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REVIEW

Lowering the Risk for Thrombus and Stroke in Atrial Fibrillation Patients: Will Dabigatran Replace Warfarin?

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Abstract: The use of oral anticoagulation to reduce stroke risk from thromboembolism has become the cornerstone of management of atrial fibrillation (AF). Dabigatran is a direct thrombin inhibitor which, in contrast to warfarin, does not require regular blood draws for monitoring effect. Randomized controlled studies suggest that dabigatran may be more effective than warfarin at higher doses, without an increased bleeding risk, and equally effective at lower doses, with lower bleeding risk. With these apparent advantages comes a higher cost, and limited use in patients with underlying renal or liver disease. In addition, the inability to measure anticoagulant effect, as with warfarin, presents drawback for clinical use of dabigatran. In this review, we discuss the mechanisms of action, clinical effect, and place in therapy of dabigatran as a possible replacement for warfarin.

Keywords: atrial fibrillation, anticoagulation, stroke

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its prevalence is increasing. AF is associated with an increased risk of mortality, which is largely due to an increased risk of thromboembolic stroke.[1,2] According to Virchow's triad, three factors increase the risk of formation of thromboembolism: hypercoagulability, endothelial dysfunction, and stasis. During AF, the coordinated contraction of the atrium ceases resulting in increased stasis of blood.[3] In addition, studies have demonstrated that AF is also associated with activation of plasmatic clotting system and of platelets,[4,5] and that endothelial adhesion molecules are upregulated in AF.[6,7] In summation, these effects act to greatly increase the risk of thrombus formation in the atrium during AF, with subsequent thromboembolization. Although thromboemboli forming in the left atrium during AF could potentially embolize to anywhere in the body supplied by the blood stream, most non-central nervous system (CNS) emboli are subclinical and make up about 7% of thromboembolic events.[8] The most serious complication is embolization to the brain causing an ischemic stroke, which is the basis for use of anticoagulation in AF.

Among patients with non-valvular AF, the risk of stroke increases with the presence of risk factors. The most common stratification scheme employed is the CHADS2 system, in which one point is given for each risk factor (congestive heart failure (CHF), hypertension, age >75, and diabetes) and two points for history of stroke.[9] The estimated risk of stroke or peripheral embolization in patients not on anticoagulation is 0.3–0.5 events per 100 person-years if the CHADS2 score is 0, but it increases to 6.3–6.9 events per 100 person-years if the CHADS2 score is 4–6.[8,10] This risk is significantly attenuated with the use of anticoagulation, with many studies demonstrating a clinical benefit with warfarin, particularly in patients with a high risk (ie, high CHADS2 score).[11–20] As a result, anticoagulation is currently recommended by the ACC/AHA/ESC in patients with non-valvular AF based on their risk factor profile, with anticoagulation recommended in anyone with one or more risk factors,[21] with a goal International Normalized Ratio (INR) of 2.0–3.0 in those on warfarin. Multiple clinical studies have highlighted the importance of anticoagulation in patients with AF to prevent thromboembolism,[22,23] all of which demonstrated superiority of warfarin over placebo as well as antiplatelet agents.[24]

Despite its clinical benefits, warfarin can be a burden for patients to take. It requires dietary discretion and adjustment due to its sensitivity to varying levels of vitamin K absorption, as well as regular monitoring with blood sampling. The possibility that newer anticoagulants without such a burden could provide equal if not greater efficacy, with greater patient convenience, has led to extensive developmental efforts. Dabigatran was among the first to emerge from these efforts without toxicity that prevented clinical use.[25] Whether this popular new medication will be the answer to those searching for the ideal oral anticoagulant and replace warfarin, or just fill a niche as a useful agent in select individuals, remains to be seen. In this review, we discuss the mechanisms, pharmacology, clinical uses, and potential role in patient care of dabigatran.

