocardial infarction complicated by cardiogenic shock: A review of contemporary literature

Ponamgi SP, Maqsood MH, Sundaragiri PR, DelCore MG, Kanmanthareddy A, Jaber WA, Nicholson WJ, Vallabhajosyula S

ORIGINAL ARTICLE

Retrospective Study

733 Prognostic value of left atrial size in hypertensive African Americans undergoing stress echocardiography

Khemka A, Sutter DA, Habhab MN, Thomaides A, Hornsby K, Feigenbaum H, Sawada SG

Observational Study

745 Highly sensitive troponin I assay in the diagnosis of coronary artery disease in patients with suspected stable angina

Ramasamy I

World Journal of Cardiology

Monthly Volume 13 Number 12 December 26, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Cardiology*, Rami N Khouzam, FACC, FACP, MD, Academic Research, Associate Professor, Attending Doctor, Chief Doctor, Lecturer, Research Scientist, Department of Medicine, The University of Tennessee Health Science Center, Memphis, TN 38104, United States. khouzamrami@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJC* as 0.36. The *WJC*'s CiteScore for 2020 is 0.3, and Scopus CiteScore rank 2020: Cardiology and Cardiovascular Medicine is 289/317.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
December 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 December 26; 13(12): 710-719

DOI: 10.4330/wjc.v13.i12.710

ISSN 1949-8462 (online)

MINIREVIEWS

Dabigatran in cardiovascular disease management: A comprehensive review

Ayesha Javed, Muhammad Ajmal, Aaron Wolfson

ORCID number: Ayesha Javed 0000-0003-3726-2584; Muhammad Ajmal 0000-0002-2463-3035; Aaron Wolfson 0000-0002-9695-185X.

Author contributions: Ajmal M came up with the idea; Javed A and Ajmal M drafted the manuscript; Wolfson A reviewed and finalized it; Javed A, Ajmal M and Wolfson A revised the manuscript.

Conflict-of-interest statement: All authors have no any conflicts of interest.

Country/Territory of origin: United States

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Ayesha Javed, Department of Internal Medicine, University of Arizona, Tucson, AZ 85719, United States

Muhammad Ajmal, Department of Cardiology, University of Arizona, Tucson, AZ 85719, United States

Aaron Wolfson, Department of Cardiology, University of Southern California, Los Angeles, CA 90007, United States

Corresponding author: Muhammad Ajmal, MD, Academic Fellow, Department of Cardiology, University of Arizona, 1625 N Campbell Ave, Tucson, AZ 85704, United States.
drajmal207@gmail.com

Abstract

Dabigatran, a direct thrombin inhibitor, has robust data for the treatment of deep venous thrombosis and pulmonary embolism, stroke prevention in non-valvular atrial fibrillation, and the prophylaxis of venous thromboembolism (VTE) after knee and hip replacement. Recent studies have evaluated dabigatran to determine its safety and efficacy in such conditions as VTE in malignancy, coronary artery disease, mechanical and bioprosthetic valves, and antiphospholipid syndrome. This article provides a comprehensive review on the role of dabigatran in various cardiovascular diseases.

Key Words: Dabigatran; Anticoagulation; Thrombus; Bleeding; Atrial fibrillation; Deep venous thrombosis; Stroke

Core Tip: Direct oral anticoagulants (DOACs) have plethora of data for the use in medical field and particularly in cardiovascular medicine. This review is focused on the dabigatran which is one of the DOAC and it is prudent for all the physicians to be familiar with this drug.

Citation: Javed A, Ajmal M, Wolfson A. Dabigatran in cardiovascular disease management: A comprehensive review. *World J Cardiol* 2021; 13(12): 710-719

Received: April 6, 2021
Peer-review started: April 6, 2021
First decision: September 2, 2021
Revised: September 27, 2021
Accepted: November 25, 2021
Article in press: November 25, 2021
Published online: December 26, 2021

P-Reviewer: Emran TB
S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

URL: https://www.wjgnet.com/1949-8462/full/v13/i12/710.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i12.710

