

## Original Research Article

# Expert opinion on the usage of novel oral anticoagulants in clinical conditions in Indian settings

### ABSTRACT

**Objective:** The current survey-based study aims to better understand expert opinion on the most commonly prescribed anticoagulants in clinical practice, with a special focus on the use of dabigatran in real-time clinical practice in an Indian setting.

**Methodology:** A cross-sectional study was conducted to examine the viewpoints of 183 experts from various regions in India regarding the use of dabigatran. The survey consisted of 16 questions to obtain expert responses regarding the usage of dabigatran in clinical practice. The data were analyzed using descriptive statistics.

**Results:** The study gathered responses from 183 clinicians. The majority of the clinicians (72%) recommended dabigatran as the most preferred anticoagulant. Approximately 76% of respondents recommended dabigatran for atrial fibrillation (AF). Dabigatran was identified as the most commonly recommended medication for both pulmonary embolism (PE) and deep vein thrombosis (DVT) by 69% of the respondents. The respondents also preferred the drug for managing other clinical conditions such as ischemic stroke and prophylaxis in hip replacement surgery. More than half (64%) of the respondents reported dabigatran to be more effective than rivaroxaban and apixaban.

**Conclusion:** Dabigatran emerged as the preferred anticoagulant in clinical practice. Dabigatran, among the anticoagulants, can be a top choice in AF, PE, DVT, ischemic stroke, and hip replacement surgery as therapy and prophylaxis.

*Keywords: Anticoagulants, Dabigatran, deep vein thrombosis, pulmonary embolism, Atrial Fibrillation, Stroke*

### 1. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, accounting for approximately 17.9 million deaths annually [1]. India has one of the world's highest burdens of CVDs and the contributing factors include changing lifestyle patterns, sedentary behaviors, unhealthy dietary habits, and increased prevalence of lifestyle diseases like hypertension, diabetes, and obesity [2]. Stroke is the second leading cause of mortality, accounting for 11.6% of all fatalities. It is the third major cause of death and disability, accounting for 5.7% of total disability-adjusted life years. The recovery process necessitates sophisticated and extensive medical procedures and rehabilitation, placing a heavy financial burden on individuals and healthcare systems [3].

Venous thromboembolism (VTE) affects approximately 1 in 1,000 individuals and causes 60,000-100,000 fatalities each year. It is the third leading cause of mortality in CVD following heart attacks and strokes [4-7]. Deep vein thrombosis (DVT) affects around 1.79 subjects per thousand in India. It is estimated that approximately 30% of individuals with symptomatic VTE develop pulmonary embolism (PE), while the remaining experience DVT [8]. Recent global epidemiological statistics have highlighted atrial fibrillation (AF) as a widespread epidemic with long-term morbidity and mortality consequences [9,10].

In patients with AF, anticoagulants remain the cornerstone of treatment for stroke and systemic embolism prevention [11]. Heparin is a parenteral anticoagulant that has been used to treat acute thrombotic events [12]. Until recently, vitamin K antagonists (VKA) like warfarin were the main oral anticoagulants available. However, the treatment approach has been shifted with the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban [13].

Dabigatran acts by specifically inhibiting the activity of activated factor II (or IIa or thrombin), while rivaroxaban, edoxaban, and apixaban act by blocking active factor X (or Xa) [14]. Dabigatran was originally licensed for the prevention of VTE following elective total knee or hip arthroplasty. However, further studies have shown that it is more effective than warfarin in preventing stroke in nonvalvular AF and non-inferior to warfarin in the treatment of VTE [15]. Unlike indirect anticoagulants like heparin, dabigatran acts directly on both free and clot-bound thrombin without the need for a cofactor. This direct inhibition of thrombin results in a dynamic and predictable response, eliminating the need for routine monitoring in individuals receiving dabigatran therapy [15,16].

The current survey-based study aims to gain further insights into the perceptions of clinicians regarding the commonly prescribed anticoagulants in clinical practice, with a specific focus on the use of dabigatran in real-time clinical practice in an Indian setting.

