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Non-vitamin K oral anticoagulants (NOAC) and the risk of myocardial infarction: Differences between factor IIa and factor Xa inhibition?

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ABSTRACT

Guidelines already recommend non-vitamin K oral anticoagulants (NOAC) over vitamin-K antagonists (VKA) for stroke prevention in patients with atrial fibrillation. However, recommendations are lacking with respect to which NOAC to use. At the moment, NOACs may employ two different molecular mechanisms: Factor IIa inhibition (dabigatran) and factor Xa inhibition (apixaban, edoxaban, rivaroxaban). The focus of this review is to compare and contrast potential differences between factor IIa- and factor Xa inhibition with respect to risk of myocardial infarction and to detail underlying mechanisms.

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Contents

1. Introduction

For almost a decade, non-vitamin K oral anticoagulants (NOAC) have expanded the choice of anticoagulation in patients with atrial fibrillation (AF). Currently, NOACs utilize two distinct molecular mechanisms of coagulation inhibition: Inhibition of factor IIa by dabigatran and inhibition of factor Xa by apixaban, edoxaban or rivaroxaban respectively. All NOACs feature a superior benefit/risk ratio in terms of bleeding, mortality and stroke prevention as compared to vitamin-k antagonists (VKA) (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011). For stroke prevention, the 2016 ESC guidelines recommend the use of NOAC over VKA. However, until now there are still no recommendations regarding the optimal type of NOAC for the individual patient. While many drug characteristics may be similar, the NOAC landmark trials have shown interesting results regarding patients' risk of myocardial infarction (MI): factor IIa inhibition by dabigatran was associated with increased risk of MI, whereas risk of MI was numerically lower as compared to VKA in the landmark trials testing factor Xa inhibiting NOACs (rivaroxaban, apixaban, edoxaban). In the context of these findings, potential underlying mechanisms have been proposed by basic

Abbreviations: ADP, adenosine diphosphate; AF, Atrial fibrillation; GP, Glycoprotein; NOAC, Non-vitamin K oral anticoagulants; MI, Myocardial infarction; PAR, Protease-activated receptor; VKA, Vitamin-K antagonist.

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and clinical science studies. To this affect, this review will summarize the differences of MI risk between different NOACs and provide related mechanistic insights.

2. Factor IIa inhibition and risk of myocardial infarction

Dabigatran is a direct thrombin (factor IIa) inhibitor. In its landmark trial, RE-LY, both dose regimens of dabigatran (110 mg b.i.d. and 150 mg b.i.d.) were associated with an enhanced risk for MI (Connolly et al., 2009). Moreover, a meta-analysis of four randomized trials demonstrated a relative risk increment of 41% for the occurrence of MI under dabigatran compared to VKA (Artang, Rome, Nielsen, & Vidaillet, 2013). However, dabigatran still obtained a superior net clinical benefit compared to VKA. The recently published RE-DUAL PCI trial compared dabigatran (110 mg or 150 mg) and P2Y12-inhibition to triple therapy (warfarin, aspirin, P2Y12-inhibition) in patients with AF undergoing percutaneous coronary interventions (PCI) (Cannon et al., 2017). The results of this trial were awaited eagerly to help guide anticoagulation following PCI in patients with AF. Especially, as RE-LY reported the above mentioned enhanced risk of MI. Fewer bleeding events occurred in patients receiving dual therapy with dabigatran (110 mg and 150 mg). Although underpowered to detect differences in ischemic events, again, a numerically higher rate of MI was found in dabigatran treated patients especially in the low-dose regimen group. This numerical higher rate reached near statistical significance in the 110 mg but not in the 150 mg dabigatran intervention. This was remarkable, especially as the sample size of RE-DUAL PCI was substantially smaller than in RE-LY (RE-DUAL PCI: 2725 patients, RE-LY: 18,113 patients).

