Dabigatran: A new oral anticoagulant

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Abstract

Dabigatran, a direct thrombin inhibitor (DTI), has been approved as a new orally administrated anticoagulant in many countries including Thailand. Food and drug administration (FDA) Thailand has approved 75, 110 and 150 mg of dabigatran since 2009 for prevention of stroke and venous thromboembolism (VTE) in atrial fibrillation (AF), orthopedic surgery as well as treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Dentists may encounter patients who receive dabigatran therapy. Although tooth extractions are minor surgery done at outpatient unit, patients with high risk of hemorrhage must be carefully assessed with proper dental management. This article describes pharmacological properties of dabigatran including discovery, pharmacokinetics, pharmacodynamics, clinical trials, and adverse effects. In addition, the suggestion for dental management of patients being treated with dabigatran has been stated.

Keywords: Pradaxa®, dabigatran, direct thrombin inhibitor, novel oral anticoagulant, bleeding, oral surgery

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Introduction

Anticoagulants are commonly used for prophylaxis and treatment of various thromboembolic diseases. Venous thromboembolism (VTE), deep vein thrombosis (DVT) after orthopedic surgery, and thromboembolic complications associated with atrial fibrillation (AF) and prosthetic heart valve can be prevented and treated by anticoagulants[1]. Most of anticoagulants such as heparin, low molecular weight heparin (LMWH) or argatroban are parentally administrated drugs. For prevention of thrombosis in chronic setting, warfarin oral anticoagulant is a mainstay drug for more than 60 years. However, warfarin has effect on several clotting factors, slow onset and offset of action, and narrow therapeutic index. Warfarin is metabolized by cytochrome P450 (CYP) 2C9 and CYP3A4 thus warfarin has significant drug-drug and drug-food interactions. In addition, genetic polymorphism of vitamin K epoxide reductase, warfarin's target enzyme, may cause warfarin resistance leading to interindividual variability[2].

Many pharmaceutical companies have been interested in the development of new oral anticoagulant to overcome the limitations of warfarin. The timeline for discovery of anticoagulants was shown in figure 1. The ideal orally administrated anticoagulants should have wide therapeutic index, no drug-drug or drug-food interactions, rapid onset of action, and no individual dose adjustment. In addition, these drugs should be effective in reducing thromboembolic events, and have comparable risk of bleeding to conventional anticoagulants[3].

Direct thrombin inhibitors (DTIs) are considered to be the new therapeutic class of anticoagulants. DTIs are synthetic small molecules that bind to the active site of thrombin leading to the inactivation of fibrin-bound thrombin. Currently, US FDA has approved four DTIs for prevention and treatment of thromboembolism given by parenteral administration. These drugs are lepirudin (out of

