Direct thrombin inhibitors

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Heparins and vitamin K antagonists have been the primary agents used for anticoagulation in certain cardiovascular and thromboembolic diseases for over 50 years. However, they can be difficult to administer and are fraught with limitations. In response to the need for new anticoagulants, direct thrombin inhibitors (DTIs) have been developed and investigated for their utility in prophylaxis and treatment of venous thromboembolism (VTE), heparin-induced thrombocytopenia (HIT), acute coronary syndromes (ACS), secondary prevention of coronary events after ACS, and nonvalvular atrial fibrillation. Currently, four parenteral direct inhibitors of thrombin activity are FDA-approved in North America: lepirudin, desirudin, bivalirudin and argatroban. Of the new oral DTIs, dabigatran etexilate is the most studied and promising of these agents. This review discusses the clinical indications and efficacy of these direct thrombin inhibitors as well as future directions in anticoagulant therapy.

Introduction

Thrombin plays a central role in the generation of a thrombus. Once formed, thrombin activates factors V, VIII and XI, which are involved in generating more thrombin, and it also activates factor XIII, a protein involved in fibrin cross-linking and clot stabilization. Thrombin's principal function is to convert soluble fibrinogen to insoluble fibrin, while also stimulating platelet activation. Thrombin can be inhibited directly or indirectly by the binding of thrombin-inhibiting drugs to one or two of its three domains: the active site and exosites 1 and 2. Exosite 1 is the fibrin-binding site of thrombin and exosite 2 serves as the heparin-binding domain [1]. Traditional anticoagulants such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) inhibit free thrombin in an indirect manner by binding simultaneously to antithrombin and exosite 2, thereby forming a heparin-thrombin-antithrombin complex (Figure 1). However, heparins also can simultaneously bind to both fibrin and thrombin and act as a bridge between them, thereby enhancing thrombin's affinity for fibrin and increasing the concentration of thrombin-bound fibrin. This fibrin-heparin-thrombin complex occupies both thrombin exosites but leaves the active site ezymatically protected from inactivation as the heparin-antithrombin complex cannot bind to fibrin-bound thrombin, resulting in further thrombus growth [2, 3]. In addition to its inability to neutralize fibrin-bound thrombin, other limitations of heparin include its binding to various plasma proteins, creating an unpredictable dose-dependent anticoagulant response, need for routine dose-adjustments and anticoagulant monitoring and heparin-induced thrombocytopenia (HIT) [4].

Direct thrombin inhibitors (DTIs) bind directly to thrombin and do not require a cofactor such as antithrombin to exert their effect. DTIs can inhibit both soluble thrombin and fibrin-bound thrombin [4]. Other key advantages include a more predictable anticoagulant effect compared with heparins because of their lack of binding to other plasma proteins [5], an anti-platelet effect [6] and the absence of immune-mediated thrombocytopenia [7].

Both parenteral and oral direct thrombin inhibitors have been investigated for prophylaxis and treatment of venous thromboembolism (VTE), prevention of thromboembolic complications in patients with HIT or at risk for HIT and undergoing percutaneous coronary intervention (PCI), acute coronary syndromes (ACS) with and without percutaneous transluminal coronary angioplasty (PTCA), secondary prevention of coronary events after ACS and nonvalvular atrial fibrillation [8, 9]. Currently, four parenteral DTIs are approved for use as anticoagulants in the United States: lepirudin, desirudin, bivalirudin and
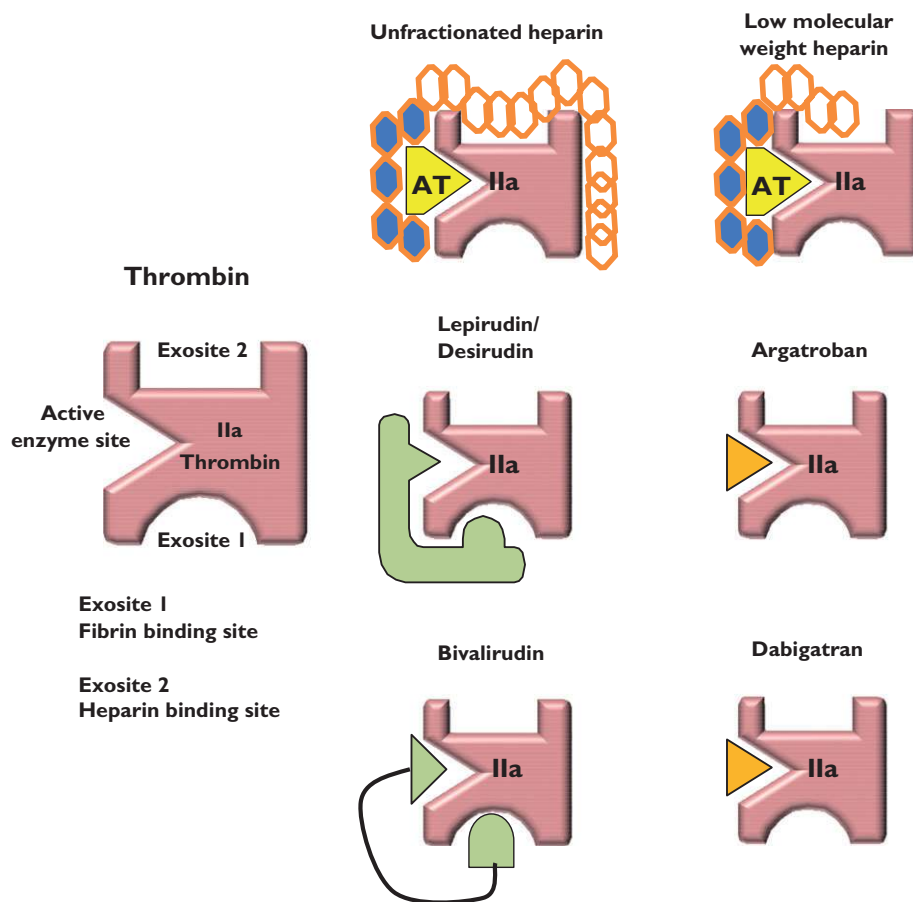
Figure 1

