

Chapter 2

Direct Thrombin Inhibitors

Anticoagulation can be achieved by inhibition of the various coagulation factors. Non-VKA oral anticoagulant (NOAC) development has focused on the synthesis of selective inhibitors of coagulation factors, preferably acting independently of cofactors. The NOACs act on a number of targets in the coagulation cascade, but two of its key factors, Xa and IIa (thrombin), are the major therapeutic targets. As they are involved in the final steps of the coagulation cascade, their inhibition allows blocking of both intrinsic and extrinsic coagulation pathways.

As the serine protease thrombin is the final mediator in the coagulation cascade that leads to the production of fibrin, is the main protein component of blood clots [1], and is also a potent activator of platelets, it has been a popular target for the development of novel anticoagulants [2]. Several direct thrombin inhibitors (DTIs) have been approved for clinical use in the prevention of thrombosis, for example desirudin. However, those agents that still require parenteral administration are not suitable for, chronic use, and the need for development of efficient, safe, convenient, and predictable oral anticoagulants led to development of oral agents.

2.1 Historical Excursus: Ximelagatran

Ximelagatran, a prodrug of melagatran, was the first oral DTI used in clinical trials from 1999. Its reproducible pharmacokinetic characteristics, rapid onset of action and relatively few interactions with food and other drugs raised hopes that it would allow effective oral anticoagulation without the need for regular INR monitoring. Advanced phase III clinical trials proved ximelagatran to be a potent anticoagulant with ability to prevent venous thromboembolism (VTE) at least as efficiently as injections of the low-molecular-weight heparin (LMWH) enoxaparin followed by administration of warfarin [3]. Ximelagatran was also found to be safe in terms of risk of hemorrhage. However, the randomized, double-blind Thrombin Inhibitor in Venous Thromboembolism Treatment (THRIVE) trial and further studies revealed that treatment with ximelagatran carried substantial risk of hepatotoxicity [4].

On the basis of health concerns ximelagatran did not receive Food and Drug Administration (FDA) approval and it was subsequently withdrawn by AstraZeneca following the EXTEND study because of fear of liver toxicity [5]. The EXTEND study was terminated due to a case of severe acute liver injury just 3 weeks after completion of the 35-day course of treatment. Even though ximelagatran has been discontinued, it is very important for practitioners to know this information since safety issues of NOACs are still a major concern.

2.2 Dabigatran Etxilate

Dabigatran is a potent nonpeptide DTI but it is not orally active and so its physicochemical characteristics were modified to produce a prodrug, dabigatran etexilate (Fig. 2.1). This differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxycarbonyl side chain at the amidine, and it has strong and long-lasting anticoagulant effects after oral

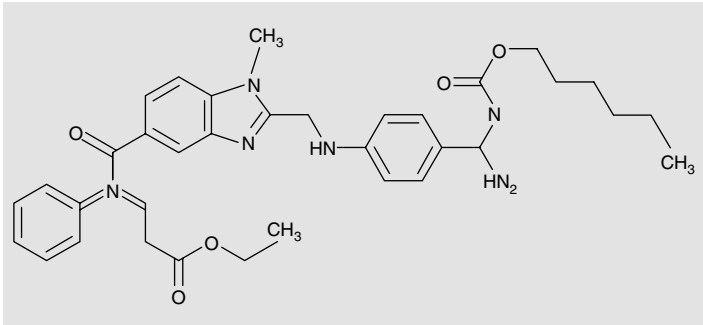


FIGURE 2.1 Dabigatran etexilate

administration [6]. Dabigatran etexilate possesses a number of qualities that make it an attractive anticoagulant. It has rapid absorption (onset of action within 2 h) and its half-life is approximately 8 h after single-dose administration and up to 14–17 h after multiple doses (Table 2.1) [7].

Dabigatran etexilate is a double prodrug that is converted by esterases into its active metabolite, dabigatran, once it has been absorbed from the gastrointestinal tract. As bioconversion of dabigatran etexilate to dabigatran begins in the gut, the drug enters the portal vein as a combination of prodrug and active compound.