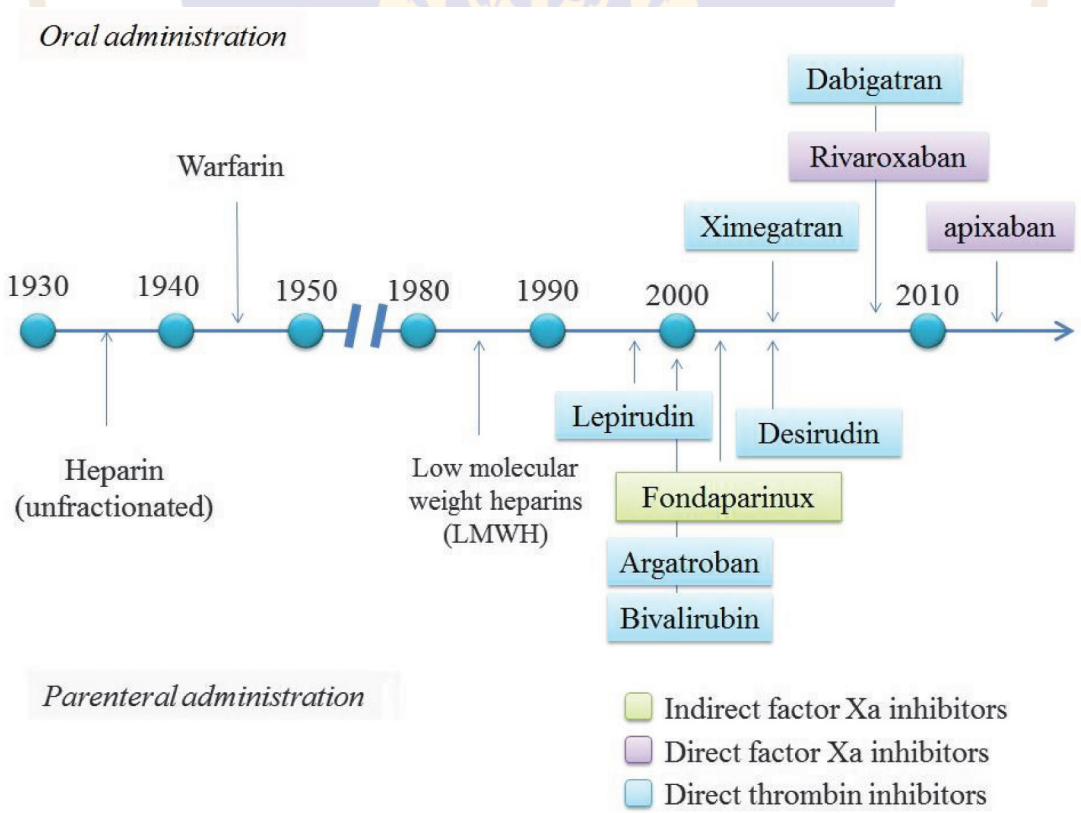

Figure 1 Timeline for the discovery of anticoagulants

the market), desirudin, bivalirudin and argatroban[4]. Ximelagatran was the first orally administrated DTIs; however, it was withdrawn due to life-threatening hepatotoxicity in 2006 (2 years after approval)[5]. Since 2008, Boehringer Ingelheim has released dabigatran etexilate (Pradaxa®, an oral DTI) and Bayer has released rivaroxaban (Xarelto®, an oral factor Xa inhibitor) into the market. Sites of action of anticoagulants were concluded in figure 2.

Discovery of DTIs

Thrombin (factor IIa) is a serine protease enzyme important in blood coagulation cascades. Prothombin (factor II) is activated to thrombin (factor IIa) through proteolytic cleavage by factor Xa in prothrombinase complex. Thrombin converts fibrinogen to fibrin leading to clot stabilization. In addition, thrombin activates platelets and amplifies coagulation response leading to the enhancement of thrombin generation[6].

The early stage work was focused on a synthetic tripeptide D-Phe-Pro-Arg as a DTI; however, it had low oral bioavailability and susceptible to degradation by proteases[7, 8], hindering its step to clinical trial. Meanwhile, the study of non-peptide thrombin inhibitor was started when the X-ray crystallography demonstrated the binding of peptide-like benzamidine-based inhibitor Nα-[(2-naphthylsulfonyl)glycyl]-dl-*p*-amidinophenylalanylpiperidine (NAPAP) with bovine thrombin[9]. The benzamidine group of NAPAP forms bidentate salt bridge with active site of thrombin (ASP189 in S1 pocket). Piperidine and naphthyl moieties of NAPAP form hydrophobic interactions with S2 and S4 pocket of active site of thrombin, respectively[10] (figure 3A). However, glycine residue in NAPAP forms hydrogen bonds with amino acids of S1 pocket leading to permanent binding[11]. The central glycine in the NAPAP was replaced with benzimidazole derivative. A substituted benzimidazole derivative was found to be a lead compound for DTI. After optimization of the structure by increasing hydrophilicity and adjusting the link between benzimidazole and

