Do non-vitamin K antagonist oral anticoagulants increase the risk of myocardial infarction?

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ABSTRACT

Non-vitamin K antagonist oral anticoagulants (NOACs), compared with warfarin, have a favorable risk-benefit profile. However, in the RE-LY study in patients with atrial fibrillation (AF), the number of patients with MI was higher in the dabigatran group as compared to the warfarin group. Many meta-analyses showed that dabigatran treatment led to an increased risk of myocardial infarction (MI). Large real-world data (RWD) did not confirm an increase in the risk of MI during dabigatran treatment. In our meta-analysis we excluded RWD, and each of the four drugs was evaluated in two key-phase III randomized controlled trials: in patients with AF and patients with AF and chronic coronary syndrome or acute coronary syndrome treated with percutaneous coronary interventions. In each study, warfarin was the comparator for NOACs. In this homogeneous group of patients, dabigatran, in direct comparison with warfarin, significantly increased the risk of MI by about 30%. Moreover, the risk of MI was also significantly higher than the opposite effect of activated factor (F) X inhibitors (FXa inhibitors) vs. warfarin. In our network meta-analysis, considering individual NOACs in recommended doses, we found an increased risk of MI compared to warfarin only in patients treated with dabigatran 150 mg twice a day and, in particular, 110 mg twice a day. In this review we present evidence supporting our opinion that in patients with AF and coronary stenting, the choice of NOACs (direct FXa vs. thrombin inhibitors) is equally as important as choosing the optimal antiplatelet therapy (single or dual antiplatelet therapy).

Key words: non-vitamin K antagonists oral anticoagulants, NOAC, myocardial infarction, risk

FROM THE RE-LY STUDY TO THE PIONEER STUDY

The use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation (AF) is widely accepted due to their greater effectiveness in the prevention of stroke and systemic embolism and a lower number of bleeding complications compared to warfarin [1]. The European Society of Cardiology (ESC) guidelines have consistently recommended their use for several years. In 2009, the results of a large randomized controlled trial (RCT) were published in which the effectiveness of dabigatran and warfarin in the treatment of patients with AF (RE-LY, Randomized Evaluation of. Long-Term Anticoagulation Therapy) was compared [2]. Dabigatran, at a dose of 110 mg twice a day, compared to warfarin, did not significantly reduce the risk of either stroke or systemic embolism, but bleeding complications were significantly less frequent. Conversely, dabigatran at a dose of 150 mg twice a day significantly reduced the incidence of stroke and systemic embolism, but bleeding complications occurred in a similar percentage of patients as in the case of those treated with warfarin. A surprising increase in the number of myocardial infarction (MI) cases was observed in patients treated with dabigatran. The corresponding numbers for the 110 mg and 150 mg dabigatran doses and warfarin were 86, 89, and 63 patients, respectively. These apparent differences increased the relative risk (RR) of MI and RR for both dabigatran doses: 1.35 (95% confidence interval [CI], 0.98–1.87) and 1.38 (95% CI, 1.0–1.91), respectively [2]. During the process of drug approval in the US, it was revealed that 69 bleeding compli-