INTRODUCTION

Warfarin, a vitamin K antagonist (VKA) and systemic anticoagulant, has been used for decades in clinical practice for a variety of clinical indications including nonvalvular atrial fibrillation, deep venous thrombosis (DVT) and pulmonary embolism (PE). Given warfarin's indirect mechanism of action, maintaining a goal international normalized ratio (INR) is a constant challenge. Patients often experience periods of over- and under-treatment and may therefore be exposed to increased risk for adverse outcomes. The two classes of direct-acting oral anticoagulants (DOACs) include direct thrombin inhibitors (DTI) and factor Xa inhibitors and both have emerged as attractive alternatives to warfarin[1,2]. Dabigitran, a DTI, and three factor Xa inhibitors including apixaban, edoxaban, and rivaroxaban are currently approved by the Food and Drug Administration (FDA) for ischemic stroke prevention in non-valvular atrial fibrillation (AF), treatment of venous thromboembolism (VTE) and the prevention of VTE after hip and knee arthroplasty[3]. Dabigatran etexilate is a small molecule prodrug that is rapidly converted by serum esterase to dabigatran, a competitive and reversible direct inhibitor of thrombin. Dabigatran is predominantly (80%) excreted through the kidneys and does not require INR[4]. The purpose of this review is to provide a comprehensive review of the current and potential indications for dabigatran use.

ANTICOAGULATION IN NONVALVULAR ATRIAL FIBRILLATION

Atrial fibrillation is a prothrombotic condition that may lead to thrombus formation in the left atrial appendage and with subsequent systemic embolization causing a cerebrovascular accident (CVA) or stroke[2,5]. The efficacy of dabigatran in non-valvular atrial fibrillation was studied in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) multicenter randomized controlled trial. In this study, patients were randomized to dabigatran 110 or 150 mg twice daily (BID) *vs* dose-adjusted warfarin. Compared to warfarin, dabigatran dosed at 150 mg twice daily was found to reduce the risk of systemic embolism and similar rates of major hemorrhage. Dabigatran was the first DOAC that received FDA approval in 2010 and by the European Medicines Agency (EMA) in 2011 for treatment of non-valvular atrial fibrillation. The recommended doses are 150 mg BID for patient with eGFR > 30 mL/min and 75 mg BID (not tested in the Re-LY trial) for patients with an eGFR of 15-29 mL/min[6]. In a meta-analysis, dabigatran was found to be associated with a lower risk of ischemic stroke, major bleeding, mortality, a similar risk of myocardial infarction, and a greater risk of gastrointestinal bleeding when compared to warfarin [7].

According to the 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Focused Update of the 2014 guidelines for the management of atrial fibrillation, dabigatran has a class 1 recommendation (level of evidence A) for the treatment of non-valvular atrial fibrillation and, similar to other DOACs, is recommended over warfarin. Dabigatran is associated with a lower risk of serious bleeding and has been proven to be either non-inferior or superior to warfarin in preventing stroke and systemic embolism[8].

TREATMENT OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Venous thromboembolism (VTE) includes the clinical entities of deep venous thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of morbidity and mortality. The role of dabigatran in the treatment of acute VTE was evaluated in the randomized, double-blind Phase III clinical trials of RE-COVER and RE-COVER II. These trials included patients with DVT and PE who were initially treated with a parenteral anticoagulant therapy for 5-10 d. Dabigatran at a dose of 150 mg twice daily was compared to dose-adjusted warfarin with an INR target of 2-3 for a 6-mo period. In both trials, dabigatran was found to be non-inferior to warfarin in reducing

recurrent VTE. In both trials, dabigatran and warfarin had similar bleeding rates and other adverse effects, while patients on dabigatran were more likely to have dyspepsia as compared to warfarin in the RE-COVER trial, presumably due to the tartaric acid component.

The extended treatment of VTE was studied in the RE-MEDY and RE-SONATE trials. The RE-SONATE trial included patients that had been previously treated for an acute DVT or PE with anticoagulant therapy for 6-18 mo. This trial found that dabigatran use had a significant reduction in symptomatic VTE and related deaths. While the RE-MEDY trial included patients, who had been previously treated for an acute DVT and PE with anticoagulant therapy for 3 to 12-mo, dabigatran 150 mg twice daily demonstrated noninferiority to dose-adjusted warfarin. An increased risk of acute coronary syndrome was observed in the RE-MEDY trial although there was no difference observed in the RE-SONATE trial[9]. In 2014, the FDA approved dabigatran 150 mg twice daily for the treatment of DVT and PE in patients with an eGFR > 30 mL/min while its use is not recommended for patients with a GFR < 30 mL/min.

The American College of Chest Physicians 2016 guidelines recommend dabigatran, along with other DOACs, over warfarin for the treatment of acute VTE in patients without cancer (Grade 2B) and recommend 3 mo of treatment for the management of DVT and PE (Grade 1B)[10]. The American Society of Hematology 2020 guidelines for VTE recommend DOACs over VKAs (conditional recommendation based on a moderate certainty in evidence) and this recommendation does not apply to a patient with low creatinine clearance, moderate to severe liver disease, or antiphospholipid syndrome. This panel does not suggest one DOAC over another (conditional recommendation based on low certainty in evidence)[11].