Schematics of the interaction of thrombin with six different anticoagulants. Unfractionated heparin (UFH) – UFH mediates its affect through binding to antithrombin and enhancing its reactivity with the enzymatic site of thrombin. UFH requires an additional 13 saccharides that bind to the heparin binding site to maximize its interaction with thrombin. UFH is thus an indirect, parenteral inhibitor of thrombin. Low molecular weight heparin (LMWH) – LMWH lacks the longer chains of UFH and has less binding to thrombin thus decreasing its ability to neutralize thrombin. LMWH is thus an indirect, parenteral inhibitor of thrombin. Lepirudin/Desirudin – Lepirudin and desirudin bind directly and strongly to both the active enzymatic site and exosite 1 of thrombin to inhibit its activity. Lepirudin and desirudin are direct, parenteral inhibitors of thrombin. Argatroban – Argatroban is a small molecule that binds reversibly to the active enzymatic site of thrombin. Argatroban is a direct, parenteral inhibitor of thrombin. Bivalirudin – Bivalirudin is a modified form of hirudin with four glycine residues connecting two amino acids sequences important for binding to thrombin. It is a more reversible inhibitor of thrombin than is lepirudin, and is a direct, parenteral inhibitor of thrombin. Dabigatran – Dabigatran is a small molecule that binds reversibly to the active enzymatic site of thrombin. Dabigatran is an oral, direct inhibitor of thrombin

agratroban. Their unique pharmacologic and clinical properties are summarized in Table 1. Several oral compounds are currently under investigation, with dabigatran etexilate furthest along in development.

Parenteral direct thrombin inhibitors

Recombinant hirudins: lepirudin and desirudin

Lepirudin and desirudin are derivatives of hirudin, a peptide originally isolated from the salivary glands of medicinal leeches [10] that were developed by recombinant technology in *Saccharomyces cerevisiae* [7]. Both

recombinant hirudins (r-hirudins) are bivalent direct thrombin inhibitors that bind simultaneously to the active site and exosite 1 domain on thrombin, an interaction that increases their specificity for thrombin [7]. They also have the highest affinity for thrombin as they rapidly form essentially irreversible, 1:1 stoichiometric complexes [11]. Compared with hirudin their affinity is 10 times weaker for thrombin, however, they are still considered the most potent of all the thrombin inhibitors [7, 10]. The plasma half-life of the r-hirudins after intravenous (i.v.) injection and subcutaneous (s.c.) administration is 60 and 120 min, respectively [12].

Lepirudin is licensed for the treatment of thrombosis complicating HIT. It is given as an intravenous infusion with

Table 1

Pharmacologic and clinical properties of the parenteral direct thrombin inhibitors

	Lepirudin	Desirudin	Bivalirudin	Argatroban
Indication	Prophylaxis or treatment of thrombosis complicating HIT	DVT prevention after THR	Patients with UA undergoing PTCA; PCI with provisional use of GPI; patients with/at risk of HIT/HITTS undergoing PCI	Prophylaxis or treatment of thrombosis complicating HIT; patients with/at risk of HIT undergoing PCI
Thrombin affinity (K_i)	Highest ($K_i = 0.23$ pM)	Highest ($K_i = 0.26$ pM)	Intermediate ($K_i = 1.9$ nM)	Lowest ($K_i = 5$–38 nM)
Route of administration	Intravenous, subcutaneous	Intravenous, subcutaneous	Intravenous	Intravenous
Dosing	± Bolus of 0.4 mg kg^{-1} followed by 0.15 mg kg^{-1} h^{-1} Monitor with aPTT for target ratio 1.5–2.5	s.c. injection 15 mg twice daily No monitoring necessary	Bolus of 0.75 mg kg^{-1} followed by 1.75 mg kg^{-1} h^{-1} × 4 h Monitor with ACT after 5 min (365 ± 100 s)	No bolus followed by 2 µg kg^{-1} h^{-1} Monitor with aPTT for target ratio 1.5–3.0
Plasma half-life	~80 min	Intravenous, 60 min; s.c., 120 min	~25 min	~45 min
Metabolism	Kidney	Kidney	Proteolysis; liver	Liver
Clearance	Kidney	Kidney	20% excreted via kidney	Liver
Dose reduction	CL$_{CR}$ 15–60 ml min^{-1}: 15–50% CL$_{CR}$ < 15 ml min^{-1}: contraindicated	*CL$_{CR}$ < 60 ml min^{-1}: dose adjustment necessary	CL$_{CR}$ 15–60 ml min^{-1}: 15–50% CL$_{CR}$ < 15 ml min^{-1}: contraindicated	Hepatic failure: 0.5 µg kg^{-1} min^{-1} Severe HF: contraindicated

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CL$_{CR}$, creatinine clearance; DVT, deep venous thrombosis; GPI, glycoprotein inhibitor; HF, hepatic failure; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia with thrombosis syndrome; PCI, percutaneous coronary intervention; PCTA, percutaneous transluminal angioplasty; s.c., subcutaneous; THR, total hip replacement; UA, unstable angina. *Recent data suggest that desirudin may be used without dose adjustments in patients with moderate impairment.

or without a bolus, and its dosing is dependent on body weight. As lepirudin is renally excreted, dose adjustments are required in patients with renal impairment [13]. Significant limitations to the use of lepirudin are its narrow therapeutic window and potential for increased bleeding events [7]. Furthermore, formation of antihirudin antibodies following treatment of HIT in 40% of patients treated with lepirudin has been reported. These immunogenic complexes may delay the renal excretion of lepirudin and cause drug accumulation [14, 15]. Therefore, dose adjustment based on aPTT is required during treatment. Although rare, anaphylaxis can also occur if patients with hirudin-induced antibodies are re-exposed to hirudin [15]. Currently, there is no specific antidote to reverse the effects of the recombinant hirudins or any of the other direct thrombin inhibititors [16].