cations, one stroke, one systemic embolism, five episodes of transient ischemic attack (TIA), and 28 oligosymptomatic and four overt clinical MI were "not noticed" [3, 4]. In 2012, Uchino presented the results of a meta-analysis assessing the influence of dabigatran on the risk of acute coronary syndrome (ACS) [5]. The author compared the effects of dabigatran use in various clinical scenarios (AF, active venous thrombosis, thrombosis prevention) and with various comparators (enoxaparin, warfarin, placebo), including the original results from the RE-LY study [2]. He showed that the drug increased the risk of MI by 30% [5]. In that situation, it became necessary to recalculate MI incidents [6]. The adjusted MI number was still higher at dabigatran doses of 110 mg and 150 mg compared to warfarin: 98, 97, and 75, respectively. The reassessed RR of MI for 110 mg and 150 mg in patients entering the study (intention to treat) was 1.29 (95% CI, 0.96–1.75) and 1.27 (95% CI, 0.94–1.71), respectively. This RR for pooled doses was 1.28 (95% CI, 0.98– 1.67). In patients taking drugs throughout the study (on-treatment), the RR for the doses of 110 mg and 150 mg were 1.32 (95% CI, 0.95–1.84) and 1.30 (95% CI, 0.98–1.81), respectively. After adjusting, the re-estimated MI risk just failed to reach statistical significance, but it was invariably around 30% [6]. Many subsequent meta-analyses have confirmed a statistically significant increase in the MI risk in patients treated with dabigatran [7–12]. Moreover, unlike rivaroxaban and apixaban, dabigatran statistically significantly increased the MI risk in various clinical scenarios (AF, ACS, active vein thrombosis, thrombosis prevention) and with various comparators (enoxaparin, warfarin, placebo) [7–10]. Lip et al. [13] indirectly compared the treatment results in AF patients with dabigatran, rivaroxaban, and apixaban [2, 13–15]. Warfarin was the common comparator in all these RCTs. In patients treated with dabigatran, the author showed a greater MI risk compared to apixaban and rivaroxaban; however, he concluded that the observed differences between NOACs required confirmation in RCTs directly comparing individual drugs [13]. Such studies have not been performed so far. In 2013, Artang et al. [9] showed that the whole group of direct thrombin inhibitors (DTI), including dabigatran, significantly increased the MI risk by about 30% compared to warfarin, while FXa inhibitors slightly reduced or had no significant effect on the MI risk. In 2016, Morimoto et al. [12] conducted a network meta-analysis comparing the NOACs mentioned above, additionally adding edoxaban at a daily dose of 30 mg and 60 mg, ximelagatran, as well as aspirin and idraparinux. Compared to warfarin, the primary composite endpoint – defined slightly differently in each of the analyzed studies — was similar for all NOACs. At the same time, the risk of MI varied, with dabigatran 110 mg having the highest one [12]. Of note, the above-cited conclusions from the meta-analyses with unfavorable effects of DTIs were based on the analysis of the RCT results.

Data from large real-world registries mostly did not confirm an increase in the risk of MI after treatment with dabigatran [16–19]. However, in one of them, switching from warfarin to dabigatran in patients with AF, in comparison with those receiving regular warfarin therapy, was associated with a statistically significant increase in the MI risk [20]. The largest meta-analysis analyzing data from RCTs and RWD in total (over 550 000 patients) showed no increase in the MI risk during treatment with dabigatran [21]. The differences in the results of RCT and RWD are mainly due to different research assumptions and not well-balance confounding variables. Nevertheless, without questioning the high informative value of RWD, RCTs are still the "gold standard" in clinical research [22–25]. Their results and periodically published meta-analyses are the basis for the frequently updated European Society of Cardiology (ESC) guidelines. In the RE-LY study, the increase in the MI risk was small and amounted to 0.74% per year in the dabigatran group and 0.53% per year — in the warfarin group [2]. The estimated number needed to harm (NNH), i.e., the number of AF patients treated with dabigatran to observe on MI, was approximately 500. The effectiveness of dabigatran in preventing stroke and systemic embolism justified the opinion that the observed benefits outweighed the slight increase in the MI risk [22]. The view was acceptable until the publication of the results of studies with AF patients treated with NOACs and undergoing percutaneous coronary interventions (PCI). The first study was PIONEER-AF PCI (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) with rivaroxaban, then REDUAL-PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) with dabigatran, another was AUGUSTUS (An Open-Label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) with apixaban, and the last one was ENTRUST-AF PCI (Edoxaban Treatment vs. Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) with edoxaban [26––29]. The treatment results with the latter drug in patients with AF were presented a few months ago, and the ENTRUST study was the last of the "big four" reported in Poland [30].

LANDSCAPE AFTER THE PIONEER STUDY

The studies mentioned above were published between 2016 and 2019, and patients with chronic coronary syndrome (CCS) accounted for 40%–50% while the rest were treated due to ACS. Only a slight increase in the number of MI was found in the ENTRUST AF-PCI study (edoxaban 60 mg compared to warfarin: 29 vs. 23) [29], while the

increase was very marked in the REDUAL-PCI study (both pooled doses compared to warfarin: 70 vs. 29) [27]. For the 110 mg dabigatran dose, the RR of death, MI, and stent thrombosis (ST) were 1.12 (95% CI, 0.76–1.65), 1.51 (95% CI, 0.94–2.41), and 1.86 (95% CI, 0.78–4.40), respectively. Better results were obtained with the dabigatran dose of 150 mg. The RR of death, MI and ST were 0.83 (95% CI, 0.51–1.34), 1.16 (95% CI, 0.66–2.04), and 0.99 (95% CI, 0.35–2.81), respectively. The ESC recommendations suggested using a higher dose of dabigatran in AF patients undergoing PCI. Obviously, PCI procedures can and are performed in AF patients receiving dabigatran. The concerns raised are not related in any way to the procedure but to potentially pro-thrombotic properties of the drug. It might be speculated that aggressive periprocedural antiplatelet therapy partially neutralizes the potentially increased MI risk; however, the increased risk might persist throughout the dabigatran use.