POSTOPERATIVE VTE PROPHYLAXIS AFTER HIP AND KNEE SURGERY

VTE is the third most common cause of cardiovascular death after myocardial infarction and stroke and has high morbidity and mortality. Major orthopedic surgeries such as total hip and knee arthroplasty are responsible for 50% of thromboembolic events in the absence of VTE prophylaxis[12]. Oral dabigatran (220 mg or 150 mg once daily) was compared to subcutaneous enoxaparin for the primary prevention of VTE in patients undergoing elective total hip or knee arthroplasty in four randomized, double-blind, non-inferiority trials[13].

Prevention of postoperative thromboembolism after knee replacement

RE-MODEL was a randomized, double-blinded trial conducted in Europe and included patients undergoing total knee replacement. In this trial, the patients were assigned to oral dabigatran 150 mg or 220 mg once daily and were compared to enoxaparin 40 mg subcutaneously once daily. Enoxaparin was given the evening before surgery while dabigatran was administered 1–4 h after completion of surgery. Treatment was continued for a total of 6–10 d and patients were assessed for 3 mo after surgery. The primary outcome (total VTE and mortality during treatment) and safety outcome (bleeding events) showed no difference between the two therapies. Dabigatran (150 mg or 220 mg) was as effective as enoxaparin and had a similar safety profile for the prevention of VTE after total knee replacement surgery[14].

RE-MOBLIZE was a double-blind, randomized trial conducted in the United States and Canada and used enoxaparin 30 mg twice daily as compared to the 40 mg daily dose used in the RE-MODEL trial. Patients with unilateral total knee arthroplasty were randomized to receive dabigatran 220 or 150 mg once daily starting 6 to 12 h after the surgery, or enoxaparin 30 mg subcutaneously twice daily starting the morning after surgery. The treatment was continued for 12-15 d. Dabigatran showed inferior efficacy to enoxaparin 30 mg twice daily while major bleeding rates were found to be similar [15].

Prevention of postoperative thromboembolism after hip surgery

The RE-NOVATE randomized phase III, double-blinded trial was conducted in Europe. This trial compared dabigatran 150 mg and 220 mg once daily to enoxaparin 40 mg subcutaneously once daily for the prevention of VTE in patients undergoing total hip replacement. The treatment duration was 28-35 d. Both dabigatran doses were found to be non-inferior to enoxaparin and the incidence of major bleeding was not significantly different[16]. The RE-NOVATE II randomized phase III, double-blinded trial was the follow-up study to further evaluate the efficacy and safety of the dabigatran 220 mg dose in a more diverse population. This trial compared dabigatran

220 mg to enoxaparin 40 mg once daily in patients undergoing total hip arthroplasty. Patients were randomized to 28–35 d of treatment of dabigatran 220 once daily or enoxaparin 40 mg subcutaneously. Subcutaneous enoxaparin was given the evening before surgery while dabigatran 110 mg was given 1–4 h after completion of surgery followed by a full dose of dabigatran 220 mg the morning after surgery. Dabigatran was as effective as enoxaparin for preventing VTE and superior to enoxaparin for reducing the risk of major VTE and major bleeding risk while adverse effects were the same for both groups[17].

In 2015, the FDA approved dabigatran 110 mg on the day of surgery followed by 220 mg the next day for prophylaxis of DVT and PE in patients undergoing hip replacement surgery. The recommended duration of prophylaxis is a minimum of 10-14 d and can be extended up to 35 d. The same dose is being used off-label for the prophylaxis of VTE after knee replacement[18]. The American College of Chest Physicians' guidelines recommend using antithrombotic prophylaxis over no prophylaxis in patients undergoing total hip and knee arthroplasty and suggest extending thromboprophylaxis for up to 35 d (Grade 1B recommendation)[19]. The American Society of Hematology 2019 guidelines also recommends using pharmacological prophylaxis for patients undergoing hip fracture repair (conditional recommendation based on very low certainty in evidence) and recommend using aspirin or a systemic anticoagulant, preferably DOACs, for prophylaxis in patients undergoing total hip or knee arthroplasty (conditional recommendation based on low certainty in evidence)[20].