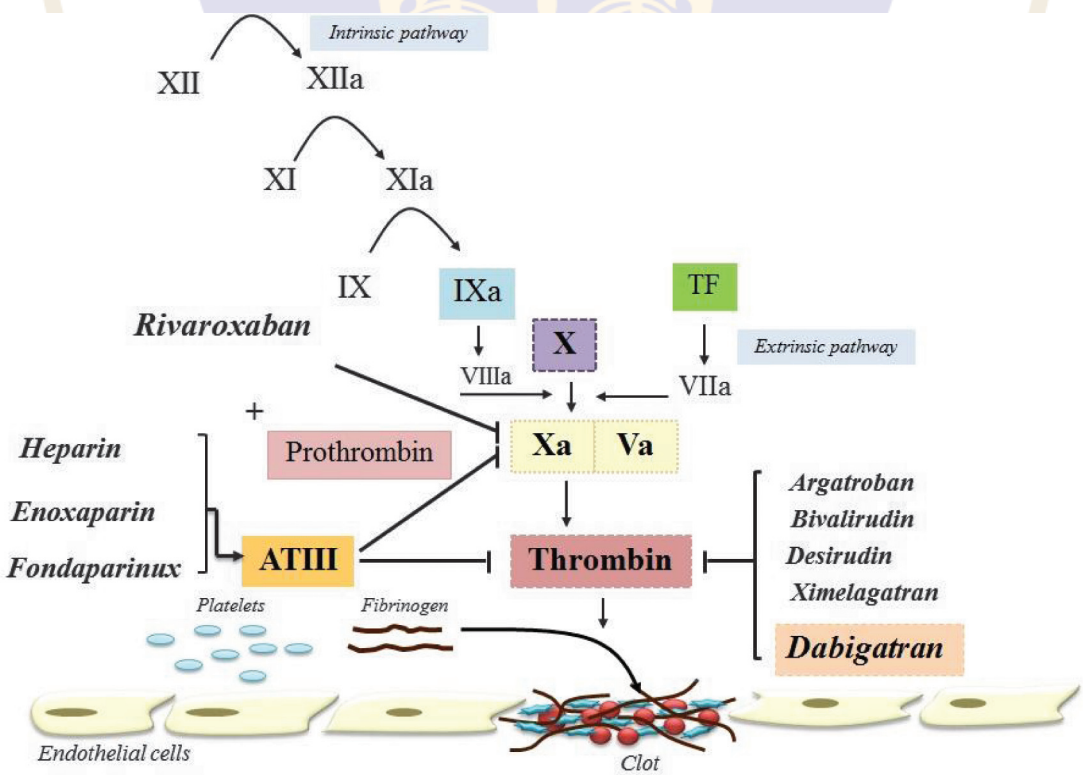

Figure 2 Coagulation cascades and sites of drug action.

benzamidine moieties, the compound BIBR 953 (or dabigatran) with IC_{50} in nanomolar range have been developed[12]. Like NAPAP, the benzamidine group of dabigatran binds to deep S1 pocket of thrombin. Methyl benzimidazole and pyridyl rings form hydrophobic interactions with S2 and S4 pockets, respectively[13](figure 3B). Due to the hydrophilicity of dabigatran, it has low oral bioavailability (poor oral absorption). Therefore, dabigatran etexilate was developed by conjugating hexacarbamate into dabigatran molecule, making the drug more lipid soluble. In blood, plasma esterases hydrolyze ester bond between dabigatran and hexacarbamate, releasing dabigatran (figure 4).

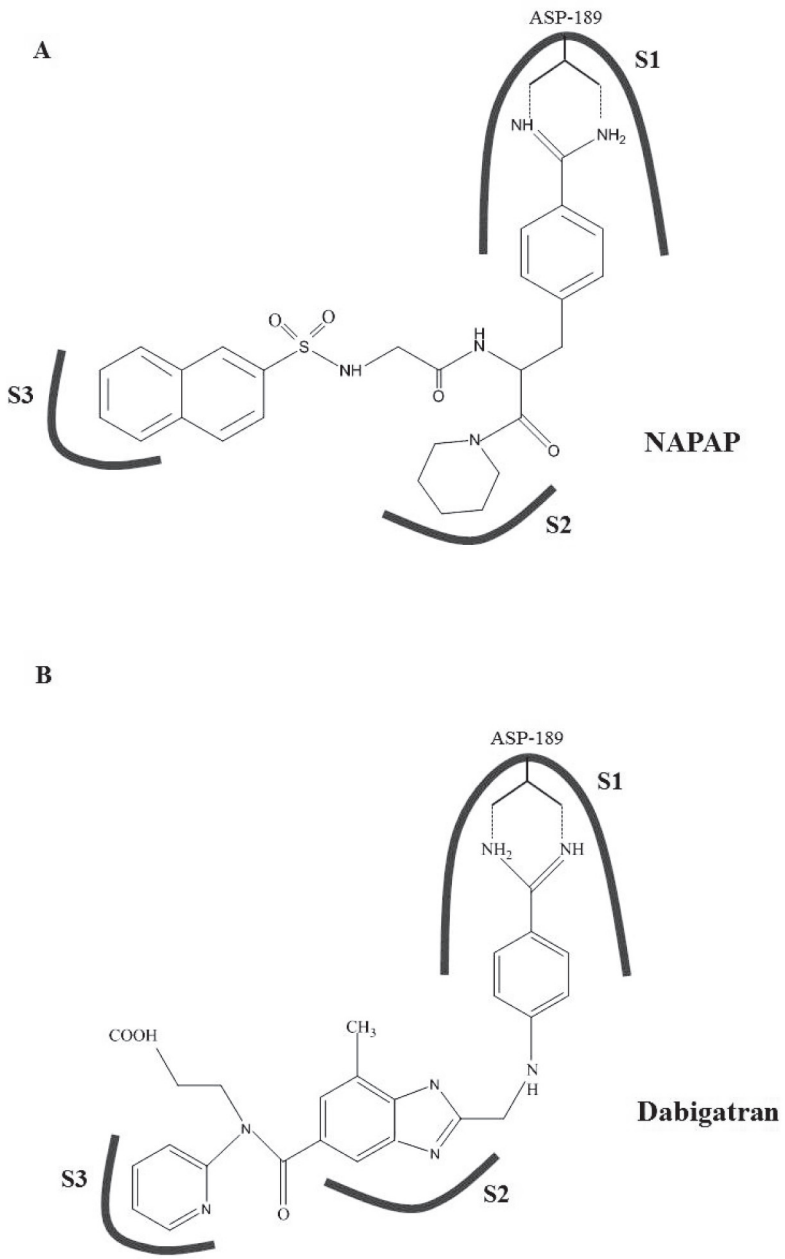

Figure 3 Binding of Nα-[(2-naphthylsulfonyl)glycyl]-dl-p-amidinophenylalanylpiperidine (NAPAP) (A) and dabigatran (B) to active site of thrombin. Benzamidine group of both NAPAP and dabigatran form bidentate salt bridge with ASP-189 at S1 pocket of active site of thrombin.