## **2. MATERIALS AND METHODS**

We carried out a cross sectional, multiple-response questionnaire-based study involved clinical professionals skilled in managing stroke patients in the major Indian cities from June 2022 to December 2022.

### **2.1 Questionnaire**

The questionnaire booklet titled DABITRAIN (Dabigatran Efficacy and Tolerability Profile) study was sent to the physicians who were interested to participate. The DABITRAIN study questionnaire consisted of 16 questions that focused on the recommended anticoagulation drugs and characteristics of dabigatran therapy in their clinical practice.

### **2.2 Participants**

An invitation was sent to leading clinicians in treating stroke in the month of March 2022 for participation in this Indian survey. About 183 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. They were instructed to answer the questionnaire on their own, without contacting any of their colleagues. Written informed consent was obtained from all the study participants prior to the initiation of the study.

### **2.3 Statistical Methods**

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

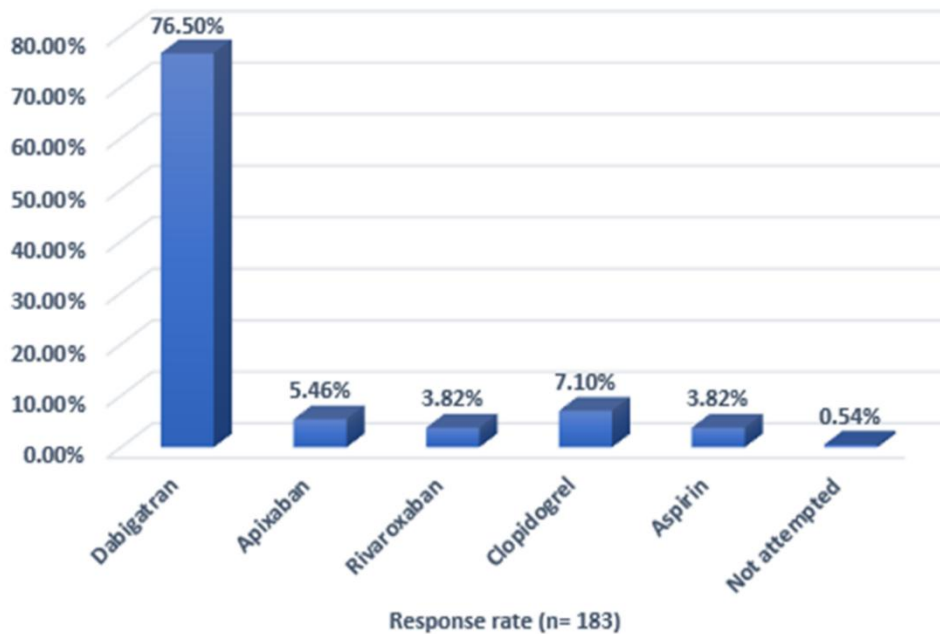
### 3. RESULTS

The present survey study included 183 clinicians. The majority of the participants (72%) recommended dabigatran as the most preferred anticoagulant in their clinical practice. Approximately 16% and 7% of respondents recommended rivaroxaban and apixaban, respectively (Table 1).

**Table 1: Distribution of response to the most recommended anticoagulant in their clinical practice**

Anticoagulant	Responses(n=183)
Dabigatran	131 (71.58%)
Rivaroxaban	29 (15.84%)
Apixaban	13 (7.10%)
Edoxaban	2 (1.09%)
Aspirin	2 (1.09%)
Not attempted	6 (3.27%)

The most recommended drug for AF was dabigatran, with 76% of respondents selecting it as their preferred choice. Apixaban was chosen by 5% of respondents as the most preferred drug, while only 4% of clinicians recommended rivaroxaban (Fig. 1).