ROLE IN CORONARY ARTERY DISEASE

The randomized controlled RE-DUAL and RE-DEEM trials assessed the efficacy and safety of DOACs in patients with coronary artery disease (CAD) including acute coronary syndrome (ACS) and stable CAD in patients with atrial fibrillation. RE-DUAL was a noninferiority trial that showed dual-pathway therapy with dabigatran 150 mg or 110 mg twice daily plus clopidogrel or ticagrelor reduced the risk of the primary bleeding outcome compared to triple therapy in patients with atrial fibrillation undergoing PCI. This dual-pathway regimen also demonstrated noninferiority for the secondary efficacy outcome (thromboembolic events, death), although there was an increase in MI and stent thrombosis in dual pathway therapy when compared to triple therapy[21]. The RE-DEEM phase II trial investigated the safety and efficacy of dabigatran in ACS. Patients with STEMI and NSTEMI were randomly assigned to dabigatran 50 mg twice daily, 75 mg twice daily, 110 mg twice daily, 150 mg twice daily or placebo. Patients already on DAPT were continued on this regimen until the end of the study. Dabigatran was found to have no association with ischemic benefit and showed a dose-dependent increase in the rate of the primary safety outcome (bleeding rate) when compared to placebo. A Phase III investigation was not conducted following the RE-DEEM trial[22].

ROLE IN TREATMENT OF VTE WITH CANCER

Patients with cancer are at four-to-seven fold higher risk of developing VTE than those without cancer. Therefore, VTE is an important cause of morbidity and mortality in patients with cancer. The role of dabigatran in the treatment of acute VTE was evaluated in the RE-COVER and RE-COVER II trials as reported above. Data from these two randomized trials were pooled to determine the primary efficacy (recurrent VTE and related death) and safety (major and non-major bleeding) outcomes of dabigatran in active cancer patients who were diagnosed with cancer in the previous 5 years. No significant difference in efficacy between dabigatran and warfarin was found. Although major bleeding and non-major bleeding events were more frequent in patients with cancer than without cancer, there were no differences in the safety outcomes between dabigatran and warfarin[23].

DABIGATRAN USE IN MECHANICAL AND/OR BIOPROSTHETIC VALVE REPLACEMENT

In the Dabigatran phase III clinical trials for atrial fibrillation, patients with mechanical heart valves were excluded. The RE-ALIGN study randomized patients with recent mechanical aortic or mitral valve replacement in a 2:1 ratio to receive dabigatran or warfarin. The patients received dabigatran doses of 150 mg, 220 mg or 300 mg twice daily based on creatinine clearance. The study was discontinued early due to more bleeding and thromboembolic events in the dabigatran-treated group. The DAWA study was initiated to evaluate the efficacy and safety of dabigatran in patients with bioprosthetic mitral and/or aortic valve replacement but the study was terminated early due to limited enrollment[24,25].

ROLE IN TREATMENT OF LEFT VENTRICULAR THROMBUS

Although DOACs have been used off-label for the treatment of left ventricular thrombus, there are currently no randomized controlled trials evaluating the safety and efficacy for this indication. There is conflicting evidence based on various observational studies and a recent systematic review recommended against DOACs for the treatment of left ventricular thrombi[26].On the other hand, a single centered, retrospective, small observational study carried out at tertiary care center found that dabigatran use in patients with left ventricular thrombus is both safe and effective[27]. Additional studies are needed the clarify the role of dabigatran in the treatment of left ventricular thrombus.

USE AFTER LEFT ATRIAL APPENDAGE OCCLUSION

Left Atrial Appendage Occlusion (LAAO) is an established alternative to oral anticoagulation in patients with atrial fibrillation and a contraindication to oral anticoagulation to prevent the risk of stroke. LAAO device placement is associated with increased postoperative stroke risk and requires anticoagulation after device implantation[28]. There is no randomized clinical trial to compare the safety and efficacy of anticoagulants after LAA occlusion. Although warfarin was used after LAAO in landmark trials DOACs have been used in the real-world setting[29].

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia leading to arterial, venous, and microvascular thrombosis. Post hoc analyses compared dabigatran with warfarin in patients with APS for the treatment and prevention of VTE and found no significant difference in symptomatic VTE or VTE-related deaths between groups. The dabigatran group showed fewer bleeding events, but differences did not reach statistical significance. The EMA recommends against the use of DOACs in patients with APS, especially those with triple positive (lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein antibodies) disease[30].