Mechanism of action

Dabigatran etexilate (also called Pradaxa) is an orally active, direct thrombin inhibitor.[26–28] The mechanism of action of dabigatran is based upon its ability to inactivate clot-bound thrombin, an action distinct from that of heparin which cannot do so because the masking of thrombin binding sites by fibrin.[29–31] In addition to this advantage over heparin, dabigatran does not bind to Platelet Factor 4 (PF4) and as such does not provoke antibody formation to heparin-PF4 complex responsible for Heparin-induced thrombocytopenia (HIT). Other types of direct thrombin inhibitors include the parenteral medications argatroban and lepirudin, which are approved for use in the case of HIT.

Metabolism and pharmacokinetic profile

The compound dabigatran etexilate is a pro-drug which is converted by ubiquitous esterases into the active compound that binds directly to thrombin. It has a half-life of approximately 12 to 14 hours in adults with normal renal function, with a maximum anticoagulant effect achieved within three hours of ingestion.[32] It is 80% eliminated by renal excretion of the unchanged drug,[33] and thus the plasma clearance will be highly effected by underlying kidney function. In patients with reduced renal function, dabigatran half-life ranges from 14 hours in normal volunteers

to 34 hours in those receiving maintenance dialysis (ie, creatinine clearance (CrCl) <10 to 20 mL/min).[34] Based on this effect, dosing of dabigatran based on renal function is recommended (see below). It is unclear how the circulating levels of dabigatran are changed in individuals with low body weight or those who are morbidly obese. Dabigatran is about one-third protein bound. It can be dialyzed in patients with renal impairment, with about 50%–60% being removed after four hours of dialysis.[35]

The absorption of dabigatran by the intestines is via the efflux transporter P-glycoprotein (P-gp), and thus dabigatran may interact with inducers or inhibitors of P-gp.[36] Certain P-gp inducers may alter dabigatran bioavailability significantly (Table 1). For example, in the Canadian and UK labeling, the use of systemic ketoconazole and dabigatran together is contraindicated, while in the European Medicines Agency labeling, the concurrent use of quinidine is contraindicated. In other labeling systems, it has been recommended that concurrent use of dabigatran with other P-gp inducers or inhibitors should either be avoided, administration separated by at least two hours, or the dose of dabigatran appropriately modified. Dabigatran has not been shown to interact with the cytochrome P450 system in any manner of clinical significance.

Because of stable and predictable pharmacokinetics, and also because the most accessible and available methods of assessing bleeding risk (ie, the thrombin time, the activated partial thromboplastin time (aPTT), and activated clotting time) found significant test-kit variability between different manufacturers,[37] routine monitoring of coagulation is not necessary in patients on dabigatran. Many of these bleeding tests were noted to have normal results despite elevated dabigatran trough levels in early studies.[38] The ecarin clotting test or thrombin time have also been suggested as methods to detect presence of dabigatran effect and level of coagulopathy,[39] however, it is not generally available.[40–46] As such, the lack of monitoring required for dabigatran acts as a double-edged sword. On the one hand, adding patient convenience, while on the other hand, creating a situation in which a clinician cannot easily deduce the level of anticoagulation (or over-anticoagulation) in a given patient on dabigatran. The latter situation has direct implications for bleeding risk, discussed below.

Table 1. Interaction data and recommendations refer to systemic drug forms.