The cytochrome P450 system plays no part in the metabolism of dabigatran etexilate; therefore, the risk of drug interactions is low. Because the bioavailability of dabigatran etexilate is only 6.5 %, relatively high doses of the drug must be given to ensure that adequate plasma concentrations are achieved [8]. The absorption of dabigatran etexilate in the stomach and small intestine is dependent on an acid environment. To promote such a microenvironment, dabigatran etexilate is provided in tartaric acid-containing capsules. Absorption is reduced by 20–25 % if patients are concurrently on proton pump inhibitors [14]. Once it reaches the liver, bioconversion of the prodrug is completed, and approximately 20 % is conjugated and excreted via the biliary system. Approximately 80 % of circulated dabigatran is

TABLE 2.1 Properties of dabigatran etexilate, rivaroxaban, apixaban, and edoxaban

	Dabigatran etexilate [8]	Rivaroxaban [8]	Apixaban [8]	Edoxaban [9-13]
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Bioavailability (%)	6.5	>80	>50	~62
Time to peak level (h)	2-3	2-4	3	1-2
Half-life (h)	14-17	9	9-14	10-14
Renal excretion (%)	80	33 (67 % by liver)	25 (~70 % in feces)	35 % (65 % in urine and feces)
Dosing	Once or twice daily	Once or twice daily	Twice daily	Once daily
Drug interactions	Potent P-glycoprotein inhibitors	Potent CYP3A4 and P-glycoprotein inhibitors	Potent CYP3A4 and P-glycoprotein inhibitors	Potent P-glycoprotein inhibitors
Antidote	No	No	No	No

Data from [8-13]

excreted unchanged via the kidneys. Consequently, plasma concentrations increase in patients with renal insufficiency. It is contraindicated in patients with severe renal failure.

It is noteworthy that dabigatran etxilate has no known interactions with food, as well as having a low potential for drug interactions [2]. Accumulated evidence from completed and ongoing trials confirms the hepatic safety of the drug [15].

Dabigatran etxilate has been evaluated in a number of phase II and phase III studies in several disorders (Table 2.2).

2.2.1 Venous Thromboembolism Prevention in Major Orthopedic Surgery

Clinical evaluation of dabigatran etxilate started in the setting of major joint surgery. In the multicenter, open-label, phase II BISTRO I trial [16], 314 patients undergoing total hip replacement (THR) were assigned to receive different doses of dabigatran etxilate (12.5, 25, 50, 100, 150, 200, or 300 mg twice daily (bid), or 150 or 300 mg qd) administered 4–8 h after surgery for 6–10 days. No major hemorrhages were observed in any group. However, non-major multiple-site hemorrhage was observed in two patients with reduced renal clearance treated with the highest dose (300 mg bid). The overall incidence of deep vein thrombosis (DVT) was 12.4 %, without a consistent relationship between incidence and dose. The lowest dose (12.5 mg bid) showed a high rate of proximal DVT (12.5 %).

In the subsequent phase II BISTRO II trial [17] the 1973 patients undergoing THR or total knee replacement (TKR) were randomized to 6–10 days of dabigatran etxilate (50, 150, or 225 mg bid, or 300 mg qd) starting 1–4 h after surgery, or enoxaparin (40 mg qd) starting 12 h prior to surgery. VTE occurred in 28.5, 17.4, 13.1, 16.6, and 24 % of patients assigned to dabigatran etxilate 50, 150, 225 mg bid, 300 mg qd, and enoxaparin, respectively. Compared with enoxaparin, VTE was significantly lower in patients receiving 150 or 225 mg bid or 300 mg qd, and major hemorrhage was significantly lower

TABLE 2.2 Clinical development program for dabigatran etexilate

Clinical condition	Trial	Comparator (n)
VTE prevention in major joint surgery	Phase II	
	BISTRO I [16]	No comparator (314)
	BISTRO II [17]	Enoxaparin (1973)
	Phase III	
	RE-MODEL [18]	Enoxaparin (2076)
	RE-NOVATE [19]	Enoxaparin (3494)
	RE-MOBILZE [20]	Enoxaparin (1896)
	RE-NOVATE II [21]	Enoxaparin (1920)
VTE treatment	Phase III	
	RE-COVER [22]	Parenteral anticoagulant/warfarin (2564)
	RE-COVER II [23]	Parenteral anticoagulant/warfarin (2589)
	RE-SONATE [24]	Placebo (1353)
	RE-MEDY [24]	Warfarin (2866)
Stroke prevention in atrial fibrillation	Phase II	
	PETRO [25]	Aspirin or warfarin (502)
	Phase III	
	RE-LY [26]	Warfarin (18,000)
	RELY-ABLE [27]	Placebo (5851)
Acute coronary syndrome	RE-DEEM [28]	Placebo (1878)
Percutaneous coronary intervention	D-fine [29]	Heparin (50)

Data from [16–29]

VTE venous thromboembolism

with 50 mg bid but elevated with higher doses, nearly achieving statistical significance with the 300 mg qd dose ($P=0.051$). Together, the BISTRO I and BISTRO II trials showed that dabigatran etxilate might be an effective and safe anticoagulant and served as a basis for dose justification in phase III trials.