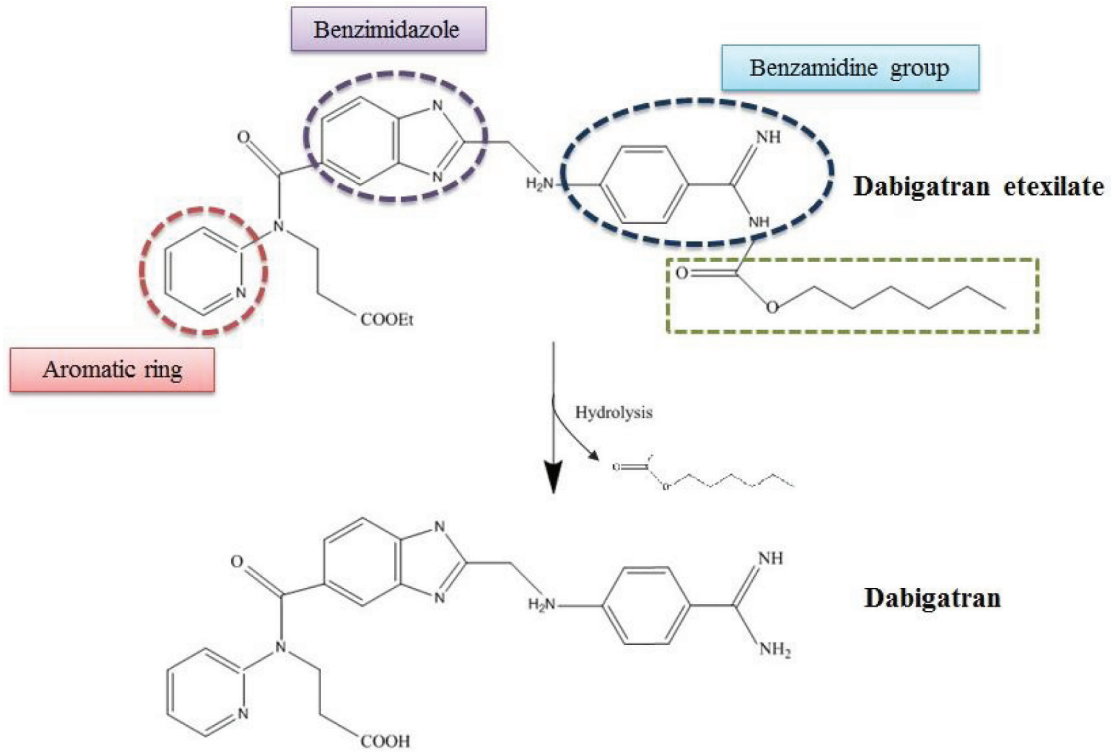

Figure 4 Structure of dabigatran etexilate and dabigatran. Dabigatran etexilate is converted to dabigatran by the hydrolysis of ester bond at hexacarbamate group. Dabigatran composes of three important structures: benzamidine, benzimedazole and aromatic ring.

Pharmacology of dabigatran

Preclinical studies of dabigatran

Dabigatran, a reversible competitive thrombin inhibitor, inhibits serine protease activity of thrombin in a concentration-dependent manner (K_i = 4.5 nM)[14]. The effect of dabigatran is highly selective to thrombin. The inhibitory constants (K_i) of dabigatran against other protease enzymes such as factor VIIa/tissue factor and factor Xa is greater than 10,000 nM and 3,800 nM, respectively. In addition, dabigatran inhibits tissue factor-induced thrombin generation and prolongs activated partial thromboplastin time (aPTT), prothrombin time (PT) and ecarin cloting time (ECT) *in vitro*[14]. Intravenous administration of dabigatran in rats and monkeys caused the prolongation of aPTT in dose and time-dependent manners *ex vivo*[14].

Dabigatran inhibited thrombosis in experimentally induced clot formation *in vivo*[15, 16]. In rabbits, dabigatran inhibited clot formation by reduction of clot weight in dose-dependent manner with EC_{50} of 0.066 mg/kg for intravenous (iv) administration and 4.7 mg/kg for oral administration. In addition, the effect of dabigatran was achieved 1 hour after oral administration indicating the rapid onset of action[15]. A study in thromboplastin-induced VTE in rat showed similar results. Dabigatran decreased thrombus dry weight in dose-dependent manner from both intravenous and oral administration. In addition, dabigatran prolonged rat-tail bleeding time and aPTT values[16].

