

Different Classes of Anticoagulant Drugs in Clinical Use. Is there a Class Effect?

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Rec date: Feb 27, 2015, Acc date: Mar 11, 2015, Pub date: Mar 18, 2015

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Short Communication

Hippocrates first proposed 'Blood thinners' in ancient Greek medicine. Historically, extracts from many plants, bloodletting, leech bleeding, acid fruits and clear wines were considered as anticoagulants. Although, Haycraft in 1884 identified the anticoagulant in the saliva of European medicinal leech, later named hirudin, the extract was found to be too toxic. Following Jay McLean's discovery of an anticoagulant in 1916, and naming of this anticoagulant as 'heparin' by Howel and Holt in 1918 and Howel's purification of this compound in 1925, it was only in 1930s that the effective anticoagulant treatment started. Soon after the discovery of the first oral anticoagulant, dicoumarin in 1935, the purified injectable preparations of heparin were used. Later, other types of antithrombotic and anticoagulant treatment, including antiplatelet drugs, snake venoms, direct and indirect thrombin inhibitors, activated protein C, direct Factor Xa inhibitors and recombinant hirudins have since been introduced [1]. Warfarin, a conventionally used oral anticoagulant, despite its limitations of drug-food, drug-drug interactions, need for frequent PT/INR monitoring, adverse drug reactions, bleeding, warfarin-induced skin necrosis, frequent need for dosage adjustments because of changes in the dietary patterns, effects due to VKORC polymorphism, has stood the test of time and still continues to be used in clinical practice. Recently the New Oral Anticoagulant drugs, direct Factor Xa such as Rivaroxaban, Apixaban and Edoxaban and direct thrombin inhibitors such as Dabigatran were approved by the USFDA. There are several limitations in the use of NOACs such as the lack of an effective test to monitor their anticoagulant activities, the lack of an effective antidote, and dose adjustments in patients with renal impairment [2]. Thus, a bewildering wide array of anticoagulant drugs are now available for use and it is interesting to see whether or not these drugs representing different classes of anticoagulant drugs, especially direct thrombin and direct Factor Xa inhibitors have any class effects in terms of differences in their clinical outcomes.

Direct thrombin inhibitors such as dabigatran and bivalirudin currently established for treatment and prevention of cardiac thromboembolism and venous thromboembolism (VTE) are reported to be repeatedly associated with a significantly increased frequency of thrombosis on abnormal cardiac endothelium when directly compared against indirectly acting therapeutic anticoagulants in studies with sufficient patient numbers and duration [3]. Other direct thrombin inhibitors such as bivalirudin, dabigatran, argatroban, desirudin indicated for therapeutic or prophylactic use. However, in clinical trials of sufficient patient numbers and sufficient duration where direct thrombin inhibitors have been compared against another active anticoagulant, there was increased incidence of myocardial infarction and/or ischemia, or coronary stent or cardiac valve thrombosis [3,4-9] (Table 1). One clinical trial was prematurely stopped when dabigatran was compared against warfarin patients for patients with mechanical heart valves when dabigatran caused high rate of adverse events

including stroke presumably related to valve thrombosis [10]. A meta-analysis including ximelagatran and dabigatran and other antithrombotic drugs for atrial fibrillation concluded that warfarin provided superior protection against myocardial infarction compared with ximelagatran or dabigatran [11]. In one study dabigatran was also evaluated against warfarin in patients with mechanical heart valves and it was concluded that dabigatran was associated with increased rates of thromboembolic and bleeding complications. The trial was stopped early because of an excess of thromboembolic and bleeding events in the dabigatran group. Most thromboembolic events in the dabigatran group occurred in patients who had started the study drug within 7 days after valve surgery and fewer in patients who had undergone valve implantation more than 3 months before randomization. Possible explanations of study investigators, as to why there was the increase in thromboembolic complications, include inadequate plasma levels of the drug and a mechanism of action that differs from that of warfarin [10]. However, thromboembolic events were also reported among patients with higher trough plasma levels of dabigatran in both groups suggesting that lower-than-expected drug levels do not fully explain the increase in the rate of thromboembolic events. Perhaps the tissue factor- and contact-activation-generated thrombin during surgery might overwhelm a pharmacokinetically controlled dabigatran level [10]. Warfarin and heparin inhibit thrombin and other clotting factors. So far no increased incidence of cardiac thrombosis have been reported with new oral Factor Xa inhibitors such as rivaroxaban and apixaban and indirect specific inhibitor of Factor Xa such as fondaparinux has been reported [3].

The exact reason or the mechanism for increased cardiac thrombosis in anticoagulation with direct thrombin inhibitors is not known. Thrombin besides having procoagulant effects also has anticoagulant effects through the activation of the protein C pathway. Perhaps following complete inhibition of the thrombin, there is none available to bind with thrombomodulin to trigger the activation of protein C to activated protein C to exhibit its endogenous anticoagulant properties via inhibition of FVa and FVIIIa. As a result increased FVa in the presence of FXa converts prothrombin to thrombin. Similarly increased FVIIIa in the presence of FIXa converts FX to FXa thereby converts prothrombin to thrombin.

Thus increased thrombin generation through these feedback loops may be responsible for the increased incidence of cardiac thrombosis seen in patients who received thrombin inhibitors. One possible reason as to why unfractionated heparin is better than the thrombin inhibitors is that unfractionated heparin is capable of triggering increased expression of Tissue Factor Pathway Inhibitor (TFPI) from the endothelium. TFPI is a protease inhibitor containing three Kunitz type domains [12]. The first domain combines with factor VIIa and inhibits it. The second domain combines with FXa and inhibits it. The function of the third domain is not completely understood. Thus TFPI

by combining with tissue factor (TF), FXa, FVIIa forms a TFPI-TF-FXa-FVIIa quaternary inhibitory complex [13].