The clinical utility of dabigatran etxilate for the prevention of VTE in patients after major joint surgery was confirmed in three large randomized, double-blind, multicenter trials (Table 2.3) [18–21]. The RE-MODEL trial [18] compared dabigatran etxilate (150 mg or 220 mg qd, starting with a half-dose 1–4 h after TKR) and enoxaparin (40 mg qd starting the evening before surgery in 2076 patients). The treatment continued for 6–10 days and patients were followed up for 3 months. The primary efficacy outcome of a composite of total VTE (venographic or symptomatic) and mortality during treatment occurred in 37.7 % of patients in the enoxaparin group, 36.4 % of the dabigatran etxilate 220 mg group and 40.5 % of the 150 mg dabigatran etxilate group. Both dabigatran etxilate doses proved to be non-inferior to enoxaparin. The incidence of major hemorrhage also did not differ significantly across the three groups (1.3 %, 1.5 %, and 1.3 %, respectively).

A similar design was used in the RE-NOVATE trial [19] to test potential non-inferiority of dabigatran etxilate for VTE prophylaxis in 3494 patients undergoing THR, except that the treatment was continued for 28–35 days. The primary efficacy outcome, a composite of total VTE and all-cause mortality during treatment, occurred in 6.7 % of individuals in the enoxaparin group, 6.0 % of patients in the dabigatran etxilate 220 mg qd group, and 8.6 % of patients in the 150 mg qd group; that is, both the dabigatran etxilate doses were non-inferior to enoxaparin. There was no significant difference in major hemorrhage rates with either dose of dabigatran etxilate compared with enoxaparin. In the phase III RE-NOVATE II trial, the efficacy and safety of oral dabigatran versus subcutaneous enoxaparin was compared for extended thromboprophylaxis in patients undergoing total hip arthroplasty.

TABLE 2.3 Efficacy and safety of dabigatran etexilate in major orthopedic surgery from phase III trials

	Duration of treatment (days)	Initiation of dabigatran etexilate	Treatment tested	VTE and all-cause mortality (%)	Major hemorrhage (%)
RE-MODEL [18] (TKA) <i>n</i> =2076	6–10	1–4 h post operation (with half dose)	Dabigatran etexilate Dabigatran etexilate 220 mg qd Enoxaparin 40 mg qd	37.7 40.5 36.4	1.3 1.5 1.3
RE-NOVATE [19] (THA) <i>n</i> =3494	28–35	1–4 h post operation (with half dose)	Dabigatran etexilate 150 mg od Dabigatran etexilate 220 mg qd Enoxaparin 40 mg qd	6.7 8.6 6.0	1.3 2.0 1.6
RE-MOBILIZE [20] (TKA) <i>n</i> =1896	12–15	6–12 h post operation	Dabigatran etexilate 150 mg qd Dabigatran etexilate 220 mg qd Enoxaparin 30 mg bid	25.3 33.7 ^a 31.1 ^a	0.6 0.6 1.4
RE-NOVATE II [21] (THA) <i>n</i> =2055	28–35	1–4 h post operation (with half dose)	Dabigatran etexilate 220 mg qd Enoxaparin 40 mg qd	7.7 8.8	1.4 0.9

Data from [18–21]

Bid twice daily, *qd* once daily, *THA* total hip arthroplasty, *TKA* total knee arthroplasty^aInferior to enoxaparin

A total of 2055 patients were randomized. The primary efficacy outcome was a composite of total VTE and death from all causes. The main secondary composite outcome was major VTE plus VTE-related death. The main safety endpoint was major bleeding. The primary efficacy outcome occurred in 7.7 % of the dabigatran group versus 8.8 % of the enoxaparin group ($P < 0.0001$ for the pre-specified non-inferiority margin). Major VTE plus VTE-related death occurred in 2.2 % of the dabigatran group versus 4.2 % of the enoxaparin group. Major bleeding events did not differ between the two arms [21].