CONSIDERATION IN KIDNEY DISEASE

A meta-analysis published by some researchers evaluated the safety and efficacy of dabigatran, apixaban and rivaroxaban in patients with renal insufficiency. DOAC use was compared to warfarin in patients with mild (defined as eGFR 50–79 mL/min) and moderate (defined as eGFR of 30–49 mL/min) renal impairment and found that DOAC use reduced the risk of stroke, systemic embolism and major and non-major bleeding[31]. Dabigatran 150 mg twice daily was approved by the FDA for atrial fibrillation for patients with eGFR > 30 mL/min and 75 mg twice daily for patients with eGFR 15-29 mL/min[6]. Based on real-world data, the use of DOACs is strongly discouraged in patients with end-stage renal disease (ESRD)[31]. After RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, the FDA approved dabigatran 150 mg BID (after 5-10 d of parenteral anticoagulation) for the treatment of DVT and PE in

patients with eGFR > 30 mL/min and recommends against the use in patients with eGFR < 30 mL/min[9]. In 2015, based on the RE-SONATE and RESONATE II trials, the FDA approved dabigatran 220 mg once daily for VTE prophylaxis in patients undergoing hip arthroplasty. This dose is used off-label in patients with knee arthroplasty; dabigatran is contraindicated for VTE prophylaxis in patients with eGFR < 30 mL/min[32]. The doses of dabigatran for various indications are shown in Table 1.

CONSIDERATION IN LIVER DISEASE

As all approved DOACs undergo some degree of hepatic metabolism, liver dysfunction may increase the risk of bleeding. Patients with liver disease have been excluded from the trials of DOACs, therefore, unlike guidelines for DOAC use in renal disease, no guidelines are available for patients with liver impairment. Dabigatran has 3%-7% bioavailability and a small fraction is metabolized in the liver while 80% is excreted through the kidney. Based on pharmacokinetic and pharmacodynamics studies, the FDA does not recommend dose adjustments for patients with mild or moderate hepatic impairment. The EMA recommends against dabigatran use in patients with elevated liver function tests (twice the upper limit of normal)[33].

CONSIDERATION IN OBESITY

The efficacy and safety of DOACs in the obese population have not been investigated in any large randomized controlled trial. DOACs are as effective as warfarin in phase III randomized trials of atrial fibrillation and VTE, however, patients weighing ≥ 100 kg were underrepresented and accounted for 20% of enrolled patients. The Scientific and Standardization Subcommittee of the International Society on Thrombosis and Hemostasis recommends against the use of DOACs in patients with a BMI > 40 kg/m^2 or a weight >120 kg[3,34].

COST-EFFECTIVENESS ANALYSIS

There is no consensus on the most cost-effective DOAC agent and future head-to-head clinical studies among DOACs are needed. One Canadian study demonstrated dabigatran to be highly cost-effective among patients with atrial fibrillation for the prevention of stroke and systemic embolism as compared to other alternatives[35]. Similarly, in the United Kingdom, Belgium, Denmark, and Taiwan studies have demonstrated dabigatran to be cost-effective in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism[35-39]. Dabigatran was found to be a cost-effective alternative compared to both warfarin and rivaroxaban for the treatment of acute VTE in the United Kingdom[40]. In one study comparing rivaroxaban and dabigatran with enoxaparin, dabigatran was found to be more cost-effective than enoxaparin and less cost-effective than rivaroxaban for thromboprophylaxis in patients undergoing total hip and knee replacements[41].

SAFETY

Dabigatran is associated with a high risk of gastrointestinal bleeding when used at higher doses. Similarly, bleeding risk increases with in treatment with concomitant aspirin use or in those with a history of bleeding[42]. According to the Beers criteria, Dabigatran should be used with caution in patients age 75 and above given an increased risk of gastrointestinal bleeding[43]. Due to the mechanism of absorption, dabigatran use is not recommended in patients with a history of gastrointestinal or bariatric surgery[44,45].

REVERSAL AGENT

Idarucizumab is a humanized monoclonal antibody fragment approved by the FDA and EMA to reverse the anticoagulant effects of dabigatran. The recommended dose of

Table 1 Indications and dosage of dabigatran

Indication	Renal function	Doses
Non-valvular atrial fibrillation	CrCl > 30 mL/min	150 mg BID
	CrCl 15-30 mL/min	75 mg BID
	CrCl < 15 mL/min	Avoid use
Venous thromboembolism treatment	CrCl > 30 mL/min	150 mg BID
	CrCl < 30 mL/min	Avoid use
Venous thromboembolism prophylaxis following hip/knee replacement surgery	CrCl > 30mL/min	110 mg one dose followed by 220 mg daily
	CrCl < 30 mL/min	Avoid use

BID: Twice daily.

idarucizumab is 5 g administered as two separate 2.5 g doses intravenously for rapid reversal of uncontrolled bleeding in dabigatran-treated patients[46]. Glund *et al*[47] conducted a randomized, controlled, phase I study in which patients received idarucizumab 20 mg to 8 g as 1-hour intravenous infusion or 1, 2, or 4 g as 5 min infusion and was found to be safe and well-tolerated in all administrated doses. In the multicenter, prospective cohort study, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial, Idarucizumab was found to reverse the anticoagulant effect of dabigatran in 88% to 98% of the patients[48].