The available data and growing doubts surrounding DTI led us to perform a meta-analysis assessing the influence of NOACs on the MI risk in AF patients [31]. Eight RCTs met the inclusion criteria. The analyzed population included 81 943 patients, of whom 1653 (2.1%) experienced MI. The selected population met the following criteria:

- all patients had permanent AF;
- each of the "big four" NOACs was presented by two RCTs; in patients not undergoing PCI and undergoing PCI;
- Warfarin was used as a comparator in all studies.

This population represented the most homogeneous group of patients among the meta-analyses cited above. Data evaluation was performed based on the original data from the RE-LY study [2] and those published by Hohnloser et al. in 2012 [6]. In addition, direct comparisons with warfarin were made twice. Firstly, the comparison of the two doses of dabigatran with warfarin allowed assessing the magnitude of the MI risk for each dose. In the RE-LY [2] and REDUAL-PCI [27] studies, the control group (warfarin) was the same for both doses of dabigatran, so this calculation method doubled the number of patients in the control group. This could have led to misreading error regarding the level of statistical significance. Therefore, the analysis was repeated a second time, summing up both subpopulations (doses: 110 mg + 150 mg) to estimate the total MI risk. A similar calculation strategy was used for the ENGAGE AF study, which tested two daily doses of edoxaban, i.e. 2 × 30 mg and 2 × 60 mg [30]. Moreover, only the recommended daily dose of rivaroxaban 15 mg [26] was assessed in the PIONEER study and apixaban dose of 5 mg twice daily in the ARISTOTLE study [28]. Figure 1A and B show the estimated MI risk when using NOACs, presented according to individual doses of dabigatran and edoxaban (Figure 1A), and after data pooling (Figure 1B). Dabigatran compared with warfarin in both assessments significantly increased the MI risk by 38%. FXa inhibitors compared with warfarin tended to reduce the MI risk by about 4%–5% (not a statistically significant difference). Moreover, there was a significant difference between dabigatran and FXa inhibitors. After applying the corrected results published by Hohnloser's et al. [6] the estimates did not change in the intention-to-treat or on-treatment analysis [31] and treatment with dabigatran vs. warfarin , as well as FXa inhibitors, was associated with a significant increase in the MI risk. The results of our meta-analysis confirmed the observations from previous years, additionally considering the studies in which PCI was performed with the use of NOACs with single (SAPT) or dual (DAPT) antiplatelet therapy. In turn, the network analysis allowed assessing the MI risk by comparing the individual doses of the analyzed drugs with each other (Figure 2). Both doses of dabigatran significantly increased the MI risk, especially when compared with rivaroxaban and apixaban, and surprisingly with warfarin. The results of our meta-analysis are consistent with network analyses published by other authors [11, 32]. Table 1 presents the estimated SUCRA (on a scale from 1% to 100%), which is a ranking of the effectiveness of the tested drugs in reducing the MI risk. Rivaroxaban 15 mg was effective in 90%, apixaban 5 mg — in 80%, dabigatran 150 mg — in 14%, dabigatran 110 mg — in 8.0%, and warfarin — in 52.0%. The weakest MI protection — worse than in the control group — was shown in the case of dabigatran in both doses. The classification revealed a diverse effect of NOACs on the MI risk, which might support the concept of no class effect in this group of drugs.