Desirudin is the only fixed-dose subcutaneously administered DTI approved by the Federal Drug Administration (FDA) for postoperative prevention of VTE in patients undergoing elective hip replacement surgery [17]. In March 2010 it became available in the United States. Two randomized, double-blind, multi-centre clinical studies compared the efficacy and safety of desirudin (15 mg s.c. twice daily injections) with unfractionated heparin (UFH) (5000 units s.c. three times daily) and enoxaparin (40 mg s.c. daily) for the prophylaxis of DVT in patients undergoing major orthopaedic surgeries. Desirudin was superior to both heparin anticoagulants (P < 0.001 for both) after 8–12 days of treatment, while showing a similar safety profile [18, 19]. Desirudin is also currently under investigation as a potential anticoagulant for

patients with HIT with or without thrombosis. The PREVENT-HIT study is a small, randomized, open-label trial comparing the clinical efficacy, safety and economic utility of fixed-dose s.c. desirudin against argatroban [20]. The study is now completed and results will be soon published. Desirudin, like lepirudin has been investigated for its anticoagulant efficacy and prevention of adverse outcomes in patients with acute coronary syndromes with or without percutaneous coronary interventions. Results from both the HELVETICA and GUSTO-IIb trials demonstrated a significant reduction in the incidence of death or MI with desirudin compared with unfractionated heparin, particularly in the most unstable patients [21, 22]. However, desirudin was associated with an increased incidence of major bleeding events.

After s.c. administration, desirudin reaches maximum plasma concentrations after 1–3 h, has a terminal half-life of 2 h and is predominantly (80–90%) renally excreted. Advantages of s.c. desirudin include the lack of weight-based dose calculations and need for routine monitoring. In the setting of severe renal insufficiency (CL$_{CR}$ ≤ 30 ml min^{-1}), dose reduction and monitoring with aPTT are strongly recommended [7, 14]. Results from a recent pharmacokinetics study suggest that dosage adjustments and aPTT monitoring are unnecessary in patients with moderate renal impairment (CL$_{CR}$ 31–60 ml min^{-1}) [23].

Bivalirudin

Bivalirudin is an engineered 20-amino acid, synthetic, bivalent analogue of hirudin with a thrombin inhibition activity nearly 800 times weaker than that of hirudin [24]. Unlike

the recombinant hirudins, the binding of bivalirudin to thrombin is reversible because once bound, it is slowly cleaved by thrombin. As a result, thrombin activity is only transiently inhibited and the enzymatic activity of the thrombin site is restored. This reversible relationship between bivalirudin and thrombin may contribute to its decreased bleeding risk and improved safety profile when compared with r-hirudins [4, 25]. Bivalirudin is given intravenously, has an immediate onset of action with therapeutic activated clotting times (ACT) achieved within 5 min after initiating therapy, and a half-life of 25 min, all characteristics that are favourable for a PCI setting [7, 14]. Bivalirudin is mainly cleared by proteolytic cleavage and hepatic metabolism [26]. However, 20% of the dose is renally eliminated and dose adjustments are necessary in patients with moderate renal insufficiency [27, 28]. Bivalirudin is contraindicated in patients with severe renal impairment [7].

Bivalirudin has been extensively investigated in various clinical trials for its efficacy in reducing death, myocardial infarction (MI) or repeat vascularization in patients with ACS undergoing PCI. Reviews of these studies are available elsewhere [14, 29, 30]. The Bivalirudin Angioplasty Study showed that bivalirudin had a better efficacy in preventing these primary outcomes as well as a lower bleeding rate when compared with UFH in over 4000 patients undergoing PTCA for unstable or post-infarct angina [31]. This led to the 2000 FDA-approval of bivalirudin as an alternative anticoagulant to heparin in patients undergoing PTCAs. In 2005, the FDA expanded its approval of bivalirudin to include provisional use of concomitant glycoprotein IIb/IIIa inhibitors (GPI) for patients undergoing elective or urgent PCI procedures [32]. This decision was based on data from the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) study, which demonstrated a non-inferiority of bivalirudin to UFH (each with provisional GPI) in regards to the combined primary endpoint (mortality, MI, urgent revascularization or severe bleeding), and with significantly less bleeding [33].

Additional studies have evaluated the use of bivalirudin in patients with ST-elevation MI (STEMI) [34], and in HIT patients undergoing PCI or cardiopulmonary bypass surgery [35–37]. Results from the ATBAT trial showed bivalirudin to have a safe and effective anticoagulant effect during PCI procedures in patients with HIT/HITTS [35]. Soon after, the FDA expanded its approval of bivalirudin to include its use as an alternative to heparin in HIT patients with or without thrombosis undergoing PCI.

Argatroban

Argatroban is a small (527 Da), univalent DTI that noncovalently and reversibly binds to the active site on thrombin [7]. Argatroban is licensed in the United States for the prophylaxis or treatment of thrombosis in patients with HIT and for anticoagulation in patients with a history of HIT or at risk of HIT undergoing PCI. It is given as an intravenous infusion with a starting dose of $2\,\mu g\,kg^{-1}\,min^{-1}$ and does not require a bolus injection [13]. Steady-state plasma concentrations are reached in 10 h, and the plasma half-life of argatroban is approximately 45 min. As argatroban is hepatically metabolized and predominantly excreted through the biliary system, dose adjustments are necessary in patients with hepatic but not renal impairment. The aPTT and ACT can be used to monitor its effect; dosing is titrated to maintain an aPTT of 1.5–3 times that of baseline. Argatroban prolongs thrombin-dependent coagulation tests and thus prolongs the prothrombin time (PT) and INR. When used together with warfarin, the INR is prolonged greater than that of warfarin alone. Separate dosing and monitoring guidelines should be followed. Argatroban therapy can be discontinued when the INR during concomitant use of warfarin and argatroban is greater than 4 [7, 14].