Potential platelet-related mechanisms that might explain an augmented risk of MI in dabigatran treated patients have been investigated: Enhanced platelet reactivity is known to be associated with the risk of MI (Mangiacapra et al., 2018) and catalytically active thrombin is a potent stimulus to induce platelet aggregation. Therefore, analyzing the interaction of dabigatran and platelet reactivity seems reasonable. It was recently shown that dabigatran enhanced platelet adhesion in an in-vitro flow chamber model and led to increased thrombus formation on human atherosclerotic plaque material (Petzold et al., 2016). These pro-thrombotic effects were shown to depend on altered thrombin glycoprotein (GP) Ibα interaction leading to an augmented GPIbα signaling downstream of von Willebrand factor binding (Petzold et al., 2016). Interestingly, this mechanism was independent of the catalytic activity of thrombin with subsequent induction of plasmatic coagulation (Franchi et al., 2016; Petzold et al., 2016). Furthermore, dabigatran enhanced thrombin-induced platelet aggregation measured by light-transmittance aggregometry, while there was no influence on aggregation induced by other agonists like adenosine diphosphate (ADP), collagen, or arachidonic acid respectively (Achilles et al., 2017). This effect was measurable after a single dose of dabigatran (Achilles et al., 2017). Repeated dosing led to additional increase of platelet reactivity (Olivier et al., 2016). These pro-thrombotic effects of dabigatran were found to be dose-dependent with higher platelet reactivity in 150 mg dabigatran b.i.d. as compared to 110 mg b.i.d. treated patients (Olivier et al., 2016). The underlying mechanism is an increased surface expression measured by fluorescence activated cell sorting analysis of platelet protease activated receptor (PAR)-1 and PAR-4 on platelets (Achilles et al., 2017). An in-vitro study found that dabigatran leads to an acute inhibition of thrombin-induced PAR-1 cleavage, activation and internalization in a dose dependent manner (Chen et al., 2015). Furthermore, it could be shown that prolonged exposure to inactivated thrombin by dabigatran resulted in increased PAR-1- surface expression (Chen et al., 2015). In summary, these studies identified potential pro-thrombotic mechanisms that might contribute to the increased frequency of MI in dabigatran treated patients seen in clinical trials (Fig. 1).

3. Factor-Xa-inhibitors and risk of myocardial infarction

In contrast to dabigatran, the factor Xa-inhibitor landmark trials revealed a numerical reduction of MI (Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011). (Table 1) A meta-analysis found a significantly reduced risk of MI and cardiovascular mortality under rivaroxaban tested against different controls (Chatterjee et al., 2013). Along this line, the results of PIONEER AF-PCI, which investigated rivaroxaban in combination with antiplatelet therapy in patients with AF undergoing PCI, found a similar trend: Again a numerical decrease of MI was observed in rivaroxaban treated patients compared to VKA (Gibson et al., 2016). In this context, the trials investigating apixaban and edoxaban with antiplatelet therapy in patients after PCI are awaited eagerly (AUGUSTUS, ENTRUST-AF-PCI).