Furthermore, the TF induced thrombin generation is downregulated by TFPI and the functional protein C pathway [14].

Thrombin-Thrombomodulin complex links coagulation with the fibrinolysis by Thrombin Activatable Fibrinolytic Inhibitor (TAFI) [15,16]. The interactive role of the thrombin-thrombomodulin

complex, TFPI, protein C, APC, TAFI in coagulation pathway needs further exploration and may hold the key in the further understanding of the increased incidence of cardiac thrombosis in patients administered with thrombin inhibitors. Personalized or individualized tailored therapy with a right anticoagulant at the right dosage to the right patient at the right time may help in avoiding adverse outcomes.

Trial Name	Design	Patients (n=)	Condition	Drugs	Outcomes	Result
EUROMAX [4]	Randomized	2218	STEMI-transported for PCI	Bivalirudin or UFH or LMWH and optional GPIIb/IIIa	Primary: Composite of death, reinfarction or non-CABG major bleeding. Secondary: 30-day Composite of death or major bleeding not associated with CABG	Bivalirudin reduced risk of primary outcome (5.1% vs. 8.5%; RR, 0.60; 95% CI, 0.43-0.82; p=0.001 and risk of principal sec outcome (6.6% vs. 9.2%; RR 0.72; 95% CI, 0.54-0.96; p=0.020. Bivalirudin also reduced risk of major bleeding (2.6% vs. 6.0%; RR, 0.43; 95% CI, 0.28 to 0.66; p<0.001) Risk of Acute Stent Thrombosis High with Bivalirudin (1.1% vs. 0.2%; RR 6.11; 95% CI, 1.37 to 27.24; P=0.007.
HORIZONS-AMI [5]	Randomized	3602	STEMI –within 12 hours of symptoms for PCI	Bivalirudin Alone Or Heparin+GPIIb/IIIa Inhibitors	Two primary endpoints: Major bleeding or major adverse CV events, including death, reinfarction, target vessel revascularization for ischemia and stroke (net adverse clinical events).	Bivalirudin reduced 30-day rate of net adverse clinical events (9.2% vs. 12.1%; RR, 0.76; 95%CI, 0.63 to 0.92; P=0.005) and lower rate of major bleeding (4.9% vs 8.3%; RR, 0.60; 95%CI, 0.46 to 0.77; P=<0.001. Risk of Acute Stent Thrombosis; Increase within 24 hrs but no change by 30 days.
HEAT-PPCI [6]	Randomized	1829	Undergoing emergency angiography in the context of primary PCI.	Heparin or Bivalirudin	The primary efficacy outcome composite of all-cause mortality, cerebrovascular accident, re-infarction, or unplanned target lesion revascularization. Primary safety outcome was incidence of major bleeding.	The primary efficacy outcome occurred in 79 (8.7%) in the Bivalirudin and 52 (5.7%) of patients in the heparin group (absolute risk difference 3.0%; RR1-52, 95%CI, 1.09-2.13, P=0.01). The primary safety outcome occurred in 32 (3.5%) of 905 patients in the bivalirudin group and 28 (3.1%) of 907 patients in heparin group

						(0.4%; 1-15, 0.70-1.89, P=0.59). Stent Thrombosis rate 3.4% in Bivalirudin group and 0.9% in Heparin group. Absolute risk difference 95%CI 2.6; RR, 3.91, P=0.001.
RE-LY [7]	Randomized, Non-inferiority	18,113	Atrial Fibrillation with a risk of stroke	Fixed dose of Dabigatran -110 mg or 150 mg twice daily (blinded) fashion or adjusted dose warfarin (unblinded).	Primary outcome was stroke or systemic embolism.	Compared with Bivalirudin, heparin reduces the incidence of major adverse events in the setting of PPCI. Stent thrombosis events: More common with bivalirudin therapy than with heparin therapy.
REMEDY [8]	Randomised (Active Control study)	2856	Recurrent VTE	Dabigatran at a dose of 150 mg twice daily vs warfarin	Primary Efficacy outcome: Recurrent symptomatic and objectively verified VTE or death associated with VTE.	Recurrent VTE occurred in 26 of 1430 patients (1.8%) in the dabigatran group and 18 of 1426 patients (1.3%) in the warfarin group. Hazard ratio with dabigatran, 1.44; 95% CI, 0.41 to 0.71). Acute coronary syndromes occurred in 13 patients in the dabigatran group (0.9%) and 3 patients in the warfarin group (0.2%) P=0.02. Recurrent or fatal VTE events with dabigatran (26 events [1.8%], vs 18 events with warfarin [1.3%].
RESONATE [8]	Randomised (Placebo control study)	1343	Recurrent VTE	Dabigatran at a dose of 150 mg twice daily vs placebo	Primary Efficacy outcome: Recurrent symptomatic and objectively verified VTE or death associated with VTE (or unexplained death).	Recurrent VTE occurred in 3 of 681 patients in the dabigatran group (0.4%) and 37 of 662 patients in the placebo group (5.6%) (Hazard ratio, 0.08; 95% CI, 0.02 to 0.25; P<.001,
Meta-analysis of seven trials [9]	Randomized controlled trials	30,514		Effect of Dabigatran on Myocardial infarction or acute coronary syndromes. Control arms: warfarin, enoxaparin or placebo	Myocardial infarction or acute coronary syndromes.	Increased risk of myocardial infarction or acute coronary syndrome with dabigatran when tested against the controls including warfarin,

						enoxaparin placebo.	or
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Table 1: Clinical trials of sufficient patient numbers.

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