Oral direct thrombin inhibitors

Oral IIa inhibitors represent a new era of anticoagulation for the prevention and treatment of venous and selected arterial thromboembolisms. Ximelagatran is the oral double prodrug of melagatran and was the first oral direct thrombin inhibitor developed. Studies demonstrated it to be as effective as the traditional anticoagulants in the prevention and treatment of venous and arterial thromboses and secondary prevention of cardiovascular events post MI. The approval of ximelagatran in Europe for prevention of venous thromboembolism in major elective orthopaedic surgeries marked a milestone in the advancement of oral anticoagulants as it had been almost 60 years prior since the introduction of oral vitamin K antagonists. However, ximelagatran was removed from the European market approximately 20 months later and was never approved in North America after studies showed that therapy greater than 35 days was associated with a risk of hepatotoxicity [38].

Like ximelagatran, dabigatran etexilate is an orally active double prodrug that is rapidly converted to dabigatran, a low-molecular weight molecule that acts as a specific, potent and reversible direct thrombin inhibitor. It is currently the most studied and promising of the oral direct thrombin inhibitors. Key clinical advantages of this drug include a rapid onset of action, lack of interaction with cytochrome P450 enzymes or with other food and drugs, excellent safety profile, lack of need for routine monitoring, broad therapeutic window and a fixed-dose administration.

The efficacy and safety of dabigatran etexilate against current standard anticoagulant therapy have been evaluated for multiple indications such as primary VTE prevention after hip and knee surgeries, treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and their secondary prevention, prevention of stroke and

systemic embolism in patients with non-valvular atrial fibrillation (AF) and secondary prevention of cardiac events in patients with ACS (Table 2). Unlike ximelagatran, long-term use of dabigatran has not been associated with liver toxicity. Dabigatran etexilate was approved in Canada and Europe in 2008 for the prevention of venous thromboembolism after elective total hip replacement and/or total knee replacement. In October 2010, the US FDA advisory committee approved dabigatran etexilate for stroke prevention in patients with AF.

Metabolism, pharmacokinetics and pharmacodynamics of oral DTIs

Dabigatran etexilate and dabigatran

Dabigatran is a small (472 Da) peptidomimetic that directly inhibits thrombin by binding to its active site via ionic interactions. Dabigatran was synthesized as a derivative of the peptide-like, benzamidine-based thrombin inhibitor AA-[alpha]-naphthylsulphonylglycyl-4-amidinophenylalanine piperidine ([alpha]-NAPAP). It rapidly and reversibly inhibits both clot-bound and free thrombin in a concentration dependent manner with an inhibition constant (K_i) of 4.5 nmol l^{-1}. It also exhibits high specificity for thrombin over other serine proteases. As a highly polar and charged molecule, dabigatran has poor intestinal absorption and no bioavailability after oral absorption. The conversion of the carboxylate group of dabigatran into an ester group and the masking of the amidinium moiety as a carbamate ester led to the development of dabigatran etexilate, a highly lipophilic and gastrointestinally absorbed double prodrug. After oral administration, dabigatran etexilate is rapidly converted to active dabigatran, via two intermediates (BIBR 951 and BIBR 1087) after cleavage of both lipophilic groups by serine esterases (39) (Figure 2).

The absolute bioavailability of dabigatran after oral absorption is low (6–7%) and is independent of the dose of the prodrug [39]. As dose-escalation studies have shown that dabigatran plasma concentrations increase in a dose-proportional manner [40], relatively high doses of dabigatran etexilate are necessary to achieve adequate plasma concentrations. Dabigatran etexilate is also optimally and more consistently absorbed in an acidic environment. To achieve this goal, a new capsule formulation containing multiple small pellets containing a tartaric acid core and coated with dabigatran etexilate was developed. The advantage of this modification is that dabigatran etexilate brings its optimal pH environment to the site of absorption (i.e. gastrointestinal tract). Therefore, variations in intrinsic gastric pH do not significantly affect the extent of its absorption, even in the presence of proton pump inhibitors [41]. Another significant characteristic of this prodrug is the lack of involvement by the P450 (CYP) isoenzymes or other oxidoreductases in the metabolism of dabigatran

etexilate to dabigatran. Rather, ubiquitous esterases present in plasma are involved in the conversion. As in vitro studies also show that dabigatran does not inhibit the cytochrome P450 enzymes, the potential for drug–drug interactions is low [39].

After absorption of dabigatran etexilate, bioconversion to dabigatran occurs in enterocytes, hepatocytes and the portal vein. Twenty percent of dabigatran is conjugated to glucuronic acid to yield pharmacologically activated glucuronide conjugates [41]. Once metabolized to dabigatran, the prodrug and its intermediate metabolites, BIBR 951 and BIBR 1087, are trace detectable (~0.5 ng ml^{-1}) in the plasma of healthy subjects for approximately 2 h after ingestion [42]. Of note, the absorption and metabolism of dabigatran etexilate has also been tested in patients with moderate hepatic impairment. Although the bioconversion rate of dabigatran etexilate to its active form was slightly slower than that in matched healthy control subjects, the mean values for the area under the plasma concentration–time curves (AUCs), terminal half-life and renal clearance were comparable between the two groups. In addition, results from several clot-based assays were also similar between the healthy controls and patients with hepatic insufficiency [43]. These findings demonstrate that moderate hepatic impairment does not affect the efficacy or safety profile of dabigatran, and that these patients can be given unadjusted doses of dabigatran etexilate.