Pharmacokinetics data

Dabigatran etexilate has oral bioavailability (F) of 7.2%[17] (table 1). Capsule of dabigatran etexilate is composed of core tartaric acid coated by dabigatran etexilate. An acidic pH from tartaric acid facilitates drug dissolution and absorption independent of gastric pH. However, coadministration of dabigatran with proton pump inhibitors (PPIs) causes 20% decrease

in dabigatran absorption[18]. After absorption, esterase enzymes convert dabigatran etexilate to dabigatran[17]. Time to peak plasma concentration (T_{max}) of dabigatran is 1.5-3 hours. Dabigatran has plasma protein binding of 35% and volume of distribution about 60-70 L. After reaching peak plasma concentration, levels of dabigatran decline in a biphasic manner. Plasma levels of dabigatran decrease about 30% at 4-6 hours after oral administration, which is followed by prolonged termination elimination phase. Half-life of dabigatran is about 12-14 hours[19]. Eighty percent of dabigatran is excreted unchanged in urine. Twenty percent of drugs are conjugated with glucuronic acid and excreted in bile[17]. Since 80% of dabigatran is excreted in urine, renal impairment decreases dabigatran clearance leading to prolonged half-life of dabigatran (table 2). Patients who have creatinine clearance < 30 mL/min have 2-fold increase in dabigatran half-life and double clotting time as tested by aPTT, thrombin time (TT), ECT and PT[20].

The metabolism of dabigatran is not associated with the activity of CYP450. *In vitro* experiments showed that microsomal carboxylesterases converted dabigatran etexilate to intermediate metabolite. Although dabigatran is not metabolized by CYP450 or phase I enzyme, 20% of dabigatran is conjugated by glucoronosyltransferase. Conjugated dabigatran is excreted in feces[17].

Table 1 Pharmacological properties of dabigatran etexilate

Characteristics	Data for dabigatran etexilate
Mechanism of action	Direct thrombin inhibitor
Bioavailability	7.2 %
Volume of distribution	60-70 L
Plasma protein binding	35 %
Half-life (hours)	12-14 hours
Route of elimination	80% excreted unchanged by renal
Routinely monitoring	No
Drug interactions	• P-glycoprotein inhibitors • P-glycoprotein inducers
Coagulation test	Prolonged TT, ECT and aPTT No effect on PT

Table 2 Half-life of dabigatran in renal impairment patients and guideline of discontinuation of dabigatran before elective surgery[22]

Groups	Renal function (Creatinine clearance, mL/min)	Dabigatran half-life (hours)	Timing of discontinuation after last dose of dabigatran before surgery	
			Standard risk bleeding	High risk of bleeding[b]
Normal	> 80	13 (11-22)	24 hours	2-4 days
Mild renal failure	> 50 to ≤ 80	15 (12-34)	24 hours	2-4 days
Moderate renal failure	> 30 to ≤50	18 (13-23)	≥ 48 hours	4 days
Severe renal failure	≤ 30[a]	27 (22-35)	2-5 days	> 5 days

[a]Dabigatran is contraindicated for use in these patients

[b]Types of surgery associated with high risk of bleeding (or in major not limited to, cardiac, neural, abdominal and those involving with major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing in ages, concomitant use of anti-platelet therapy

Unlike warfarin, the anticoagulant effect of dabigatran is assessed by aPTT, TT and ECT but not PT or internationalized ratio (INR) (table 1). The levels of aPTT do not correlate well with levels of dabigatran. *In vitro*, the effect (prolonged aPTT) is proportional to dabigatran concentration up to 200 ng/mL. The directly proportional of aPTT and dabigatran is limited at dabigatran 200 ng/mL[21]. Therefore, aPTT is not suitable for precise quantification of effect especially at high concentration[19]. TT is theoretically proposed to be a sensitive assay to assess the anticoagulant effect of dabigatran; however, TT is too sensitive for assessment of dabigatran at concentration higher than 25 ng/mL and not well standardized[22]. ECT is one of sensitivity assay, which showed linear relationship with levels of dabigatran. However, the accuracy of ECT assay requires laboratory experience and the test is not widely used[23].

Clinical studies

Increased risks of stroke and systemic embolism have well documented in patients with AF. Warfarin is a mainstay drug for stroke prevention in patients with AF for more than 60 years with lots of drawback effects. Attempt to develop a new oral drug such as dabigatran for prevention of stroke and systemic embolism had been done in clinical trial in 18,000 patients with AF[24]. Dabigatran at dose of 150 mg twice daily was superior to warfarin for stroke and systemic embolism prevention whereas dabigatran at dose of 110 mg twice daily was non-inferior to warfarin. Long term (median 2.3 years) used of both doses of dabigatran showed similar rate of stroke and dead in patients with AF[25].