Category	Effect	Recommendations
Antacids, Histamine-2 (H2B) antagonists, proton pump inhibitors (PPIs)	Decreased dabigatran concentration (modest effect)	Administer dabigatran at least two hours before acid suppressive medications.
Inhibitors of P-gp efflux transporter (abiraterone, alfentanil, amiodarone, atorvastatin, azithromycin, carvedilol, clarithromycin, cobicistat containing coformulations, conivaptan, crizotinib, cyclosporine, darunavir, diltiazem, dipyridamole, dronedarone, duloxetine, erythromycin, fenofibrate, grapefruit and grapefruit juice, indinavir, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir, lovastatin, mefloquine, mifepristone, nelfinavir, nicardipine, nifedipine, nilotinib, posaconazole, progesterone, propafenone, propranolol, quinidine, quinine, ranolazine, reserpine, ritonavir, ritonavir containing coformulations, saquinavir, sunitinib, tacrolimus, tamoxifen, telaprevir, telithromycin, ticagrelor, tolvaptan, ulipristal, vandetanib, vemurafenib, verapamil)	Increased dabigatran concentration (variable effect)	Avoid use of ketoconazole, cyclosporine, itraconazole and tacrolimus with dabigatran. Avoid use of any P-gp inhibitor with dabigatran if moderate or severe renal insufficiency (CrCl <50 mL/minute) or in any patient aged ≥80 years. Where concomitant use of a P-gp inhibitor is necessary, administer dabigatran at least two hours before P-gp inhibitor which may decrease severity of interaction; monitor closely for bleeding.
Inducers of P-gp efflux transporter (carbamazepine, dexamethasone, doxorubicin, nefazodone, pentobarbital, phenobarbital, prazosin, rifampin, St. John's wort, tenofovir, tipranavir, trazodone, vinblastine)	Decreased dabigatran concentration (significant effect)	Avoid concurrent use of dabigatran with P-gp inducers. Decreased concentrations of dabigatran may persist for nearly 7 days after stopping use of a potent inducer of P-gp (eg, rifampin).

Abbreviations: CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein efflux transporters; VTE, venous thromboembolism.

Clinical studies and efficacy

The first clinical evaluation of dabigatran compared with warfarin was the PETRO Study, in which 502 patients were treated with doses of dabigatran ranging from 50 mg to 300 mg twice daily.[26] This study demonstrated feasibility and safety, with only the 300 mg dose being associated with major bleeding events and the 50 mg dose with thromboembolic episodes. Based on this preliminary study, the RELY study was performed. Published in 2009, RELY was designed as a non-inferiority trial comparing the risk of stroke in 18,113 patients randomly assigned to dabigatran doses of 150 mg twice daily, 110 mg twice daily, or warfarin with goal INR of 2–3.[47] This study demonstrated that the 110 mg dose was non-inferior to warfarin (1.53% risk/year vs. 1.69% risk/year) and that the 150 mg dose was superior to warfarin (1.11% risk/year). In addition, the rate of major bleeding was significantly less in those on the 110 mg dose compared with warfarin (2.71% per year vs. 3.36% per year) and not significantly different with the 150 mg dose (3.11% per year, $P = 0.31$). Interestingly, the rate of hemorrhagic stroke was significantly lower with both doses of dabigatran than warfarin (0.38% per year for warfarin, 0.12% per year for the 110 mg dose, and 0.10% per year for the 150 mg dose). The overall mortality rate, which was not the primary endpoint, was not significantly different between all groups (4.13% per year for warfarin, 3.75% per year for the 110 mg dose, and 3.64% per year for the 150 mg dose). Patients with a CrCl <30 mL/min, a high risk of bleeding (recent or planned surgery, active bleeding diathesis, or GI bleed within the last year), active liver disease, as well as valvular AF patients, and pregnant women were excluded from this study. A follow-up study also demonstrated a benefit regardless of whether patients were warfarin-naïve or had been on warfarin previously.[48] The RELY study demonstrated the efficacy of dabigatran for anticoagulation in AF, with outcomes from both dose regimens being significant improvements over warfarin—the 150 mg dose being associated with a decreased stroke risk without an increased risk of bleeding, and the 110 mg dose being associated with a decreased bleeding risk, without an increased risk of stroke.

Safety

Initial studies raised a concern for elevation in liver aminotransferases with dabigatran.[26] Although patients with liver disease were excluded from the RELY study, this has not generally been seen as a safety concern. The principle safety concerns with dabigatran have focused on four major safety considerations: a signal of increased risk of myocardial infarction, risk of bleeding in patients with renal impairment, the concern about a lack of antidote in patients with active bleeding while on dabigatran, and the newly recognized lack of efficacy in patients with prosthetic valves.