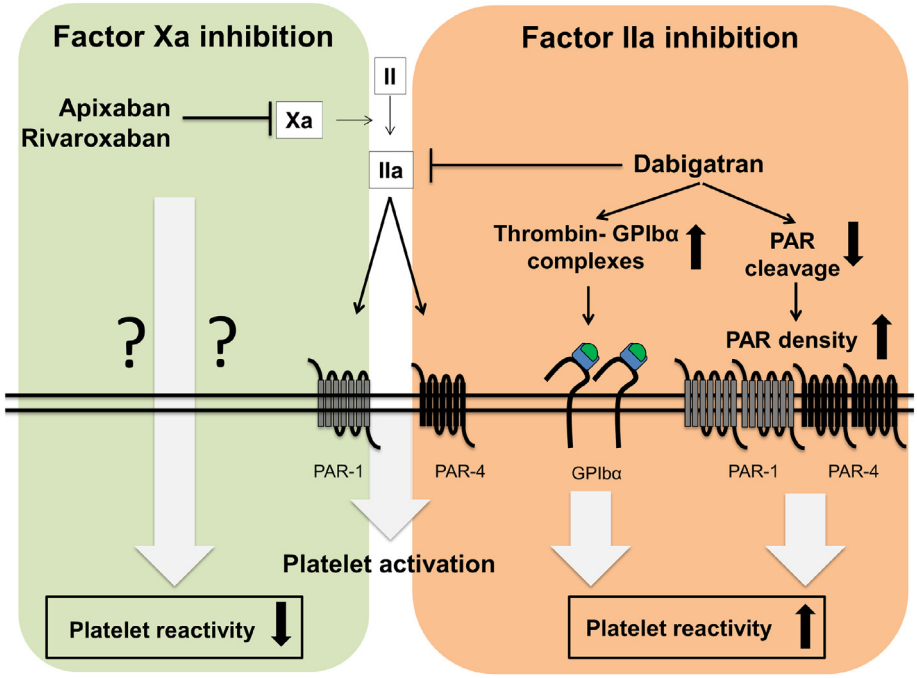

Fig. 1. Mechanisms of factor IIa- and Xa- inhibitors on platelet activation.

Table 1
Rate of myocardial infarction (MI) in NOAC landmark trials.

Study	Myocardial infarction no. (%/year)				Comparison (HR, CI 95%, p-value)		
RE-LY (Connolly et al., 2009)	Dabigatran, 110 mg bd (N = 6015)	Dabigatran, 150 mg b.i.d. (N = 6076)	Warfarin (N = 6022)		Dabigatran, 110 mg, vs. Warfarin	Dabigatran, 150 mg, vs. Warfarin	Dabigatran, 110 mg, vs. Dabigatran, 150 mg
	86 (0.72)	89 (0.74)	63 (0.53)		1.35 (0.98–1.87), 0.07	1.38 (1.00–1.91), 0.048	1.02 (0.76–1.38), 0.88
Rocket-AF (Patel et al., 2011)	Rivaroxaban, 20 mg od (N = 7131)		Warfarin (N = 7133)		Rivaroxaban 20 mg o.d. vs. Warfarin		
	101 (0.91)		126 (1.12)		0.81 (0.63–1.06), 0.121		
Aristotle (Granger et al., 2011)	Apixaban, 5 mg bd (N = 9120)		Warfarin (N = 9081)		Apixaban 5 mg b.i.d. vs. Warfarin		
	90 (0.53)		102 (0.61)		0.88 (0.66–1.17), 0.37		
Engage-AF (Giugliano et al., 2013)	Edoxaban, 30 mg od (N = 7034)	Edoxaban, 60 mg od (N = 7035)	Warfarin (N = 7036)		Edoxaban 30 mg o.d. vs. Warfarin	Edoxaban 60 mg o.d. vs. Warfarin	
	169 (0.89)	133 (0.70)	141 (0.75)		1.19 (0.95–1.49), 0.13	0.94 (0.74–1.19), 0.6	
Pioneer-AF (Gibson et al., 2016)	Group 1[a] (N = 709)	Group 2[b] (N = 709)	Group 3[c] (N = 706)		Group 1 vs. Group 3	Group 2 vs. Group 3	
	19 (3.0)	17 (2.7)	21 (3.5)		0.86 (0.46–1.59) 0.62	0.75 (0.4–1.42) 0.37	
Re-Dual (Cannon et al., 2017)	110 mg Dual Therapy Group (N = 981)	Corres-ponding Triple Therapy Group (N = 981)	150 mg Dual Therapy Group (N = 763)	Corres-ponding Triple Therapy Group (N = 764)	110 mg Dual Therapy Group vs. Triple Therapy Group	150 mg Dual Therapy Group vs. Triple Therapy Group	
	44 (4.5)	29 (3.0)	26 (3.4)	22 (2.9)	1.51 (0.94–2.41) 0.09	1.16 (0.66–2.04) 0.61	