No significant differences in the incidences of liver enzyme elevation and acute coronary events were observed during treatment or follow-up in the RE-MODEL or the RE-NOVATE I and II trials.

The successful record of dabigatran etexilate in preceding clinical trials was partly compromised in the double-blind, centrally randomized RE-MOBILIZE trial [20], in which the North American recommended dose for VTE prophylaxis was used for the enoxaparin comparator (i.e., 30 mg bid rather than 40 mg qd). Dabigatran etexilate 220 or 150 mg qd was compared with enoxaparin 30 mg bid after knee arthroplasty surgery. Among 1896 patients, dabigatran etexilate at both doses showed inferior efficacy to enoxaparin, with VTE rates of 31 % for 220 mg qd ($P = 0.02$ versus enoxaparin), 34 % for 150 mg qd ($P < 0.001$ versus enoxaparin), and 25 % for enoxaparin. Major hemorrhage was uncommon in all groups: 0.6 % for dabigatran 220 mg qd, 0.6 % for dabigatran 150 mg qd, and 1.4 % for enoxaparin (no significant differences). Serious adverse events occurred in 6.9 % of dabigatran 220 mg qd patients, 6.5 % of dabigatran 150 mg qd patients, and 5.2 % of enoxaparin patients.

An interesting clinical difference between European and North American prophylactic dosing regimens for antithrombotic drugs for perioperative orthopedic patients is that, historically, European dosing regimens administered these drugs before surgery, whereas in North America dosing began postoperatively, sometimes at a higher total daily

dosage [30]. Because dabigatran was first investigated in European joint arthroplasty patients, the LMWH control therapy, enoxaparin, was initiated the evening before the day of surgery at the standard dosage of 40 mg qd in the phase II studies.

In March 2008, the European Commission granted marketing authorization for dabigatran etexilate for the prevention of VTE in adults who have undergone THR or TKR. The drug was launched in the UK in April 2008.

A number of observational cohort studies aimed to further optimize clinical management with dabigatran in VTE following joint surgery by selecting specific patient groups and treatment regimens. A recently completed study (ClinicalTrials.gov Identifier NCT00846807) [31] investigated the safety and efficacy of dabigatran 220 mg in patients with an increased risk of bleeding or VTE and an ongoing study (ClinicalTrials.gov Identifier NCT00847301) [32] evaluating the safety and efficacy of dabigatran 150 mg in patients with renal impairment has been recently completed and its results are awaited.

2.2.2 Venous Thromboembolism Treatment

The promising efficacy results for dabigatran in the prevention of thromboembolic disorders following major joint surgery prompted the developers to test the drug's utility in VTE treatment (Table 2.2) [16–27].

The RE-COVER study was a randomized, double-blind, non-inferiority trial involving 1274 patients with acute VTE who were initially given parenteral anticoagulation therapy for a median of 9 days [22]. The RE-COVER population was assigned to dabigatran, administered at a dose of 150 mg bid, or dose-adjusted warfarin. The primary outcome was the 6-month incidence of recurrent VTE and related deaths. Safety endpoints included bleeding events, acute coronary syndrome (ACS) events, other adverse events, and results of liver-function tests. The RE-COVER investigators concluded that for the treatment of acute VTE, a fixed dose of

TABLE 2.4 Efficacy and safety of dabigatran etexilate in phase III VTE trials

	Duration of treatment (months)	Dabigatran		Comparator	
		VTE and all-cause mortality n/N (%)	Major hemorrhage n/N (%)	VTE and all-cause mortality n/N (%)	Major hemorrhage n/N (%)
RE-COVER [22] n=2564	6	30/1274 (2.4)	20/1274 (1.6)	27/1265 (2.1)	24/1265 (1.9)
RE-COVER II [23] n=2589	6	30/1279 (2.3)	15/1279 (1.2)	28/1289 (2.2)	22/1289 (1.7)
RE-MEDY [24] n=2866	6–36	26/1430 (1.8)	13/1430 (0.9)	18/1426 (1.3)	25/1426 (1.8)
RE-SONATE [24] n=1353	6–18	3/681 (0.4)	2/681 (0.3)	37/662 (5.6)	0/0 (0.0)