Anticoagulant is also a mainstay treatment for VTE including DVT and PE. VTE has increasing rate of occurrence with mortality rate about 5-30%[26]. Parental anticoagulants such as LMWH are used for initial phase of VTE for 7-10 days. In order to prevent new episode of VTE, warfarin is used in long-term and extended treatment[27]. Phase III clinical studies named RE-COVER, RE-MEDY and RE-SONATE were designed to evaluate therapeutic effect of dabigatran in VTE. In RE-COVER study, 10 days after initial parental anticoagulant, patients were received either 150 mg of dabigatran twice daily or warfarin at INR of 2.0-3.0 for 6 months. The incidence of recurrent VTE or related death was similar between dabigatran and warfarin treated group indicating non-inferior effect of dabigatran to warfarin[28]. In addition, extended treatment of dabigatran for 6-36 months in RE-MEDY study showed non-inferior to warfarin[29]. The effect of dabigatran compared to placebo was investigated in RE-SONATE study. Patients with lower risk of VTE from RE-COVER study were enrolled in RE-SONATE study. Dabigatran caused 92% reduction in risk of recurrent VTE compared to placebo group[29]. Base on this phase III clinical data; US FDA has approved dabigatran for prevention of stroke in AF patients and recurrence of VTE.

In contrast to the successful treatment of dabigatran against AF and VTE, phase II study of dabigatran in patients with mechanical heart valves has been prematurely terminated. In this study, patients were divided to receive warfarin with INR 2-3 or 2.5-3.5 dependent on risk of thromboembolism of each patient and dabigatran. Dabigatran at dose of 150-300 mg twice daily (target plasma concentration of 50 ng/mL) was given to patients. After recruitment of 252 patients, ischemic or unspecified stroke was found in 5% of patients received dabigatran but not found in warfarin group[30]. This study suggests that there is no additional benefit with high risk when use dabigatran in patients with mechanical heart valve.

The most important adverse effect of dabigatran is bleeding. Rate of major bleeding between patients taking 150 mg of dabigatran

and warfarin was not different; however, dabigatran at dose of 110 mg had lower risk of major bleeding[24]. Patients who received dabigatran had lower risk of intracranial and minor bleeding compared to warfarin however, dabigatran at dose of 150 mg caused further increased risk of bleeding in patients over age of 75 years[31]. Gastrointestinal tract, intracranial cavity and urogenital tract are most common sites of bleeding[32]. In addition to bleeding, gastrointestinal discomforts including dyspepsia, nausea, upper abdominal pain, diarrhea and gastritis can be found[33].

Drug interactions

In contrast to warfarin, dabigatran and dabigatran etexilate are not metabolized by CYP450 therefore they have less drug-drug and drug-food interactions. *In vitro* study showed that dabigatran was not CYP450 substrate, inducer or inhibitor[17]. However, dabigatran etexilate but not dabigatran is a substrate of P-glycoprotein (P-gp)[34]. P-gp is an efflux transporter located at epithelial cells of gastrointestinal lumen. Substrates of P-gp are pumped out of epithelial cells leading to the reduction of absorption[35]. Some of available drugs are P-gp inducers or inhibitors therefore; concomitant administration of dabigatran with P-gp inducers or inhibitors may increase or decrease dabigatran absorption, respectively[36] (figure 5). P-gp inducers including rifampin, dexamethasone and carbamazepine significantly decreased AUC of dabigatran therefore; concurrent used of dabigatran with these P-gp inducers was not recommended[37,38]. Ketoconazole, a strong P-gp inhibitor, caused 135% and 138% increase in AUC and C_{max} of dabigatran,