Renal excretion is the primary elimination pathway for dabigatran in humans. The remainder undergoes conjugation with glucuronic acid to form acylglucuronides, which are excreted via the bile. Both the bioavailability and extent of exposure to dabigatran are elevated in renal insufficiency ($CL_{CR} < 50$ ml min^{-1}) and appropriate dose-reduction of dabigatran etexilate is required. Although dabigatran is dialyzable, it is contraindicated in patients with severe renal impairment ($CL_{CR} < 30$ ml min^{-1}) [42].

The key pharmacokinetics and pharmacodynamics properties of dabigatran etexilate are summarized in Table 3. After oral administration of the prodrug, dabigatran etexilate is rapidly converted to dabigatran, with peak plasma concentrations (C_{max}) achieved within 1.5–2 h in healthy volunteers regardless of age or gender [39, 42, 44]. After absorption, a rapid distribution phase occurs followed by a prolonged elimination time. The volume of distribution of dabigatran is 60–70 l, indicating moderate volume distribution [42]. The mean plasma terminal half-life of dabigatran in healthy young and elderly volunteers is 12–14 h, independent of dose, and accordingly steady-state concentrations are attained within 3 days with multiple dosing and without evidence of significant accumulation [40, 45]. The overall exposure is increased by 40–60% in healthy elderly volunteers compared with younger subjects primarily secondary to reduced renal clearance and slower elimination of dabigatran [45]. Food can prolong the time to peak plasma dabigatran concentrations by 2 h without having an effect on its extent of

Table 2
Completed phase III clinical trials of dabigatran etexilate

Study	Target population	Dabigatran etexilate regimen	Comparator regimen	1° outcome measure	1° outcome measure results (%)	Analysis	Major bleeding (%)
RE-MODEL [54]	VTE prevention after TKR	150 mg or 220 mg once-daily (starting with a half-dose 1–4 h post-op) for 6–10 days	Enoxapain 40 mg qd (starting the evening before surgery) for 6–10 days	Total VTE and all-cause mortality	Dabigatran (150 mg), 40.5% Dabigatran (220 mg), 36.4% Enoxaparin, 37.7%	Both doses of dabigatran etexilate are non-inferior to enoxaparin	Dabigatran (150 mg), 1.3% Dabigatran (220 mg), 1.5% Enoxaparin, 1.3%
RE-NOVATE [55]	VTE prevention after THR	150 or 220 mg once-daily (starting with a half-dose 1–4 h post-op) 28–35 days	Enoxaparin 40 mg once-daily pre-op for 28–35 days	Total VTE and all-cause mortality	Dabigatran (150 mg), 8.6% Dabigatran (220 mg), 6% Enoxaparin, 6.7%	Both doses of dabigatran etexilate are non-inferior to enoxaparin	Dabigatran (150 mg), 1.3% Dabigatran (220 mg), 2% Enoxaparin, 1.6%
RE-MOBILIZE [56]	VTE prevention after TKR	150 or 220 mg once-daily (starting with a half-dose 6–12 h post-op) for 12–15 days	Enoxaparin 30 mg twice-daily starting post-op for 12–15 days	Total VTE and all-cause mortality	Dabigatran (150 mg), 33.7% Dabigatran (220 mg), 31.1% Enoxaparin, 25.3%	Both dabigatran etexilate doses are inferior to enoxaparin	Dabigatran (150 mg), 0.6% Dabigatran (220 mg), 0.6% Enoxaparin, 1.4%
RE-NOVATE II [57]	VTE prevention after THR	220 mg once-daily (starting with a half-dose 1–4 h post-op) 28–35 days	Enoxaparin 40 mg once-daily pre-op for 28–35 days	Total VTE and all-cause mortality	Dabigatran, 2.2% Enoxaparin, 4.2%	Dabigatran etexilate is non-inferior to enoxaparin	Dabigatran, 1.4% Enoxaparin, 0.9%
RE-COVER [58]	Treatment in acute VTE	150 mg twice-daily (starting after 8–11 days of parenteral therapy) for 6 months	Warfarin (dose adjusted for INR 2.0–3.0) after 8–11 days of initial parenteral anticoagulation	Recurrent VTE and related deaths	Dabigatran, 2.4% Warfarin, 2.1%	Dabigatran etexilate is non-inferior to warfarin	Dabigatran, 16.1% Warfarin, 21.9%
RE-LY [60]	Prevention of stoke in non-valvular atrial-fibrillation	110 mg or 150 mg twice daily for 2 years	Warfarin (dose adjusted for INR 2.0–3.0) for 2 years	Stroke and systemic embolism	Dabigatran (110 mg), 1.54%/year Dabigatran (150 mg), 1.11%/year Warfarin, 1.71%/year	Both doses of dabigatran etexilate are non-inferior to warfarin	Dabigatran (110 mg), 2.87%/year Dabigatran (150 mg), 3.32%/year Warfarin, 3.57%/year