Data from [22–24]

VTE venous thromboembolism

dabigatran is as effective as warfarin (primary outcome rate 2.4 % versus 2.1 %, respectively; $P < 0.001$ for the pre-specified non-inferiority margin) and has a safety profile that is similar to that of warfarin (Table 2.4) [22]. Based on the success of RE-COVER, RE-COVER II was initiated to confirm the low rate of recurrent VTE observed. RE-COVER II was a 6-month, double-blind, randomized trial comparing treatment with dabigatran to warfarin in 2589 VTE patients (either acute symptomatic proximal DVT or pulmonary embolism). Patients were randomized to dabigatran 150 mg bid or dose-adjusted warfarin (INR 2.0–3.0). The primary efficacy and safety outcomes were the same as those used in RE-COVER. RE-COVER II confirmed the non-inferiority of dabigatran (primary outcome occurred in 2.3 % of patients treated with dabigatran vs 2.2 % of patients treated with warfarin; $P < 0.001$) (Table 2.4). Additionally, RE-COVER II

confirmed the superiority of dabigatran for clinically relevant non-major (CRNM) bleeding and for any bleeding [23].

In a separate phase III randomized multicenter trial, RE-SONATE, the efficacy of prolonged (additional 12 months) administration of dabigatran etexilate in 1547 patients with VTE was compared with placebo. In RE-SONATE, extended treatment with dabigatran was associated with a 92 % relative risk reduction for recurrent VTE and a low risk for major bleeding [24]. Additionally, the RE-MEDY trial evaluated the comparative safety and efficacy of dabigatran etexilate and warfarin for the long-term treatment and secondary prevention of symptomatic VTE in 2866 patients already successfully treated with a standard anticoagulant approach for 3–6 months for confirmed acute symptomatic VTE. In RE-MEDY, dabigatran demonstrated non-inferiority to warfarin for the outcome of recurrent VTE (primary outcome rate 1.8 % vs 1.3 % respectively; $P=0.01$ for non-inferiority), with fewer bleeds (19.4 % vs 26.2 %, respectively; $P<0.001$), but there were more ACS events in the dabigatran group than in those taking warfarin (0.9 % vs 0.2 %; $P=0.02$) (Table 2.4) [24].

2.2.3 *Stroke Prevention in Atrial Fibrillation*

The clinical safety of dabigatran etexilate (with or without aspirin) in patients with atrial fibrillation (AF) was first assessed in the phase II dose-range Prevention of Embolic and ThROMbotic Events in Patients with Persistent Atrial Fibrillation (PETRO) trial [25]. In this trial, 502 patients with AF were randomized to receive dabigatran etexilate 50, 150, or 300 mg bid alone or combined with 81 mg or 325 mg of aspirin or warfarin qd for 12 weeks. Major hemorrhage was limited to the group treated with 300 mg dabigatran plus aspirin (4 of 64), and the incidence was significant versus 300 mg dabigatran alone (0 of 105, $P<0.02$). Total hemorrhage events were more frequent in the 300 mg (23 %) and 150 mg (18 %) dabigatran groups compared with the 50 mg

groups (7 %; $P=0.0002$ and $P=0.01$, respectively). The study demonstrated that major hemorrhages were limited to patients treated with dabigatran 300 mg plus aspirin, and thromboembolic episodes were limited to the 50 mg dabigatran groups. On the basis of the PETRO study, 150 and 220 mg doses were chosen for further development in phase III studies of stroke prevention in AF.