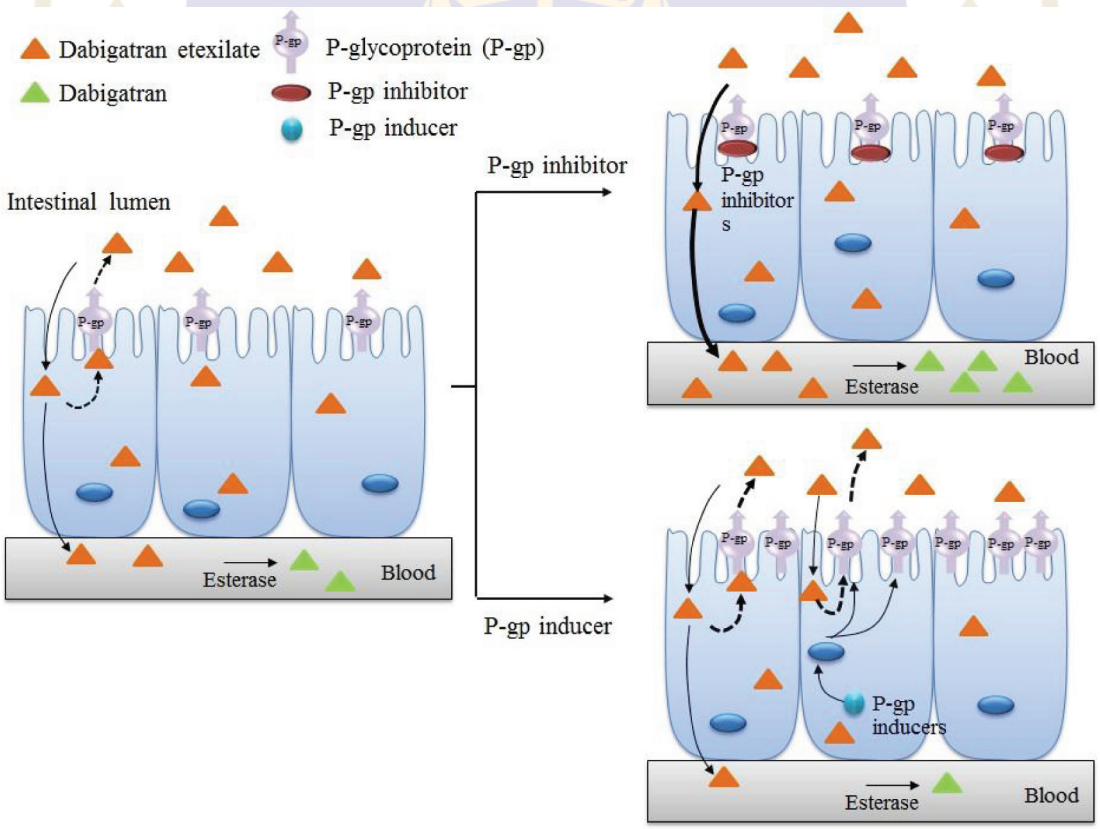

Figure 5 P-glycoprotein (P-gp) mediated drug interactions of dabigatran. Dabigatran is a P-gp substrate. Once absorbed, some of dabigatran is transported back to intestinal lumen leading to decrease absorption. While P-gp inhibitors increase, P-gp inducers decrease dabigatran absorption

respectively[39]. In contrast, clarithromycin, moderate P-gp inhibitor, slightly increased AUC and C_{max} of dabigatran[39]. Immediate-released verapamil increased dabigatran levels when administrated at the same time however, no significant effect was found when administrated verapamil 2 hours after dabigatran[37]. Amiodarone, a P-gp inhibitor, also increased dabigatran absorption however; the interaction between amiodarone and dabigatran was mitigated by elevated dabigatran clearance by renal[36]. Therefore, the concomitant administration of dabigatran with P-gp inhibitors should be avoided, if possible. However, in patients with renal impairment the dose of dabigatran should be reduced when administrated together with P-gp inhibitors. Increase gastric pH from PPIs or H2 blockers may affect dabigatran absorption but it is not consider significant[19]. Anti-platelet drugs such as aspirin and clopidogrel increased risk of bleeding in patients who received dabigatran and the risk of bleeding was further increased when dual anti-platelet drugs were used[40]. However, concomitantly taking of NSAIDs had similar risk of bleeding compared to dabigatran alone[41]. However, NSAIDs may cause gastrointestinal bleeding, sign and symptoms of bleeding in patients concurrent use of dabigatran with NSAIDs should be monitored.

Dental management for patients taking dabigatran

As dabigatran is a recently approved drug, there is no clinical trial or evidence-based data for the recommendation for management of dental patients. The management of patients receiving dabigatran who undergo dental surgery was suggested by a review literature based on the recommendation for patients who require minor surgery[22]. Patients should continue dabigatran in uncomplicated tooth extractions while dabigatran should temporarily discontinue at least 24 hours in case of oral/maxillofacial surgery with possible excessive bleeding. According to the guideline of previous publication[38], case report of no prolonged bleeding was observed after temporarily discontinued dabigatran 24 hours prior multiple tooth extraction and no other adverse medical outcomes found in a period of 7-months after temporary dabigatran discontinuation[42]. There is no bleeding complication in 2 patients with dabigratran who underwent single tooth extractions while a minor postoperative bleeding for 3 hours was reported in one other case[43]. In contrast, excessive bleeding was found in the extraction of tooth 18 with the drainage of abscess in patients who continued dabigatran. After ceasing dabigatran, the bleeding stopped within 24 hours[43].

According to the available data, cessation of dabigatran is unnecessary for general dental procedure including scaling, endodontic treatment and single tooth extraction like the recommendation for warfarin. Hemostatic measures should be used in case of prolonged bleeding. In multiple tooth extractions with high risk of excessive bleeding, consultation with hematologist is recommended. The risk of stroke is outweighed bleeding during dental procedure. Stopping of dabigatran in AF patients who have low risk of thromboemoboic event is considered to be safe. However, alternative anticoagulant such as heparin or LMWH should be prescribed in patients at high risk of thrombosis[44, 45]. The cessation of dabigatran for 24 hours (2 x half-life) is enough for reducing risk of bleeding in patients without renal impairment. However, cessation may be longer in renal impairment patients who have creatinine clearance less than 50 mL/min. As NSAIDs may increase risk of bleeding in dabigatran treated patients, postoperative analgesic with NSAID or aspirin should be avoided and acetaminophen or opioid should be used instead.

