Discovery and development of dabigatran
Preetpal S. Sidhu
Department of Chemistry and Biochemistry, University of Wisconsin, 2200 E. Kenwood Blvd.,
Milwaukee, WI 53201-0413, USA
Email: Sidhup@uwm.edu

Abstract
Thrombin is key protease involved in regulation of coagulation cascade and thus, highly targeted to
design the newer anticoagulant. Various direct and allosteric inhibitors of thrombin were designe
d but few made their way to clinic. Dabigatran is direct inhibitors of thrombin approved by FDA for clinical use.
This article highlights the discovery and development of dabigatran as newer anticoagulant drug.

Keywords: allosteric inhibitors, anticoagulant, dabogatran, coagulation cascade, thrombin

Thromboembolic disorders are a major cause of
death in the modern society due to life-style
changes [1]. Current therapies include indirect
thrombin inhibitors (heparin and low molecular
weight heparin), Vitamin K antagonist
(warfarin), and direct thrombin inhibitors
(argatroban and bivalirubin) [2, 3]. Recently the
focus has been on the discovery of selective and
safer inhibitors of thrombin targeting the active
site and exosites of thrombin [4-8]. Thrombin is
the main effector protease involved in the
coagulation cascade. Thrombin is activated
upon contact with tissue factor on exposed
extravascular tissues [3]. Thrombin activates
upstream factors in the coagulation cascade to
initiate and propagate—coagulation thereby
enhancing its own generation. The
procoagulant activity of thrombin is inhibited by
circulating anticoagulant biomolecules such as
antithrombin, heparin cofactor II and protein C.
Thrombin also induces many cellular effects via
a family of G-protein coupled pro-tease
activated receptors (PAR), PAR1, PAR3, and
PAR4 [9].

Dabigatran is a synthetic, reversible DTI
with high affinity and specificity for its target,
binding both free and clot-bound thrombin, and
offers a favorable pharmacokinetic profile [11].
Based on X-ray crystal structure of a bovine
thrombin complex with peptide-like
benzamidine based inhibitor NAPA, a lead
compound was identified because of its
favorable selectivity profile and strong in vitro
and in vivo activity, exhibited prolonged
anticoagulant effect and high dose tolerance in
rats after i.v. administration [12]. However, it
was not orally active due to its polarity. The
compound was converted into an orally active
prodrug dabigatran etexilate. Based on its
promising profile, dabigatran etexilate was
selected for clinical development [13].

Dabigatran is a reversible competitive inhibitor
with a $Ki$ of 4.5 nM. It inhibits both clot-bound
and free thrombin. Dabigatran inhibits both
thrombin induced platelet aggregation and
tissue factor induced thrombin generation [13].
Dabigatran has fast onset of action (peak
plasma concentration in 2-3 hours) with half-life
of 12-14 hours. Contrary to current
antithrombotic therapies, dabigatran does not
require routine coagulation monitoring. It is not
metabolized by cytochrome P450 and does not
have drug-drug interactions. It has low plasma
protein binding and undergoes about 80% renal
excretion. One of the most common side

The work summarized the discovery and
development of anticoagulant drug dabigatran
effects of dabigatran is bleeding [14]. Dabigatran etexilate is contra-indicated in severe renal impairment, paediatric populations, pregnancy, and lactation due to inadequate evidence of safety and efficacy. It also inhibits or induces both CYP3A4. Dabigatran do not require formal therapeutic drug monitoring but by their nature they can lead to increased bleeding and thus monitoring Hb may be advised. Dabigatran etexilate can also lead to epistaxis, anaemia, nausea and gastrointestinal discomfort, including diarrhoea. [14].

Preclinical investigations reveal that dabigatran is effective in both venous and arterial models. In clinical trial program, dabigatran has shown good safety profile. Dabigatran is also shown to be effective in the prevention of venous thrombosis after orthopedic surgery, acute thrombosis, and secondary prevention of VTE with no increased risk of bleeding [14, 15]. It has been studied in more than 10,000 patients in clinical trials for treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis in major orthopedic surgery [16]. In clinical trial RE-LY, there was a significantly higher risk of gastrointestinal bleeding with dabigatran 150 mg bid compared with warfarin [17]. No statistical significant difference was seen when using the 110 mg BID dabigatran dose. Mild to moderate dyspepsia related to dabigatran was also reported. The side effect tended to be transient, and may be managed by giving dabigatran with a large glass of water, with food, or a proton-pump inhibitor [18, 19].

In the treatment of VTE, dabigatran etexilate was compared to standard warfarin treatment [20-22]. Dabigatran demonstrated the same efficacy in thrombosis prevention with significantly less minor bleeding and similar major bleeding [23, 24]. Dabigatran also demonstrated efficacy in atrial fibrillation similar to standard warfarin therapy [17]. Dabigatran is approved for prevention of stroke and systemic embolism associated with nonvalvular atrial fibrillation with dosage of 150 mg PO BID. The cost of dabigatran ($3000/year) is substantially higher than those of warfarin ($48/year), but reduces the cost associated with regular clinical monitoring. There is a significant unmet need to develop anticoagulation treatment that is effective, easy and safe. More than 50 years after the discovery of warfarin, the development of dabigatran is considered as breakthrough achievement for the treatment of thromboembolic disease including the prevention of catastrophic strokes in patients [15].

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