MECHANISMS

The mechanism underlying potential pro-coagulant activity of dabigatran is unclear. Thrombin suppression after dabigatran is weaker than after warfarin. The effect depends on dabigatran's concentration in the serum. When the level of the drug decreases, the paradoxical thrombin generation may occur [33]. The hypercoagulation paradox may be a consequence of suppressing the thrombin-thrombomodulin (TM) complex and activating a negative feedback mechanism by inhibiting the activation of protein C [34]. Artang et al. [9] described the mechanism of "thrombin explosion", i.e., the cleavage of the thrombin-drug complex in the presence of elevated concentrations of tissue factor (TF) released from a ruptured atherosclerotic plaque. Regardless of TM or protein C activity and TF concentrations, drugs that block FXa do not affect thrombin generation in that way and do not show similar pro-coagulant properties, based on the available data [34]. Some investigators have postulated an increase in platelet activity by upregulation of the expression of platelet PAR-1 and PAR-4 thrombin receptors [35]. Others suggest an increase in inflammatory markers during DTI treatment [33]. Due to in-stent thrombosis and an increased MI risk [38, 39], the recommendations for bivalirudin, an intravenous DTI, in the latest guidelines were lowered from class I to IIa in patients with non-ST-segment elevation myocardial infarction (NSTEMI) and from class IIa to IIb — in patients with T-segment elevation myocardial

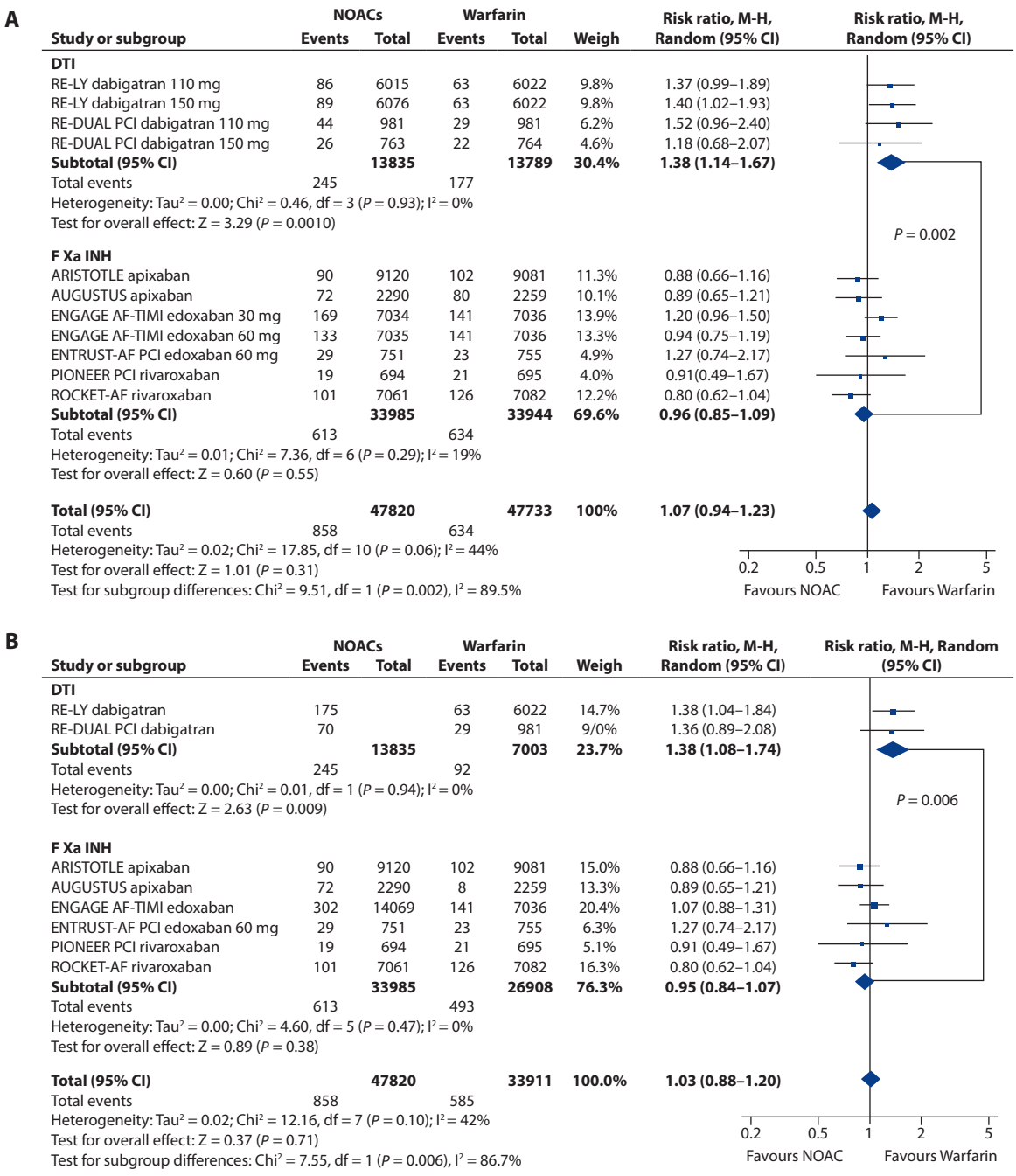

Figure 1. The meta-analysis results for myocardial infarction [31]