CONCLUSION

Dabigatran has strong data supported by randomized-controlled trials, observational studies, systemic reviews, and meta-analysis for its role in stroke prevention in non-valvular atrial fibrillation, treatment and prophylaxis of VTE, and treatment of VTE in cancer patients. It has also been used off-label for the treatment of left ventricular thrombus and post LAAO, but further randomized trials are needed to determine the safety and efficacy of dabigatran in these indications. Current data do not support the use of dabigatran in patients with mechanical or bioprosthetic valves and acute or chronic CAD.

REFERENCES

1 **Wigle P**, Hein B, Bernheisel CR. Anticoagulation: Updated Guidelines for Outpatient Management. *Am Fam Physician* 2019; **100**: 426-434 [PMID: 31573167 DOI: 10.1093/med/9780199558278.003.0014]

2 **Vimalesvaran K**, Dockrill SJ, Gorog DA. Role of rivaroxaban in the management of atrial fibrillation: insights from clinical practice. *Vasc Health Risk Manag* 2018; **14**: 13-21 [PMID: 29391805 DOI: 10.2147/VHRM.S134394]

3 **Martin K**, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016; **14**: 1308-1313 [PMID: 27299806 DOI: 10.1111/jth.13323]

4 **Blair HA**, Keating GM. Dabigatran Etexilate: A Review in Nonvalvular Atrial Fibrillation. *Drugs* 2017; **77**: 331-344 [PMID: 28185082 DOI: 10.1007/s40265-017-0699-z]

5 **Davidson T**, Husberg M, Janzon M, Oldgren J, Levin LÅ. Cost-effectiveness of dabigatran compared with warfarin for patients with atrial fibrillation in Sweden. *Eur Heart J* 2013; **34**: 177-183 [PMID: 22733833 DOI: 10.1093/eurheartj/ehs157]

6 **Mumoli N**, Mastroiacovo D, Tamborini-Permunian E, Vitale J, Giorgi-Pierfranceschi M, Cei M, Dentali F. Dabigatran in nonvalvular atrial fibrillation: from clinical trials to real-life experience. *J Cardiovasc Med (Hagerstown)* 2017; **18**: 467-477 [PMID: 28509761 DOI: 10.2459/JCM.0000000000000524]

7 **Carmo J**, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost* 2016; **116**: 754-763 [PMID: 27465747 DOI: 10.1160/TH16-03-0203]

8 **January CT**, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 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**: e125-e151 [PMID: 30686041 DOI: 10.1161/CIR.0000000000000665]

9 **Ogbonna KC**, Dixon DL. Critical appraisal of dabigatran in the treatment of deep vein thrombosis and pulmonary embolism. *J Blood Med* 2015; **6**: 177-184 [PMID: 26185477 DOI: 10.2147/JBM.S54033]

10 . Correction to Grade in: Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; **150**: 988 [PMID: 27719823 DOI: 10.1016/j.chest.2016.08.1442]

11 **Ortel TL**, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C, Vedantham S, Verhamme P, Witt DM, D Florez I, Izcovich A, Nieuwlaat R, Ross S, J Schünemann H, Wiercioch W, Zhang Y. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020; **4**: 4693-4738 [PMID: 33007077 DOI: 10.1182/bloodadvances.2020001830]

12 **Gómez-Outes A**, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban *vs* enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012; **344**: e3675 [PMID: 22700784 DOI: 10.1136/bmj.e3675]

13 **Huo MH**, A Kurth AA, Dahl OE, Clemens A, Hantel S, Feuring M, Friedman RJ, Eriksson BI. Oral Dabigatran Etexilate Versus Enoxaparin for Prevention of Venous Thromboembolism After Total Hip or Knee Arthroplasty: A Pooled Analysis of Four Randomized Trials. *Blood* 2011; **118**: 2312-2312 [DOI: 10.1182/blood.v118.21.2312.2312]