[a] Group 1: Rivaroxaban 15 mg o.d. (10 mg o.d. in case of GFR 30–50 ml/min) + clopidogrel 75 mg o.d. (or ticagrelor 90 mg b.i.d or prasugrel 10 mg o.d. in ≤15% of participants) for 12 months.
[b] Group2: Rivaroxaban 2.5 mg b.i.d. + aspirin (75 to 100 mg o.d.) and clopidogrel 75 mg o.d. (or ticagrelor 90 mg b.i.d. or prasugrel 10 mg o.d. in ≤15% of participants) for 1, 6, or 12 months. Participants with treatment for 1 or 6 months received rivaroxaban 15 mg o.d. afterwards (or 10 mg o.d. if they had moderate renal impairment) + aspirin (75 to 100 mg o.d.) for the remainder of the 12-month treatment period.
[c] Group 3: Warfarin o.d. (target INR 2–3) + aspirin (75 to 100 mg o.d.) and clopidogrel 75 mg o.d. (or ticagrelor 90 mg b.i.d. or prasugrel 10 mg o.d. in ≤15% of participants) for 1, 6, or 12 months. Participants with treatment for 1 or 6 months received warfarin o.d. afterwards (target INR 2–3) + aspirin (75 to 100 mg o.d.) for the remainder of the 12-month treatment period.

Beside its role in AF, factor Xa inhibition has previously been well investigated in patients with coronary artery disease without AF. Rivaroxaban in conjunction with antiplatelet therapy reduced the rate of death from cardiovascular causes, myocardial infarction and stroke in patients after myocardial infarction in ATLAS ACS 2-TIMI (Mega et al., 2012). Additionally, the recent COMPASS trial revealed improved cardiovascular outcome in patients with stable coronary artery disease additionally treated with rivaroxaban and low-dose aspirin (Eikelboom et al., 2017). However, these benefits did not hold true for all factor Xa inhibitors: Apixaban was unable to obtain a net clinical benefit on top of antiplatelet medication in patients after acute coronary syndrome due to an increase in major bleeding events in APPRAISE-2 (Alexander et al., 2011). However, in contrast to reduced-dose regimen in COMPASS or ATLAS-ACS (2.5 mg rivaroxaban b.i.d.), the apixaban dose used for stroke prevention due to AF was applied in APPRAISE-2 (5 mg b.i.d.) (Alexander et al., 2011). This might have contributed to the increase in major bleedings. Despite this, the rate of MI was decreased in APPRAISE-2 as well (Alexander et al., 2011).

There are several basic science studies that aim to investigate potential mechanisms behind the reduced incidence of MI in factor Xa inhibitor treated patients. Perzborn et al. reported that in-vitro addition of rivaroxaban reduced tissue-factor induced platelet aggregation (Perzborn, Heitmeier, & Laux, 2015). Additionally, Nehaj et al. showed reduced thrombin receptor activating peptide induced platelet aggregation in a time-series analysis of rivaroxaban and apixaban treated patients (Nehaj et al., 2017). Furthermore, Pignatelli et al. revealed in a cross-sectional study that rivaroxaban and apixaban significantly reduce both thromboxane B2 secretion and of soluble GPVI expression as compared to VKA (Pignatelli et al., 2016). In contrast, Banovcin et al. did not observe reduced ADP, epinephrine or collagen induced platelet reactivity in rivaroxaban treated patients (Banovcin Jr. et al., 2017). The reason for these discrepant results remains insufficiently understood. In summary, clinical trials emphasize a reduction of MI in factor Xa treated patients. Further studies are needed to confirm this trend and investigate potential mechanisms.

4. Conclusion

Factor IIa inhibition by dabigatran might increase the risk of MI by enhancing platelet reactivity through several potential mechanisms. In contrast, factor Xa inhibition might reduce the risk of MI. However, more basic and clinical science studies are needed to further determine exact mechanisms. Clinical studies (or meta-analyses) will hopefully illustrate whether the hypothesis of increased risk of MI in factor IIa inhibition and decreased risk of MI in factor Xa inhibition holds true in large patient cohorts. Investigation of the risk of MI associated with different types of NOAC is crucial to identify the optimal NOAC for the individual patient.

Authors' contributions

A.P., L.D., T.P., G.W., C.H. and A.A. wrote the manuscript. T.H., T.Z., M.K. and S.M. revised the manuscript.

Conflict of interest disclosures

No conflicts to disclose.

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