The Randomized Evaluation of Long term anticoagulant therapy (RE-LY) with dabigatran etexilate trial compared the efficacy and safety of two doses of dabigatran etexilate with warfarin in over 18,000 patients with AF with an average age of 71 years. The primary outcome measure was the incidence of stroke (including hemorrhagic) or systemic embolism at the median 2-year follow-up period. Treatment with the higher, 150 mg bid dose significantly reduced the rate of stroke and systemic embolism (with a relative risk of 0.66, $P<0.001$; the rate of hemorrhagic stroke was 0.38 % per year in the warfarin group versus 0.10 % per year with dabigatran, $P<0.001$), with a similar overall risk to warfarin for major bleeding [26]. The lower, 110 mg bid dose resulted in a similar risk for stroke as warfarin but with a significantly reduced major bleeding event rate (20 % relative risk reduction, 3.36 % per year in the warfarin group versus 2.71 % per year with dabigatran, $P=0.003$). The rate of hemorrhagic stroke was 0.38 % per year in the warfarin group, as compared with 0.12 % per year with 110 mg dabigatran ($P<0.001$) and 0.10 % per year with 150 mg of dabigatran ($P<0.001$). Annual mortality rate was 4.13 % in the warfarin group, 3.75 % with 110 mg of dabigatran and 3.64 % with 150 mg of dabigatran (borderline significance, $P=0.051$) [26] (Fig. 2.2). The long-term extension study, RELY-ABLE, investigated the safety of prolonged treatment with dabigatran etexilate; 5851 patients who completed dabigatran treatment in the RE-LY study were enrolled into RELY-ABLE to continue with the two effective doses of dabigatran (110 and 150 mg). Primary outcomes for RELY-ABLE were the same as those for RE-LY. For both doses studied, the rates of major ischemic,

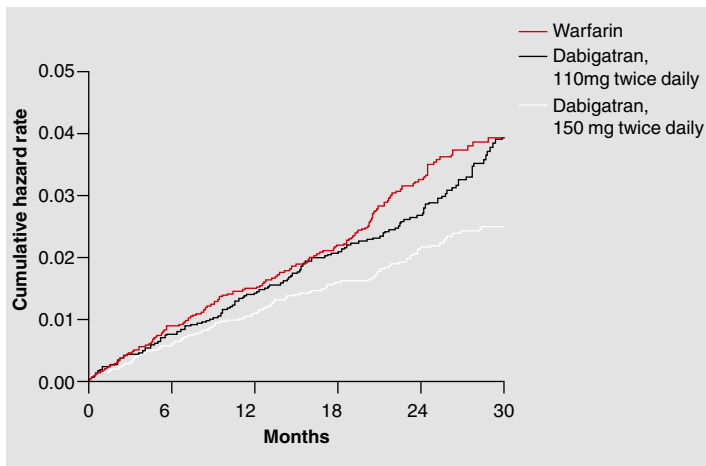


FIGURE 2.2 Cumulative hazard rates for the primary outcome of stroke or systemic embolism, according to treatment group (Reproduced with permission from Connolly et al. [26])

hemorrhagic and fatal outcomes were consistent with those seen in RE-LY, demonstrating the safety of both doses in long-term treatment. RELY-ABLE did not show any significant differences between the two doses in the rate of stroke (1.46 %/year for 150 mg vs 1.60 %/year for 110 mg) or mortality (3.02 %/year for 150 mg vs 3.10 %/year for 110 mg), however there was a higher rate of bleeding in the 150 mg patient group (3.74 %/year vs 2.99 %/year) [27].

In view of the results of the RE-LY trial, dabigatran has been included in the latest European guidelines for management of AF as an alternative to VKAs for primary or secondary prevention of stroke in patients with AF. In October 2010 the United States (US) FDA approved the 150 mg bid dosage, which should be reduced to 75 mg bid in selected cases (e.g., creatinine clearance 15–30 mL/min). Dabigatran is licensed by the European Medicines Agency (EMA) at two dosages (110 mg and 150 mg bid), depending on the balance between thromboembolic and bleeding risk factors.

2.2.4 Other Directions

The potential application of DTIs is not limited to conditions related to venous thrombosis, and dabigatran etexilate has also been tested in phase II trials in clinical settings of arterial thrombosis. In the phase II, randomized, open-label D-fine study of dabigatran etexilate in elective percutaneous coronary intervention (PCI) two doses of dabigatran etexilate (110 mg and 150 mg bid) were compared with heparin (both in addition to a standard dual antiplatelet regimen) in 50 patients undergoing elective PCI. The results of this study suggested that treatment with dabigatran (both 110 and 150 mg) may not provide sufficient anticoagulation during PCI [29]. RE-DEEM (Dose-Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome), a larger ($n=1878$) placebo-controlled trial, evaluated the safety and potential efficacy of four different dabigatran doses administered twice daily for 6 months in addition to dual antiplatelet treatment in patients with ACS at high risk of cardiovascular complications [28]. In the RE-DEEM study dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events compared with placebo and significantly reduced coagulation activity in patients with a recent myocardial infarction [28].

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