14 **Eriksson BI**, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Kälebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Büller HR; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5**: 2178-2185 [PMID: 17764540 DOI: 10.3410/f.1098385.554441]

15 **RE-MOBILIZE Writing Committee**, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA. Oral thrombin inhibitor dabigatran etexilate *vs* North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009; **24**: 1-9 [PMID: 18534438 DOI: 10.1016/j.arth.2008.01.132]

16 **Montoya RC**, Gajra A. Current status of new anticoagulants in the management of venous thromboembolism. *Adv Hematol* 2012; **2012**: 856341 [PMID: 22496694 DOI: 10.1155/2012/856341]

17 **Eriksson BI**, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, Schnee JM, Friedman RJ; RE-NOVATE II Study Group. Oral dabigatran *vs* enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011; **105**: 721-729 [PMID: 21225098 DOI: 10.1160/TH10-10-0679]

18 **Eikelboom JW**, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; **358**: 9-15 [PMID: 11454370 DOI: 10.1016/S0140-6736(00)05249-1]

19 **Falck-Ytter Y**, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e278S-e325S [PMID: 22315265 DOI: 10.1378/chest.11-2404]

20 **Anderson DR**, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv* 2019; **3**: 3898-3944 [PMID: 31794602 DOI: 10.1182/bloodadvances.2019000975]

21 **Turgeon RD**, Ackman ML, Babadagli HE, Basaraba JE, Chen JW, Omar M, Zhou JS. The Role of Direct Oral Anticoagulants in Patients With Coronary Artery Disease. *J Cardiovasc Pharmacol Ther* 2019; **24**: 103-112 [PMID: 30122072 DOI: 10.1177/1074248418795889]

22 **Moon JY**, Nagaraju D, Franchi F, Rollini F, Angiolillo DJ. The role of oral anticoagulant therapy in patients with acute coronary syndrome. *Ther Adv Hematol* 2017; **8**: 353-366 [PMID: 29204262 DOI: 10.1177/2040620717733691]

23 **Schulman S**, Goldhaber SZ, Kearon C, Kakkar AK, Schellong S, Eriksson H, Hantel S, Feuring M, Kreuzer J. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015; **114**: 150-157 [PMID: 25739680 DOI: 10.1160/TH14-11-0977]

24 **Eikelboom JW**, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F; RE-ALIGN Investigators. Dabigatran *vs* warfarin in patients with mechanical heart valves. *N Engl J Med* 2013; **369**: 1206-1214 [PMID: 23991661 DOI: 10.1056/NEJMoa1300615]

25 **Anderson SL**, Marrs JC. Direct Oral Anticoagulant Use in Valvular Heart Disease. *Clin Med Insights Ther* 2018; **10**: 1179559X17751638 [DOI: 10.1177/1179559x17751638]

26 **Sedhom R**, Abdelmaseeh P, Megaly M, Asinger R. Use of Direct Oral Anticoagulants in the Treatment of Left Ventricular Thrombi: A Systematic Review. *Am J Med* 2020; **133**: 1266-1273.e6 [PMID: 32565258 DOI: 10.1016/j.amjmed.2020.05.012]

27 **Verma B**, Singh A. Clinical spectrum of renal disease in hospitalized HIV/AIDS patients: A teaching hospital experience. *J Family Med Prim Care* 2019; **8**: 886-891 [PMID: 31041219 DOI: 10.4103/jfmpc.jfmpc_98_19]

28 **Ahuja T**, Murphy S, Sartori DJ. Antithrombotic Dilemmas after Left Atrial Appendage Occlusion Watchman Device Placement. *Case Rep Cardiol* 2019; **2019**: 5247105 [PMID: 31183220 DOI: 10.1155/2019/5247105]

29 **Ajmal M**, Hutchinson MD, Lee K, Indik JH. Outcomes in patients implanted with a Watchman device in relation to choice of anticoagulation and indication for implant. *J Interv Card Electrophysiol* 2021 [PMID: 33576934 DOI: 10.1007/s10840-021-00958-4]

30 **Goldhaber SZ**, Eriksson H, Kakkar A, Schellong S, Feuring M, Fraessdorf M, Kreuzer J, Schueler E, Schulman S. Efficacy of dabigatran *vs* warfarin in patients with acute venous thromboembolism in the presence of thrombophilia: Findings from RE-COVER®, RE-COVER™ II, and RE-MEDY™. *Vasc Med* 2016; **21**: 506-514 [PMID: 27807306 DOI: 10.1177/1358863x16668588]