In a post-hoc analysis of RELY, the rate of myocardial infarction was found to have non-significantly increased with dabigatran at both doses compared to warfarin (HR 0.81 for 150 mg, 0.82 for 110 mg, vs. 0.64 for warfarin),[49] with the effects of dabigatran compared to warfarin being consistent in patients with and without a history of documented coronary artery disease. This finding was explored further in a 2012 meta-analysis of 7 trials (30,514 individuals) comparing dabigatran with warfarin, enoxaparin, and placebo in treatment of AF, as well as in DVT prophylaxis and treatment, and treatment of acute coronary syndromes. It was found to indeed be significantly associated with myocardial infarction, cardiac death, or unstable angina (OR 1.27, CI 1.0–1.61), although the absolute risk difference was very small (0.27%).[50] Given that the risk was irrelevant of history of coronary artery disease, no recommendations have been made with regard to restricting use of dabigatran.

Due to its predominant renal metabolism, the manufacturers recommend that renal function be determined in all patients prior to initiation, and exclud use in those with CrCl <15 mL/min (CrCl <30 mL/min in Europe), as well as in those with fluctuating renal function. Of note, in the United States, dabigatran has been approved at the 150 mg dose only, with a 75 mg dose used in patients with renal disease (GFR 15–30 mL/min), although this lower dose has not been tested in clinical trials to date. Based on the lack of current clinical efficacy of the 75 mg dose, some practitioners have avoided this dose, preferring warfarin in patients with CrCl <30 mL/min.[51] Since many elderly individuals have a lower CrCl, this tends to limit the utility of use in this population.

In November 2012, the U.S. Food and Drug Administration (FDA) issued a statement that the rate of bleeding with dabigatran was not higher than with warfarin in patients using either drug for the

first time.[52,53] Overall, bleeding risk with dabigatran has been estimated at 8%–33%, with major bleeding in <6% of patients.[39] A recent database query of the FDA Mini-Sentinel database identified a rate of gastrointestinal hemorrhage of 1.6 events/100,000 patient-days and intracranial hemorrhage rate of 0.8–0.9 events/100,000 patient-days (vs. 3.1 events/100,000 patient-days and 1.9 events/100,000 patient-days for warfarin, respectively).[52] Since its approval, there have been post-marketing reports of a potential for a higher rate of serious bleeding with dabigatran vs. warfarin that have not been systematically validated.[52]

One notable limitation to use is that no specific antidote exists for dabigatran reversal,[32,34,38,40,44,54] with therapy for severe hemorrhage often including transfusion of fresh frozen plasma (FFP), packed red blood cells (RBCs), and surgical intervention.[55] Of note, prothrombin complex concentrate (not available in the U.S.) has been shown to be ineffective for reversal.[42] Drug discontinuation is usually sufficient to control bleeding in most clinical settings, since its half-life is relatively short (12 to 14 hours) in subjects with normal renal function. Unlike use of the INR with warfarin, there is no clear method to detect excessive anticoagulation on dabigatran, although it has been suggested that an aPTT over 2.5 times control may indicate excessive anticoagulation.[39] As above, the ecarin clotting test or thrombin time have also been suggested as methods to detect presence of dabigatran effect and level of coagulopathy,[39] although the sensitivity of these assays makes practical use difficult. Otherwise, careful monitoring for bleeding and routine screening of blood counts is recommended as with any patient taking anticoagulation.

For cases of bleeding, charcoal hemofiltration has been suggested to hasten excretion. If given within 2 hours of ingestion, use of activated charcoal may also remove unabsorbed drug from the gastrointestinal tract. For those with life-threatening bleeding, the use of unactivated 4 factor prothrombin complex concentrates (PCC), activated PCC (eg, FEIBA), or recombinant Factor VIIa in high doses may be considered,[54] but may precipitate thromboembolism and thus should be used with caution. Notably, in one study of 12 normal volunteers, the use of 4 factor unactivated PCC did not reverse dabigatran-associated prolongations in the aPTT, ecarin clotting time, or thrombin time.[42] It is important to note that 4 factor unactivated PCC are available in Canada, Europe and other countries, but not in the United States, where only 3 factor PCCs (factor IX complex, Bebulin, Profilnine) are available.