Other phase III trials currently evaluating dabigatran etexilate include: RE-COVER II (acute VTE treatment); RE-MEDY and RE-SONATE (secondary prevention of VTE); RE-LYABLE (stroke prevention in atrial fibrillation). A phase II trial currently evaluating dabigatran etexilate in the secondary prevention of cardiac events in ACS is RE-DEEM (completed in October 2009). (VTE: Venous thromboembolism – includes deep vein thrombosis and pulmonary embolism; TKR: total knee replacement; THR: total hip replacement; pre-op: pre-operatively; post-op: post-operatively).
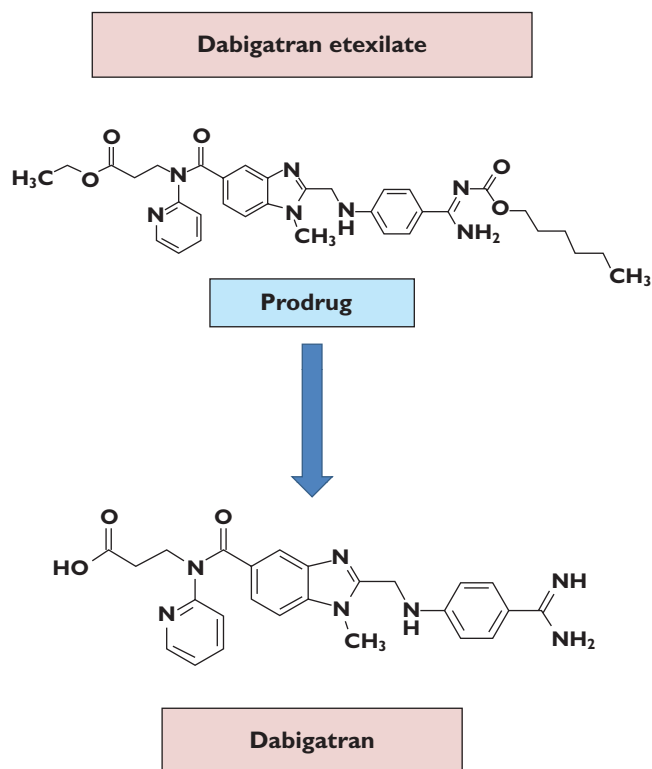
Figure 2

Chemical structures of the double prodrug, dabigatran etexilate and its active form, dabigatran

Table 3

Main characteristics of dabigatran etexilate

Pharmacology	
Route of administration	Oral
Inhibitor type	Selective, reversible DTI (K_i = 4.5 nM L^{-1})
Molecular Weight	628 Da (prodrug); 472 Da (active)
Prodrug	Double prodrug converted to active form via two intermediates
Absorption & Metabolism	
Oral bioavailability	6–7% (decreased by PPI by 20–25%)
Involvement of CYP450	No
Food Effect	Delayed absorption
Plasma protein binding	35%
Metabolism	Occurs in hepatocytes and enterocytes; 20% metabolized to yield activated glucuronide conjugates
Elimination	Biliary 20%; Renally 80%
Pharmacokinetics	
Pharmacokinetic profile	Linear
T_{max} (hr)	1–3
Half-life (hr)	12–14
Clinical considerations	
Approved indications	VTE prophylaxis after hip- or knee-replacement surgery (EU and Canada)
Dosage	150 or 220 mg once daily (VTE prophylaxis)
Dose reduction	Moderate renal impairment (CrCl < 50 ml min^{-1}); contraindicated when CrCl < 30 ml min^{-1})
Monitoring	Not needed
Potential drug interactions	Quinidine, verapamil, amiodarone, rifampicin, St. John's wort, strong P-glycoprotein inhibitors

DTI, direct thrombin inhibitor; CrCl, creatinine clearance; EU, European Union; PPI, proton pump inhibitor; VTE, venous thromboembolism.

absorption (AUC) [44]. However the pharmacokinetic profile of dabigatran is not affected by the use of co-medications, such as opioids [44], diclofenac [46], atorvastatin [47] or digoxin [9, 41]. A reduced dose of dabigatran etexilate is recommended when co-administered with amiodarone or other strong P-glycoprotein (P-gp) inhibitors like verapamil, clarithromycin and others. Dabigatran is contraindicated with quinidine use. Other potent P-gp inducers such as rifampicin or St John's wort may reduce the systemic exposure of dabigatran [48, 49].

Prolongation of blood coagulation parameters (aPTT, PT, TT, ECT) occurs in parallel with increasing concentrations of dabigatran, and peak clotting times coincide with the C_{max} of dabigatran (2 h after oral administration). Similarly, 12 h after oral administration of dabigatran (time of first half-life), the prolongation of blood coagulation returned to 50% of the maximum effect [40, 42]. The thrombin time (TT) is most responsive to dabigatran in the clinically relevant plasma concentration range whereas the aPTT and prothrombin time (PT) are least so. The ECT assay may be the most useful test for measuring thrombin inhibition as it has been reported as having adequate sensitivity and precision with predictable and reproducible results [41, 50]. Currently under development is a diluted thrombin time assay (Hemoclot® Thrombin Inhibitor Assay),

which uses dabigatran standards for quantitative measurement of DTI activity in plasma. A direct relationship between dabigatran concentration and clotting time (from 30–75 s) has been reported [50].

Clinical efficacy of dabigatran etexilate

Prevention of venous thromboembolism after hip or knee replacement surgery

The efficacy and safety of dabigatran for prevention of VTE in elective major orthopaedic surgeries was first demonstrated in the Boehringer Ingelheim Study in ThROmbosis (BISTRO) phase II trials [44, 51, 52]. The principle results from this set of studies showed that increasing doses of dabigatran etexilate decreased total VTE in a dose-dependent manner, and the incidence of major VTE (proximal DVT and/or PE) was lower in groups with any dose of dabigatran etexilate (1.7%–5.0%) compared with enoxaparin (5.6%). Although the incidence of major bleeding events was significantly lower with 50 mg twice daily of dabigatran etexilate when compared with enoxaparin (0.3

vs. 2.0%, *P* = 0.047), this increased at the higher, more effective doses (3.8–4.7%). The efficacy and safety profile between once daily and twice daily dosing of dabigatran etexilate (same total daily dose) was comparable. Further pharmacokinetic and pharmacodynamic studies on patients enrolled in BISTRO II supported an optimal efficacy-safety dosing regimen for phase III trials, consisting of once daily doses of 150 mg or 220 mg, with half doses of 75 mg and 110 mg given on the day of surgery [52].