**Fig. 1: Distribution of response to commonly prescribed drugs for atrial fibrillation**

Dabigatran was the most commonly prescribed medicine for PE and DVT, according to 69% and 69% of clinicians, respectively. Rivaroxaban, heparin, apixaban, and warfarin were rated as optimal medications PE treatment by 8%, 8%, 5%, and 5% of respondents. Rivaroxaban, heparin, apixaban, and warfarin were all advised by 6%, 6%, 6%, and 6% responders in the case of DVT (Table 2).

**Table 2: Distribution of response to recommended drug for venous thromboembolism (Pulmonary embolism and deep vein thrombosis)**

Recommended drug	Responses (n=183)	
	Pulmonary embolism	Deep vein thrombosis
Dabigatran	126 (68.85%)	127 (69.39%)
Apixaban	10 (5.46%)	11 (6.01%)
Rivaroxaban	15 (8.19%)	11 (6.01%)
Clopidogrel	3 (1.63%)	6 (3.27%)
Heparin	14 (7.65%)	11 (6.01%)
Warfarin	9 (4.91%)	11 (6.01%)
Not attempted	6 (3.27%)	6 (3.27%)

Forty-three percent of clinicians reported that <20% of patients in their clinical practice were on dabigatran treatment, followed by 20-40% (38%) and 40-60% (16%). The daily recommended dose of dabigatran was reported as 110 mg/day by 50% of clinicians, while the corresponding responses received for 220 mg/day, 150 mg/day, and 75 mg/day were 17%, 16%, and 10% respectively. The majority of respondents (38%) reported that 40-60% of patients showed improved outcomes following dabigatran therapy. Approximately 57% of clinicians reported that only <2% of the patients experienced gastrointestinal bleeding while on dabigatran, while 38% reported the incidence as <3-5%. Around 42% of the respondents reported nausea and vomiting as the most prevalent adverse events observed with dabigatran usage. Other common side effects reported were gastrointestinal hemorrhage (36%) and indigestion (10%).

Majority (58%) of the respondents observed the occurrence of gastrointestinal bleeding with dabigatran medication in patients over the age of 60, while 22% and 13% reported it in middle-aged patients (30-45 years) and all age groups, respectively. According to 40% of respondents, the commencement of gastrointestinal bleeding in stroke patients began between 2-4 weeks after starting dabigatran medication, whereas 33% and 23% reported it within 2 and >4 weeks, respectively. In stroke patients who do not respond to dabigatran medication, 50% of the clinicians responded that they would opt for a dosage increase, whereas 47% preferred switching to another anticoagulant. Monitoring of the international normalized ratio (INR) during dabigatran treatment was recommended by approximately 50% of the clinicians, while 48% disagreed with it. Most responders (41%) noted adverse effects as the most common cause for patients switching from dabigatran to alternative anticoagulants. Furthermore, 36% and 20% of the respondents cited dosage titration and effectiveness as reasons for switching.

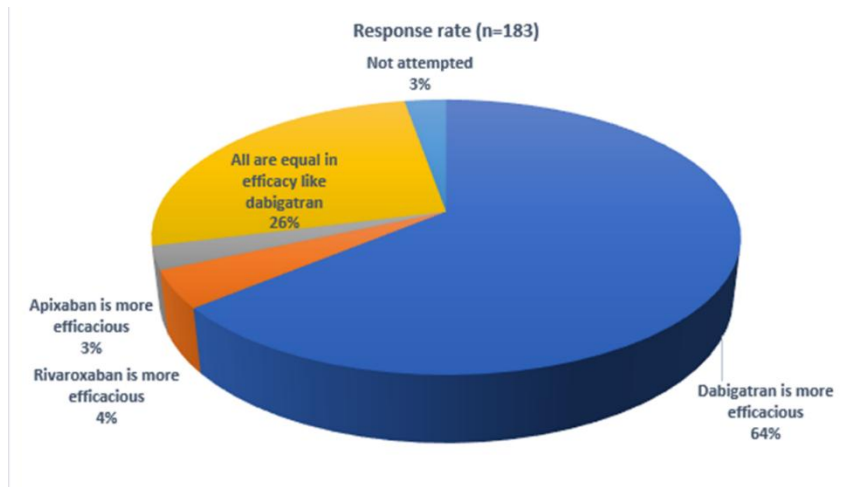
Apart from AF, PE, and DVT, the survey also assessed the usage of dabigatran therapy in other clinical conditions. The results indicated that the majority (48%) of the clinicians recommended dabigatran therapy for ischemic stroke, while 17% preferred it as prophylaxis in hip replacement surgery. Furthermore, 37% of the respondents advocated the use of dabigatran for both purposes (Table 3).