A recent alert by the U.S. FDA and Health Canada warned against the use of dabigatran in patients with mechanical prosthetic heart valves based on results from the RE-ALIGN clinical trial,[56] due to an increased risk of stroke, myocardial infarction, and mechanical valve thrombosis compared with warfarin.[57] In addition to these considerations, the most common side effects reported has been dyspepsia (11% including abdominal discomfort/pain and epigastric discomfort),[39] which in practice is probably the leading cause of intolerance leading to discontinuation or choice of alternatives.

Patient preference

The convenience to patients of not needing routine blood checks for INR is a clear benefit of dabigatran compared with warfarin, and subjectively has been among the most favorable effects of changing to dabigatran from warfarin in patients.

The cost of dabigatran at ~$3000/year in the U.S. is substantially more than warfarin (~$48/year), even after adding in the extra cost of INR testing and provider visits for dose adjustments.[58] It is this added cost that in practice is the most frequent reason for patients to opt against use, particularly in those patients in whom the full cost is not covered by insurance. The cost effectiveness of dabigatran compared with warfarin has been studied in several countries to date.[59–62] In one study by Freeman et al,[59] assessing quality adjusted life years (QALY) and incremental cost-effectiveness found that the quality adjusted life expectancy was 10.28 QALYs with warfarin, 10.70 QALYs with 110 mg dabigatran, and 10.84 QALYs with 150 mg dabigatran, with incremental cost-effectiveness ratios of $51,229 per QALY for the 110 mg dose and $45,372 per QALY for the high dose.[59] These models were sensitive to the cost of dabigatran with increased cost-effectiveness of 150 mg dose with increased risk of stroke and intracranial hemorrhage. This value, which is below the commonly used cutoff of $50,000/QALY, has resulted in dabigatran being

covered by multiple payer programs. However, with increasing attention to rising medical costs, and the likelihood that more of these costs will be shifted to the patients, it is unclear whether this cost effect will play a role in preferential use of dabigatran over warfarin.

Place in therapy

In one survey of 181 doctors in California, Huang et al[63] noted that cost (25%), renal function (21%), and CHADS2 score (18%) were the most important factors in deciding a patient's eligibility for dabigatran among warfarin-naïve patients, with unstable INRs (37%) and missed appointments (17%) being considerations against warfarin.[63] Overall, cardiologists were more comfortable prescribing dabigatran than general internists.[63] Whether these results reflect a greater appreciation for stroke reduction among cardiologists, or greater concern about overall costs of medications by general internists is unclear. What is clear is that many in the field of managing patients with AF were enthusiastic about the emergence of alternative oral anticoagulants, such as dabigatran, to warfarin.

Anecdotally, we have found it easier to convince patients with lower CHADS2 scores to take anticoagulation with dabigatran than 'burdening' them with initiating warfarin, with the subsequent blood draws and clinic visits. Other experts also recommend dabigatran (or other new factor Xa inhibitors, apixiban, or rivaroxiban) over warfarin as a 2B recommendation (Weak recommendation; alternative approaches may be better for some patients under some circumstances).[51] The 150 mg dose is recommended in most patients unless there is concern about a risk of bleeding or in patients over 75 years of age, in which case the 110 mg dose is suggested if available.[51] Warfarin is a reasonable choice if patients are comfortable with periodic INR monitoring and have stable INRs, in patients for whom the cost of the medication is a concern, and in patients with contraindications to dabigatran such as CrCl $<$30 mL/min or prosthetic valves. It should also be noted that certain drugs have interactions with dabigatran, including antacids, H2B, and proton pump inhibitors which decrease effect (should be given at least 2 hours after dabigatran), P-glycoprotein inhibitors (such as amiodarone, atorvastatin, diltiazem, ketoconazole, and grapefruit juice) which can increase dabigatran effect, and P-glycoprotein inducers (phenobarbital, rifampin, dexamethasone), which can decrease effect. An additional consideration is that in patients with whom compliance might be an issue, warfarin would allow a method of validation of use (via INR).