Pooled analysis of the results from the completed RE-MOBLIZE, RE-MODEL and RE-NOVATE phase III trials, which involved a combined total of 8 210 patients, concluded that dabigatran etexilate is as efficacious and safe as enoxaparin in the prevention of VTE after hip or knee arthroplasty [53]. Two different doses of dabigatran etexilate, 150 mg or 220 mg once daily with half doses, 75 mg or 110 mg, on the first day were examined and compared against the approved enoxparin regimen for the respective region in all three trials. RE-MODEL and RE-NOVATE, both performed in the European Union and other non-North American countries, found both doses of dabigatran non-inferior to enoxaparin (40 mg, 12 h presurgery). Rates of total VTE and all-cause mortality were 36.4% (*P* < 0.0003) and 40.5% (*P* < 0.017) for doses of 220 mg and 150 mg, respectively, *vs.* 37.7% for enoxaparin in RE-MODEL [54]. Similar findings were observed in RE-NOVATE [6.0% (*P* < 0.0001), 8.6% (*P* < 0.0001), and 6.7% in dabigatran 220 mg, 110 mg, and enoxaparin 40 mg daily, respectively,] [55]. In both studies, rates of major bleeding events were similar across all treatment groups. Data from these two trials led to the approval of use of dabigatran etexilate for the primary prevention of VTE after total knee or hip replacement in the EU. However, results from RE-MOBILIZE failed to show non-inferiority of dabigatran (started 6–12 h after surgery) to enoxaparin (30 mg twice daily started 12–24 h post surgery). Total VTE and all-cause mortality rates were significantly higher in the dabigatran 220 mg (31.1%, *P* = 0.02) and 150 mg (33.7%, *P* < 0.001) groups compared with enoxaparin (25.3%) [56]. Rates of major bleeding were not significantly different between both dabigatran groups and enoxaparin group. The failure to achieve non-inferiority is likely secondary to the delay in the administration of dabigatran etexilate after surgery as well as the higher dosing of enoxaparin [56]. In response to these results, a fourth phase III trial, RE-NOVATE II, was initiated and recently completed. This double-blind, non-inferiority trial examined 2055 patients in North America with a goal to evaluate the efficacy of dabigatran 220 mg once daily *vs.* enoxaparin 40 mg once daily over a course of 28–35 days for VTE prevention post-hip replacement surgery. Dabigatran was found to be at least as effective as enoxaparin in preventing total VTE and all-cause mortality (7.7% *vs.* 8.8%, *P* < 0.0001) and also associated with significantly lower rates of VTE-related death (2.2% *vs.* 4.2%, *P* < 0.03). The rates of major bleeding were not significantly different from

each other [57]. These results, in addition to the results from RE-NOVATE confirm that once daily dosing of dabigatran is as efficacious and safe as enoxaparin in preventing VTE after total hip replacement surgery.

Treatment and secondary prevention of venous thromboembolism

The RE-COVER trial demonstrated that 150 mg twice daily dabigatran etexilate had a similar efficacy and safety profile as warfarin (adjusted for INR 2–3) in the treatment of acute symptomatic venous thromboembolism. Patients (*n* = 2539) with acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism were randomized to receive 6 months of either oral dabigatran etexilate 150 mg twice daily or warfarin (adjusted for INR 2–3) after initial parenteral anticoagulation therapy (median = 9 days). The primary endpoint of either recurrent venous thromboembolism or fatal pulmonary embolism during the treatment period occurred in 2.4% of patients treated with dabigatran compared with 2.1% of patients receiving warfarin. Rates of major bleeding with dabigatran were similar to warfarin (1.6% *vs.* 1.9%, respectively). However a significant decrease in any bleeding events was observed for dabigatran when compared with warfarin (16.1% *vs.* 21.9%, hazard ratio of 0.71, 95% CI 0.59, 0.85, *P* < 0.001) [58]. A second trial comparing dabigatran etexilate with warfarin in the treatment of acute VTE is underway (RE-COVER II). As well, two trials (RE-MEDY and RE-SONATE) are currently ongoing to evaluate dabigatran etexilate against warfarin in the secondary prevention of venous thromboembolism.

Prevention of stroke in non-valvular atrial fibrillation

Results from the double-blind, dose-escalating phase II trials PETRO and PETRO-Ex showed that a dose of 150 mg twice daily was as effective and safe as warfarin in the prevention of thromboembolic events in patients with non-valvular atrial fibrillation [59]. More recently, results from the phase III trial RE-LY demonstrated that the rate (percent per year) of the primary outcome (stroke or systemic embolism) was significantly lower with dabigatran etexilate 150 mg twice daily (1.11%) and non-inferior with 110 mg twice daily (1.54%) compared with warfarin (1.71%) in patients with AF and at least one additional risk factor for stroke (CHADS$_2$ score $\geq$ 1). The rates of haemorrhagic stroke were significantly lower with 150 mg (0.10%, *P* < 0.001) and 110 mg (0.12%, *P* < 0.001) twice daily doses of dabigatran etexilate *vs.* warfarin (0.38%). The rate of major bleeding was significantly higher in the group receiving warfarin (3.57%) compared with those receiving the lower dose of dabigatran (2.87% for 110 mg twice daily) and was non-inferior to those receiving the higher dose (3.32% for 150 mg twice daily). The study concluded that when compared with adjusted-dose warfarin, 110 mg twice daily dabigatran was associated with a similar rate of

stroke but less risk of major bleeding, while a dose of 150 mg twice daily prevented more strokes but had a similar rate of major haemorrhage [60]. A long-term study, RELY-ABLE, is currently underway to evaluate the safety profile of dabigatran in these patients. These findings also suggest the potential ability to choose appropriately the dose of dabigatran depending on the patient's risk profile for stroke and bleeding.