**Table 3: Response to dabigatran therapy recommendation for other clinical indications**

Indications	Responses(n=183)
As prophylaxis in hip replacement surgery	31 (16.93%)
Ischemic stroke	80 (43.71%)
Both	67 (36.61%)
Not attempted	5(2.73%)

The majority of the clinicians (64%) agreed that dabigatran is more effective than rivaroxaban and apixaban, whereas a minor percentage of 4% and 3% respondents

considered rivaroxaban and apixaban to be more effective. However, 26% of the respondents stated that all three medications were equally effective (Fig. 2).



**Fig. 2: Response to the comparison of efficacy of dabigatran to rivaroxaban and apixaban**

#### 4. DISCUSSION

In the current study, the majority of the respondents reported dabigatran as the ideal anticoagulant for preventing stroke and for preventing and treating VTE. Dabigatran exhibits a predictable pharmacokinetic and pharmacodynamic profile, with few drug-drug interactions and no drug-food interactions. Furthermore, it has a sustained anticoagulant effect and does not necessitate frequent anticoagulation monitoring [17].

Warfarin and acenocoumarol are the two most often used VKAs in India. In order to achieve successful anticoagulation with VKAs, it is important to maintain the prothrombin time (PT) /INR within the approved range, and monitor INR on a regular basis with dose adjustments. However, certain remote clinical settings in India lack laboratories that can perform standardized PT/INR assays, posing a challenge to the management of VKA therapy. Additionally, specific dietary practices in India, such as the consumption of green vegetables, cauliflower, cabbage, and other vitamin K-rich foods, can interfere with VKAs, leading to INR instability and making it increasingly difficult to maintain the PT/INR within the desired range. Furthermore, over-the-counter drugs have the potential to cause fluctuations in INR readings, resulting in either under- or over-anticoagulation. Consequently, these challenges emphasize the need for an alternative anticoagulant that can overcome these limitations. Dabigatran emerges as a suitable option in such cases [18].

In the present study, the experts highly recommended the usage of dabigatran in AF. The RE-LY trial reported that in AF patients, dabigatran 150 mg was superior to warfarin for the primary efficacy endpoint of stroke or systemic embolism (SE), whereas dabigatran 110 mg was non-inferior. Both dosages of dabigatran significantly reduced the annual risk of hemorrhagic stroke [19]. In a subgroup analysis of the RE-LY study for treatment effects, dabigatran was compared to warfarin for secondary prevention in patients with prior stroke or transient ischemic attack (TIA). The study findings showed that both the dosages of dabigatran were associated with reduced incidence of stroke or systemic embolism than warfarin [20]. A real-world retrospective cohort study by Huang et al. reported that in AF

patients with extreme obesity, dabigatran was useful in lowering the risk of thromboembolism and death [21].

The current study revealed that dabigatran is the most commonly recommended medication for PE and DVT. The RE-COVER and RE-COVER II trials demonstrated that dabigatran is non-inferior to warfarin in reducing recurrent VTE and superior in terms of clinically significant bleeding and any bleeding [22,23]. In the RE-SONATE study, dabigatran demonstrated a significant decrease in the primary endpoint of objectively verified symptomatic VTE or unexpected mortality, indicating its superiority over placebo [24]. The PEITHO-2 study reported that early switching from heparin to dabigatran, after routine clinical evaluation, was efficacious and safe in patients with intermediate-risk PE [25]. Brandão et al. showed that dabigatran was non-inferior to standard care in terms of effectiveness and safety for acute VTE in children with thrombophilia. It also demonstrated a favorable safety profile in the secondary prevention of VTE in children with thrombophilia [26]. Dabigatran also showed a low risk of recurrent VTEs in cerebral venous thrombosis (CVT) patients [27].