Conclusion

In summary, dabigatran is one of several new oral anticoagulants now reaching the market which offer added benefits of convenience and superior clinical outcomes to warfarin. Warfarin has been in use for many years and, as such, the majority of its side effects are known. Other than in certain populations, such as patients with renal insufficiency, dabigatran appears to be well-tolerated broadly. Post-marketing studies will continue to be required to monitor such effects of dabigatran. Regardless, it is not unlikely that eventually the majority of individuals needing anticoagulation for non-valvular AF will opt for these newer agents over warfarin.

Author Contributions

Conceived the concept: MR, AT. Analyzed the data: MR, AT. Wrote the first draft of the manuscript: MR, AT. Contributed to the writing of the manuscript: MR, AT. Agree with manuscript results and conclusions: MR, AT. Jointly developed the structure and arguments for the paper: MR, AT. Made critical revisions and approved final version: MR, AT. All authors reviewed and approved of the final manuscript.

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nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The framingham heart study. *Circulation*. 1998;98(10):946–52.
2. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271(11):840–4.
3. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: Evidence for "atrial stunning" as a mechanism of thromboembolic complications. *J Am Coll Cardiol*. 1994;23(2):307–16.
4. Sohara H, Amitani S, Kurose M, Miyahara K. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: A study in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 1997;29(1):106–12.
5. Goette A, Ittenson A, Hoffmanns P, et al. Increased expression of p-selectin in patients with chronic atrial fibrillation. *Pacing Clin Electrophysiol*. 2000;23(11 Pt 2):1872–5.
6. Goette A, Bukowska A, Lendeckel U, et al. Angiotensin ii receptor blockade reduces tachycardia-induced atrial adhesion molecule expression. *Circulation*. 2008;117(6):732–42.
7. Hammwohner M, Ittenson A, Dierkes J, et al. Platelet expression of cd40/cd40 ligand and its relation to inflammatory markers and adhesion molecules in patients with atrial fibrillation. *Exp Biol Med (Maywood)*. 2007;232(4):581–9.
8. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: How well do randomized trials translate into clinical practice? *JAMA*. 2003;290(20):2685–92.
9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. *JAMA*. 2001;285(22):2864–70.
10. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2008;51(8):810–5.
11. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The boston area anticoagulation trial for atrial fibrillation investigators. *N Engl J Med*. 1990;323(22):1505–11.
12. Stroke prevention in atrial fibrillation study. Final results. *Circulation*. 1991;84(2):527–39.
13. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke prevention in atrial fibrillation ii study. *Lancet*. 1994;343(8899): 687–91.
14. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1(8631):175–9.
15. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans affairs stroke prevention in nonrheumatic atrial fibrillation investigators. *N Engl J Med*. 1992;327(20):1406–12.
16. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian atrial fibrillation anticoagulation (cafa) study. *J Am Coll Cardiol*. 1991;18(2):349–55.
17. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449–57.
18. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857–67.
19. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs. aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288(19):2441–8.
20. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med*. 2006;166(12):1269–75.
21. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 accf/aha/esc and 2011 accf/aha/hrs recommendations): A report of the american college of cardiology/american heart association task force on practice guidelines. *Circulation*. 2013;127:1916–26.
22. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825–33.
23. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347(23):1834–40.
24. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (active w): A randomised controlled trial. *Lancet*. 2006;367(9526):1903–12.
25. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: A randomized trial. *JAMA*. 2005;293(6):690–8.
26. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (petro study). *Am J Cardiol*. 2007;100(9):1419–26.
27. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: A randomised, double-blind, non-inferiority trial. *Lancet*. 2007;370(9591):949–56.
28. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342–52.
29. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med.* 2005;353:1028–40.
30. Berry CN, Girardot C, Lecoffre C, Lunven C. Effects of the synthetic thrombin inhibitor argatroban on fibrin- or clot-incorporated thrombin: Comparison with heparin and recombinant hirudin. *Thromb Haemost*. 1994;72(3):381–6.
31. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin iii but is susceptible to inactivation by antithrombin iii-independent inhibitors. *J Clin Invest*. 1990;86(2):385–91.
32. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103(6):1116–27.
33. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos*. 2008;36(2):386–99.
34. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: An open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49(4):259–68.
35. Khadzhynov D, Wagner F, Formella S, et al. Effective elimination of dabigatran by haemodialysis. A phase i single-centre study in patients with end-stage renal disease. *Thrombosis Haemost*. 2013;109(4):596–605.
36. Delavenne X, Ollier E, Basset T, et al. A semi-mechanistic absorption model to evaluate drug-drug interaction with dabigatran: Application with clarithromycin. *Br J Clin Pharmacol*. 2012.