31 **Molteni M**, Bo M, Di Minno G, Di Pasquale G, Genovesi S, Toni D, Verdecchia P. Dabigatran etexilate: appropriate use in patients with chronic kidney disease and in the elderly patients. *Intern Emerg Med* 2017; **12**: 425-435 [PMID: 28439778 DOI: 10.1007/s11739-017-1660-6]

32 **Tun NM**, Oo TH. Prevention and treatment of venous thromboembolism with new oral anticoagulants: a practical update for clinicians. *Thrombosis* 2013; **2013**: 183616 [PMID: 23533745 DOI: 10.1155/2013/183616]

33 **Qamar A**, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral Anticoagulation in Patients With Liver Disease. *J Am Coll Cardiol* 2018; **71**: 2162-2175 [PMID: 29747837 DOI: 10.1016/j.jacc.2018.03.023]

34 **Piran S**, Traquair H, Chan N, Bhagirath V, Schulman S. Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kg: A retrospective study. *Res Pract Thromb Haemost* 2018; **2**: 684-688 [PMID: 30349887 DOI: 10.1002/rth2.12146]

35 **Sorensen SV**, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost* 2011; **105**: 908-919 [PMID: 21431243 DOI: 10.1160/TH11-02-0089]

36 **Wouters H**, Thijs V, Annemans L. Cost-effectiveness of dabigatran etexilate in the prevention of stroke and systemic embolism in patients with atrial fibrillation in Belgium. *J Med Econ* 2013; **16**: 407-414 [PMID: 23320796 DOI: 10.3111/13696998.2013.766200]

37 **Langkilde LK**, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. *J Med Econ* 2012; **15**: 695-703 [PMID: 22397590 DOI: 10.3111/13696998.2012.673525]

38 **Chang CH**, Yang YH, Chen JH, Lin LJ. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation in Taiwan. *Thromb Res* 2014; **133**: 782-789 [PMID: 24642004 DOI: 10.1016/j.thromres.2014.02.024]

39 **Kansal AR**, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, Cowie MR. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. *Heart* 2012; **98**: 573-578 [PMID: 22422743 DOI: 10.1136/heartjnl-2011-300646]

40 **Jugrin AV**, Hösel V, Ustyugova A, De Francesco M, Lamotte M, Sunderland T. Indirect comparison and cost-utility of dabigatran etexilate and rivaroxaban in the treatment and extended anticoagulation of venous thromboembolism in a UK setting. *J Med Econ* 2016; **19**: 1-10 [PMID: 26390231 DOI: 10.3111/13696998.2015.1078340]

41 **McCullagh L**, Tilson L, Walsh C, Barry M. A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the irish healthcare setting. *Pharmacoeconomics* 2009; **27**: 829-846 [PMID: 19803538 DOI: 10.2165/11313800-000000000-00000]

42 **Loffredo L**, Perri L, Violi F. Impact of new oral anticoagulants on gastrointestinal bleeding in atrial fibrillation: A meta-analysis of interventional trials. *Dig Liver Dis* 2015; **47**: 429-431 [PMID: 25732432 DOI: 10.1016/j.dld.2015.01.159]

43 **By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel**. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2019; **67**: 674-694 [PMID: 30693946 DOI: 10.1111/jgs.15767]

44 **Hakeam HA**, Al-Sanea N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). *J Thromb Thrombolysis* 2017; **43**: 343-351 [PMID: 28050755 DOI: 10.1007/s11239-016-1465-x]

45 Physical Therapy Graduate Schools Ranked Top ByU.S. News & World Report. *Rehabil Oncol* 19995; **13**: 20 [DOI: 10.1097/01893697-199513020-00011]

46 **Hutcherson TC**, Cieri-Hutcherson NE, Bhatt R. Evidence for Idarucizumab (Praxbind) in the Reversal Of the Direct Thrombin Inhibitor Dabigatran: Review Following the RE-VERSE AD Full Cohort Analysis. *P T* 2017; **42**: 692-698 [PMID: 29089725 DOI: 10.4274/tnd.37233]

47 **Glund S**, Moschetti V, Norris S, Stangier J, Schmohl M, van Ryn J, Lang B, Ramael S, Reilly P. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost* 2015; **113**: 943-951 [PMID:

25789661 DOI: 10.1160/TH14-12-1080]

48 **Pollack CV Jr**, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med* 2017; **377**: 431-441 [PMID: 28693366 DOI: 10.1056/NEJMoa1707278]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com