The present study found that, in addition to AF, PE, and DVT, the experts recommended the use of dabigatran for ischemic stroke and as prophylaxis in hip replacement surgery. Dabigatran use is associated with a decreased incidence of ischemic stroke and cerebral hemorrhage [28]. Alrohani et al. Corroborated the safety of early dabigatran treatment after a transient ischemic attack or mild ischemic stroke in AF patients [29]. Kate et al. demonstrated the feasibility of dabigatran therapy within 24 hours after a mild stroke in acute ischemic stroke patients without AF [30]. The BISTRO I study indicated a satisfactory therapeutic window for dabigatran in patients undergoing total hip replacement, with modest risks of thrombosis and hemorrhage [31]. In BISTRO II randomized trial, dabigatran demonstrated a dose-dependent antithrombotic effect in patients undergoing total hip or knee replacement. As compared to enoxaparin, dabigatran 150 mg twice a day resulted in a decreased risk of VTE. Furthermore, dabigatran treatment at a dosage of 50 mg twice a day was associated with a decreased hemorrhagic risk compared to enoxaparin [32]. RE-NOVATE trial reported that dabigatran is as effective as enoxaparin in lowering the risk of VTE after total hip replacement surgery, with a similar safety profile [33]. Similarly, the RE-NOVATE II study demonstrated that dabigatran is an excellent oral alternative to enoxaparin for thromboprophylaxis in Indian patients following total hip arthroplasty [34].

In the current study, the majority of the respondents reported that dabigatran is more effective than rivaroxaban and apixaban. In contrast, a study conducted by Rutherford et al. found no statistically significant differences in the risk of stroke or systemic embolism between dabigatran, rivaroxaban, and apixaban in propensity-matched comparisons in AF patients. However, both dabigatran and apixaban were associated with a significantly reduced risk of severe bleeding compared to rivaroxaban [35]. Noseworthy et al. and Grymonprez et al. reported comparable effectiveness among dabigatran, rivaroxaban, and apixaban [36,37]. Villines et al. observed that in non-valvular atrial fibrillation (NVAf) patients, dabigatran use was linked to a considerably decreased risk of serious bleeding compared to rivaroxaban, but no significant change in stroke risk [38]. Furthermore, a study by Mantha et al. found no significant difference in effectiveness between dabigatran 150 mg and apixaban for stroke or systemic embolism prevention in individuals with NVAf. However, apixaban was associated with less severe bleeding compared to dabigatran 150 mg or rivaroxaban, while rivaroxaban was found to be less effective than dabigatran 150 mg in preventing stroke or systemic embolism [39].

The current expert opinions emphasize the important role of dabigatran in the prevention of stroke and the prevention and treatment of VTE across various clinical conditions. These

findings were obtained through a meticulously designed and validated questionnaire-based survey, allowing for expert insights based on evidence-based practices. By considering expert viewpoints and evidence-based practices, healthcare practitioners can make informed decisions regarding treatment approaches, including the potential utilization of dabigatran to enhance patient outcomes. However, it is important to acknowledge the significant limitations of the study. The generalizability of the study findings may be restricted due to the very small sample size. The findings may be more representative of the general population of patients if the sample was larger and more varied. Furthermore, the study's dependence on expert judgments raises the possibility of bias since individual viewpoints and preferences may have impacted the reported outcomes. It is critical to understand the findings while keeping these limitations in mind and to consider additional studies to confirm and expand on the findings.

## **5. CONCLUSION**

Dabigatran is recommended by experts as the preferred anticoagulant in clinical practice. It is commonly prescribed for various conditions including AF, PE, and DVT. Furthermore, experts also endorse the usage of dabigatran for ischemic stroke and in hip replacement surgery as prophylaxis. Dabigatran has demonstrated its efficacy as an anticoagulant and has shown a potential to be more effective compared to rivaroxaban and apixaban.