37. Dager WE, Gosselin RC, Kitchen S, Dwyre D. Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: A multicenter, in vitro study. *Annals Pharmacother*. 2012;46(12):1627–36.
38. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA. Dabigatran etexilate in clinical practice: Confronting challenges to improve safety and effectiveness. *Pharmacotherapy*. 2011;31(12):1232–49.
39. Dabigatran: Drug information.
40. Hankey GJ, Eikelboom JW. Dabigatran etexilate: A new oral thrombin inhibitor. *Circulation*. 2011;123(13):1436–50.
41. Freyburger G, Macouillard G, Labrouche S, Sztark F. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing total hip or total knee replacement. *Thromb Res*. 2011;127(5):457–65.
42. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573–9.
43. Lindahl TL, Baghaei F, Blixter IF, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost*. 2011;105(2):371–8.
44. Miyares MA, Davis K. Newer oral anticoagulants: A review of laboratory monitoring options and reversal agents in the hemorrhagic patient. *Am J Health Syst Pharm.* 2012;69(17):1473–84.
45. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW. Recombinant factor viia (rfviia) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood*. 2012;119(9): 2172–4.
46. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med*. 2011;365:2039–40.
47. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139–51.
48. Ezekowitz MD, Wallentin L, Connolly SJ, et al. Dabigatran and warfarin in vitamin k antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation*. 2010;122:2246–53.
49. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the re-ly (randomized evaluation of long-term anticoagulation therapy) trial. *Circulation*. 2012;125(5):669–76.
50. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: Meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med*. 2012;172(5):397–402.
51. Manning WJ, Singer DE, Lip GY, Zimetbaum P, Kasner SE, Sapeira GM. Antithrombic therapy to prevent embolization in atrial fibrillation. *UpToDate*. 2013.
52. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med*. 2013;368(14):1272–4.
53. Pradaxa (dabigatran etexilate mesylate): Drug safety communication—safety review of post-market reports of serious bleeding events. 2012.
54. Alberts MJ, Bernstein RA, Naccarelli GV, Garcia DA. Using dabigatran in patients with stroke: A practical guide for clinicians. *Stroke.* 2012;43(1): 271–9.
55. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2011;57(2):223–42.
56. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: The randomized, phase ii study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (re-align). *Am Heart J*. 2012;163(6):931–7. e1.
57. FDA drug safety communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. 2012.
58. Gage BF. Cost of dabigatran for atrial fibrillation. *BMJ*. 2011;343:d6980.
59. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154(1):1–11.
60. Kansal AR, Sorensen SV, Gani R, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. *Heart*. 2012;98(7):573–8.
61. 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(3):407–14.
62. Pletscher M, Plessow R, Eichler K, Wieser S. Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in switzerland. *Swiss Med Wkly*. 2013;143:w13732.
63. Huang C, Siu M, Vu L, Wong S, Shin J. Factors influencing doctors' selection of dabigatran in non-valvular atrial fibrillation. *J Eval Clin Prac*. 2012.