Prospective indications for dabigatran etexilate

Secondary prevention of coronary events after acute coronary syndrome

The placebo-controlled, dose-finding phase II trial, RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel (RE-DEEM), was completed in October 2009. Over 1800 patients with an acute ST-segment elevation or non ST-segment elevation MI and at least one risk factor for a new ischaemic cardiovascular event were randomized to receive either placebo or one of four doses of dabigatran etexilate ranging from 50 to 150 mg twice daily in conjunction with standard dual antiplatelet therapy. The primary aim of the study was to evaluate the safety of dabigatran as measured by the composite of major and clinically relevant minor bleeding events during 6 months of treatment. Although a dose-dependent increase in bleeding complications was observed, the 6 month rates of major bleeding did not exceed 2% ($P < 0.001$). Deemed as safe to use in patients after an acute coronary syndrome, the investigators supported dabigatran doses of 110 mg or 150 mg twice daily for future large-scale studies [61].

Prevention of thrombosis in elective percutaneous coronary intervention (PCI)

A randomized, open-label phase II trial (ClinicalTrials.gov Identifier: NCT00818753) comparing dabigatran 110 and 150 mg twice daily to unfractionated heparin, both in addition to standard dual antiplatelet regimen, in providing sufficient anticoagulation during cardiac catheterization was completed in September 2010. The efficacy of the anticoagulant effect of dabigatran was based on the number of patients who required rescue anticoagulant during the PCI as well as the number of patients who displayed signs of catheter-related thrombosis during the procedure. The incidence of major bleeding occurring up to 3 days after the PCI was also evaluated. Results from this study have not yet been published.

Prevention of thrombus formation on mechanical heart valves

Patients who receive an artificial heart valve require life long oral anticoagulation for the prevention of throm-

boembolic events. As RE-LY showed dabigatran to be as effective, if not superior in preventing stroke in patients with AF and with less risk of major bleeding, investigation into whether dabigatran may serve as an alternative anticoagulant to heparin or LWMH in thromboprophylaxis and stroke prevention in patients with a mechanical heart valve has commenced. The efficacy of dabigatran compared with enoxaparin in the prevention of valve thrombus was studied in swine implanted with a mechanical aortic valve. Data revealed that dabigatran was as effective as enoxaparin for short-term thromboprophylaxis of mechanical valves as it best prevented valve thrombus and platelet deposition at 30 days without increased adverse events [62]. Another *in vitro* study compared thrombus formation on mechanical heart valve prostheses exposed to blood anticoagulated with dabigatran *vs.* unfractionated heparin or LMWH. The mean thrombus weight was comparable between each group and electron microscopy did not reveal any significant difference in thrombus formation [63]. Results from these early preclinical studies should encourage further investigation into the efficacy and safety of dabigatran for prevention of thrombus formation and stroke in patients with mechanical heart valves.

Potential oral IIa inhibitors

In addition to dabigatran etexilate, other novel direct thrombin inhibitors are currently being evaluated in phase I, II and III studies for the prevention of venous thromboembolism. The most investigated potential DTI is AZD0837 (AstraZeneca), a prodrug that is rapidly converted to its active form, H067637 via the intermediate H069927, and which has been reported to have superior pharmacologic properties compared with ximelegatran without its associated toxicities. It has an oral bioavailability of 22%–55% and a time to C_{max} of 0.7–1.5 h after oral administration. The half-life of H067637 is 9 h after a single dose. However the development of an extended release formulation allows once daily administration [64]. A multi-centre, randomized, parallel, dose-guiding phase II study compared the efficacy and safety of 150 or 250 mg twice daily doses of AZD0837 with warfarin (adjusted for goal INR 2–3) in the prevention of systemic embolism and stroke in patients with atrial fibrillation. AZD0837 at a dose of 150 mg twice daily had a similar efficacy and tolerability profile to warfarin [64]. Gastrointestinal side effects were noted at increasing doses of AZD0837. AZD0837 has now entered a large phase III warfarin-controlled trial to determine its efficacy and safety for stroke prevention in atrial fibrillation.

Conclusions

In response to the limitations of heparins and vitamin K antagonists, research has focused on the development and

utilization of direct thrombin inhibitors for the prevention and treatment of venous and selected arterial thromboembolism, heparin-induced thrombocytopenia, and acute coronary syndromes with and without PCI. These newer anticoagulants offer several advantages over the traditional agents: direct inhibition of free and clot-bound thrombin, lack of required co-factors, a more predictable anticoagulant response, inhibition of thrombin-induced platelet aggregation and absence of immune-mediated thrombocytopenia. Currently, four parenteral DTIs are available in the United States, each licensed for a specific indication.

In the last decade there has been a strong drive to understand and investigate the use of oral direct thrombin inhibitors. Dabigatran etexilate is currently the most promising of the oral DTIs and offers various advantages, such as oral administration, predictable and reliable pharmacokinetic and pharmacodynamic profile, lack of interaction with cytochrome P450 enzymes or with other food and drugs, rapid onset of action, excellent safety profile, lack of need for routine monitoring, broad therapeutic window and fixed-dose administration, all qualities that make it an ideal anticoagulant. However, like all other anticoagulants, dabigatran etexilate carries a risk of bleeding. Currently, there is no established specific antidote to reverse its anticoagulant effect. Supportive strategies such as discontinuation of dabigatran etexilate, surgical haemostasis and transfusion of blood products are first line therapies to control severe bleeding. In the event of a potential overdose with dabigatran, early administration of activated charcoal or haemodialysis may be considered. Clotting agents such as recombinant activated factor VIIa and prothrombin complex concentrates are also being investigated as potential therapies for the rapid reversal of dabigatran's anticoagulant effect in severe or life-threatening bleeding [50].

Dabigatran etexilate has recently been FDA-approved and made available for stroke prevention in patients with atrial fibrillation, an action that will offer patients and clinicians the first new treatment option for this indication in more than 50 years. We look forward to seeing its impact on medical care and its potential to finally fulfill the unmet needs of anticoagulation therapy for the prevention and treatment of thromboembolic diseases.

Competing Interests

Dr Ansell has consulted for Boehringer Ingelheim, Ortho McNeil, Bristol Myers Squibb, and Daiichi.

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