### **Ethical Approval:**

The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

### **Consent**

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

### **COMPETING INTERESTS**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

## REFERENCES

1. Cardiovascular diseases [Internet]. [cited 2023 Jul 19]. Available from: <https://www.who.int/health-topics/cardiovascular-diseases>
2. Sreeniwas Kumar A, Sinha N. Cardiovascular disease in India: A 360 degree overview. *Med J Armed Forces India*. 2020 Jan;76(1):1–3.
3. Jaberinezhad M, Farhoudi M, Nejadghaderi SA, Alizadeh M, Sullman MJM, Carson-Chahhoud K, et al. The burden of stroke and its attributable risk factors in the Middle East and North Africa region, 1990–2019. *Sci Rep*. 2022 Feb 17;12(1):2700.
4. Waheed SM, Kudravalli P, Hotwagner DT. Deep Vein Thrombosis. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 19]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK507708/>
5. General (US) O of the S, National Heart L. INTRODUCTION: Definitions of Deep Vein Thrombosis and Pulmonary Embolism. In: *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism* [Internet]. Office of the Surgeon General (US); 2008 [cited 2023 Jul 19]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK44184/>
6. Stone J, Hangge P, Albadawi H, Wallace A, Shamoun F, Knuttien MG, et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. *Cardiovasc Diagn Ther*. 2017 Dec;7(Suppl 3):S276–84.
7. Vyas V, Goyal A. Acute Pulmonary Embolism. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 19]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK560551/>
8. Report of task force on Venous Thrombo Embolism, national academy of medical sciences (India) Ministry of Health & family welfare government of India [Internet]. [cited 2023 Jul 19]. Available from: <https://www.nams-india.in/downloads/Taskforce/01%20NAMS%20%20Task%20Force%20report%20%20on%20Venus%20Thrombo.pdf>
9. Saggi DK, Rangaswamy VV, Yalagudri S, Sundar G, Reddy NK, Shah V, et al. Prevalence, clinical profile, and stroke risk of atrial fibrillation in rural Andhra Pradesh, India (the AP-AF study). *Indian Heart J*. 2022;74(2):86–90.
10. Raja DC, Kapoor A. Epidemiology of Atrial Fibrillation - An Indian Perspective. *J Assoc Physicians India*. 2016 Aug;64(8 Suppl):7-10.
11. Tsai Hobart. *Pharmacological Review of Anticoagulants*. Mina Kelleni. (ed). Anticoagulation Drugs - the Current State of the Art. 2020.
12. Batta A, Kalra BS, Khirasaria R. Critical Issues and Recent Advances in Anticoagulant Therapy: A Review. *Neurology India*. 2019 Sep 1;67(5):1200.
13. Yeh CH, Hogg K, Weitz JI. Overview of the New Oral Anticoagulants. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015 May;35(5):1056–65.