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International Abstract

Marginal adaptation of class II cavities restored with bulk-fill composites

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Objectives: To determine the marginal adaptation of bulk-fill composites in class II MO cavities.

Methods: Standardized class II MO cavities with bevelled enamel margins were prepared in 40 extracted human molars. The teeth were randomly assigned to one of the five experimental groups (n=8). The teeth were restored with two horizontal increments of composite (4mm and 2mm thickness). The experimental groups were (1st/2nd increment): Gr. A - Venus Bulk-Fill/Venus Diamond; Gr. B - Tetric EvoCeram BulkFill/Tetric EvoCeram; Gr. C - Surefil SDR/Ceram-X; Gr. D - SonicFill; Gr. E - Ceram-X/Ceram-X (control). After finishing procedures, impressions were made using a polyvinyl siloxane and epoxy resin replicas were obtained. Thermo-mechanical stressing was carried out 24h after the restorative procedure. All specimens were submitted to 240,000 occlusal loading and simultaneous 600 thermal cycles in water at 5°C and 50°C. After loading, a new set of epoxy resin replicas was obtained. Scanning electron microscopy was carried out at 200× magnification. Results for the marginal adaptation were expressed as percentages of continuity relative to the exposed interface and analyzed by ANOVA and Duncan post hoc test (p<0.05).

Results: In enamel, no significant differences were detected before and after thermo-mechanical loading between groups. In dentine, the worst results were observed in Gr. A.

Conclusion: By applying simple layering techniques, bulk-fill materials do not allow better marginal adaptation than a standard composite.

Clinical significance: A new class of resin-base composite (bulk-fill) was recently launched on the market. The bulk-fill composites exhibited adequate marginal adaptation and similar to the results of the standard composite.

Labial soft tissue volume evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial

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Objective: To volumetrically evaluate soft tissue changes of different ridge preservation techniques compared to spontaneous healing 6 months after tooth extraction.

Materials and Methods: In each of 40 patients, one single-rooted tooth was extracted and four treatment modalities were randomly assigned to the following groups (n = 10 each): A) ß-tricalcium-phosphate-particles with a polylactid coating (ß -TCP), B) demineralized bovine bone mineral with 10% collagen covered with a collagen matrix (DBBM-C/CM), C) DBBM with 10% collagen covered with an autogenous soft tissue punch graft (DBBM-C/PG), D) spontaneous healing (control). Impressions were obtained before extraction and 6 months later, casts were digitized and volumetric changes at the buccal soft tissues were determined. One way ANOVA was performed and pair-wise Wilcoxon rank sum test with Bonferroni- Holm method was applied for comparison of differences between two groups.

Results: After 6 months, horizontal contour changes accounted for _1.7 _ 0.7 mm (A), _1.2 _ 0.5 mm (B), _1.2 _ 0.7 mm (C) and _1.8 _ 0.8 mm (D). None of the group comparisons reached statistical significance.

Conclusions: Six months after tooth extraction all groups revealed a horizontal volume change in the buccal soft tissue contour. Application of DBBM-C/CM or DBBM-C/PG reduced the amount of volume resorption compared to ß-TCP or spontaneous healing without reaching statistically significant difference.

Long-Term Stability of Soft Tissues Following Alveolar Ridge Preservation: 10-Year Results of a Prospective Study Around Nonsubmerged Implants

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The purpose of this study was to evaluate the long-term clinical outcomes around implants placed in sites previously augmented with demineralized bovine bone mineral with 10% collagen (Bio-Oss Collagen, Geistlich). In this prospective study, 36 consecutive, healthy patients, in need of a single-tooth extraction (incisors, canines, and premolars) and implant replacement, were included. After tooth extraction, Bio-Oss Collagen was inserted in the socket and covered either with a double layer of collagen membrane (test) or with a few drops of a flowable polylactide polymer (control). Following a healing period of 4 to 6 months, a single nonsubmerged implant surgery was performed. After cementation of a single ceramic crown, patients were asked to follow an individualized supportive periodontal therapy program. Clinical and radiographic data were obtained after prosthesis delivery (baseline) and at the 10-year follow-up visit. At the 10-year examination, two patients were lost to follow-up. All implants demonstrated healthy peri-implant soft tissues as documented by standard parameters (full-mouth plaque score, full-mouth bleeding score, local bleeding on probing) in both groups. Mean soft tissue recession (REC) was 0.39 ± 0.54 mm for the test group and 0.50 ± 0.33 mm for the control, with no significant difference between the two groups. The results of this prospective study confirmed the long-term stability of the peri-implant marginal soft tissues supported by regenerated bone by means of the described technique using Bio-Oss Collagen. If the patient is properly followed throughout time, the risk for mucosal recession is low, with < 1 mm of mean REC after 10 years.