14. Thachil J. The newer direct oral anticoagulants: a practical guide. *Clinical Medicine*. 2014 Apr 1;14(2):165–75.
15. Dabigatran - an overview | ScienceDirect Topics [Internet]. [cited 2023 Jul 19]. Available from: <https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dabigatran>
16. Muñoz-Corcuera M, Ramírez-Martínez-Acitores L, López-Pintor RM, Casañas-Gil E, Hernández-Vallejo G. Dabigatran: A new oral anticoagulant. Guidelines to follow in oral surgery procedures. A systematic review of the literature. *Med Oral Patol Oral Cir Bucal*. 2016 Nov;21(6):e679–88.
17. Tran A, Cheng-Lai A. Dabigatran etexilate: the first oral anticoagulant available in the United States since warfarin. *Cardiol Rev*. 2011;19(3):154–61.
18. railokya A, Hiremath JS. Dabigatran - the First Approved DTI for SPAF. *J Assoc Physicians India*. 2018 Apr;66(4):85-90.
19. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009 Sep 17;361(12):1139–51.
20. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010 Dec;9(12):1157–63.
21. Huang CW, Duan L, An J, Sim JJ, Lee MS. Effectiveness and Safety of Dabigatran in Atrial Fibrillation Patients with Severe Obesity: a Real-World Retrospective Cohort Study. *J Gen Intern Med*. 2022 Sep;37(12):2982–90.
22. 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 Dec 10;361(24):2342–52.
23. 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 Feb 18;129(7):764–72.
24. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013 Feb 21;368(8):709–18.
25. Klok FA, Toenges G, Mavromanoli AC, Barco S, Ageno W, Bouvaist H, et al. Early switch to oral anticoagulation in patients with acute intermediate-risk pulmonary embolism (PEITHO-2): a multinational, multicentre, single-arm, phase 4 trial. *Lancet Haematol*. 2021 Sep;8(9):e627–36.
26. Brandão LR, Tartakovsky I, Albisetti M, Halton J, Bomgaars L, Chalmers E, et al. Dabigatran in the treatment and secondary prophylaxis of venous thromboembolism in children with thrombophilia. *Blood Adv*. 2022 Nov 22;6(22):5908–23.

27. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhão P, et al. Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis: A Randomized Clinical Trial. *JAMA Neurology*. 2019 Dec 1;76(12):1457–65.
28. Butcher KS, Ng K, Sheridan P, Field TS, Coutts SB, Siddiqui M, et al. Dabigatran Treatment of Acute Noncardioembolic Ischemic Stroke. *Stroke*. 2020 Apr;51(4):1190–8.
29. Alrohimi A, Ng K, Dowlatshahi D, Buck B, Stotts G, Thirunavukkarasu S, et al. Early Dabigatran Treatment After Transient Ischemic Attack and Minor Ischemic Stroke Does Not Result in Hemorrhagic Transformation. *Can J Neurol Sci*. 2020 Sep;47(5):604–11.
30. Kate M, Gioia L, Buck B, Sivakumar L, Jeerakathil T, Shuaib A, et al. Dabigatran Therapy in Acute Ischemic Stroke Patients Without Atrial Fibrillation. *Stroke*. 2015 Sep;46(9):2685–7.
31. Eriksson BI, Dahl OE, Ahnfelt L, Kälebo P, Stangier J, Nehmiz G, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J ThrombHaemost*. 2004 Sep;2(9):1573–80.
32. Eriksson BI, Dahl OE, Büller HR, Hettiarachchi R, Rosencher N, Bravo ML, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J ThrombHaemost*. 2005 Jan;3(1):103–11.
33. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet*. 2007 Sep 15;370(9591):949–56.
34. Malhotra R, Babhulkar S, Sanjib KB, Clemens A, Dadi A, Iyer R, et al. Thromboprophylaxis with dabigatran after total hip arthroplasty in Indian patients: A subanalysis of a double-blind, double-dummy, randomized RENOVATE II study. *Asian J Surg*. 2017 Apr;40(2):145–51.
35. Rutherford OCW, Jonasson C, Ghanima W, Söderdahl F, Halvorsen S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2020 Apr 1;6(2):75–85.
36. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation. *Chest*. 2016 Dec;150(6):1302–12.
37. Grymonprez M, De Backer TL, Bertels X, Steurbaut S, Lahousse L. Long-term comparative effectiveness and safety of dabigatran, rivaroxaban,

apixaban and edoxaban in patients with atrial fibrillation: A nationwide cohort study. *Front Pharmacol.* 2023;14:1125576.

38. Villines TC, Ahmad A, Petrini M, Tang W, Evans A, Rush T, et al. Comparative safety and effectiveness of dabigatran vs. rivaroxaban and apixaban in patients with non-valvular atrial fibrillation: a retrospective study from a large healthcare system. *Eur Heart J Cardiovasc Pharmacother.* 2019 Apr 1;5(2):80–90.
39. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. *ThrombHaemost.* 2012 Sep;108(3):476–84.

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