[a]Original data from RE-LY study [2]

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DTI, direct thrombin inhibitors; F Xa INH, factor X inhibitors; M-H, Mantel-Haenszel; NOAC, new oral anticoagulant; PCI, percutaneous coronary interventions

infarction (STEMI) [37]. It seems that DTI as a group, under certain non-physiological conditions, may show a paradoxical pro-coagulant effect.

CLINICAL IMPLICATIONS

The data on potential prothrombotic properties of dabigatran should not be ignored in our opinion. After the RE-LY study [2], the MI risk was in one out of approximately 500 treated AF patients (NNH, 500) [3] and this slight increase could be disregarded considering other benefits of dabigatran treatment [22]. After publications assessing the effect of NOACs in AF patients undergoing PCI, the estimated MI risk increased. The NNH for both doses of dabigatran was 219 (95% CI, 1057–122), 184 — for the dose of 110 mg, and 231 — for the dose of 150 mg. After reanalysis of the RE-LY study by Hohnloser et al. [6], the corresponding values were 232, 184, and 268, respectively [31]. The use of angiotensin-converting enzyme inhibitors (ACE-I) in

Dabigatran 110 mg RR (95% CI)				Treatment 1	
1.05 (0.72–1.55) 1.09 (0.75–1.56) 1.10 (0.75–1.63)	Dabigatran 150 mg RR (95% CI)			MI[a] MI[b] "intention to treat" MI[b] "on treatment"	Treatment 2
1.60 (1.14–2.24) **1.55 (1.12–2.14)** **1.53 (1.09–2.15)**	**1.52 (1.07–2.15)** **1.43 (1.02–2.00)** 1.39 (0.98–1.97)	Apixaban RR (95% CI)			
1.43 (1.02–2.01) 1.38 (0.99–1.92) 1.37 (0.97–1.92)	1.36 (0.96–1.93) 1.27 (0.91–1.79) 1.24 (0.87–1.77)	0.89 (0.66–1.20) 0.89 (0.66–1.20) 0.89 (0.66–1.20)	Edoxaban 60 mg RR (95% CI)		
1.73 (1.20–2.49) **1.67 (1.17–2.38)** **1.65 (1.14–2.39)**	**1.64 (1.14–2.37)** **1.54 (1.08–2.19)** **1.50 (1.03–2.17)**	1.08 (0.79–1.48) 1.08 (0.79–1.48) 1.08 (0.79–1.48)	0.89 (0.66–1.20) 0.89 (0.66–1.20) 0.89 (0.66–1.20)	Rivaroxaban RR (95% CI)	
1.42 (1.09–1.84) **1.37 (1.06–1.76)** **1.35 (1.03–1.76)**	**1.34 (1.02–1.77)** 1.26 (0.97–1.64) 1.23 (0.92–1.63)	0.88 (0.72–1.09) 0.88 (0.72–1.09) 0.88 (0.72–1.09)	0.99 (0.79–1.23) 0.99 (0.79–1.23) 0.99 (0.79–1.23)	0.82 (0.65–1.04) 0.82 (0.65–1.04) 0.82 (0.65–1.04)	Warfarin RR (95% CI)

Figure 2. Direct and indirect comparison between warfarin and non-vitamin K antagonist oral anticoagulants for myocardial infarction [31]

[a]Original data from the RE-LY study [2]. [b]Results from reanalysis of the RE-LY study [6]
Abbreviations: MI, myocardial infarction; RR, relative risk; other — see Figure 1

Table 1. The surface under the cumulative ranking curve (SUCRA) of myocardial infarction (MI) [31]

Treatment	MI[a]	MI[b] "intention to treat"	MI[b] "on treatment"
	SUCRA		
Rivaroxaban 20/15 mg a day	90.1	90.3	90.0
Apixaban 5/2.5 mg twice daily	79.1	78.8	78.5
Edoxaban 60 mg a day	56.4	55.7	54.9
Warfarin	**52.2**	**51.5**	**50.9**
Dabigatran 150 mg twice daily	14.0	16.4	18.5
Dabigatran 110 mg twice daily	8.2	7.4	7.3

[a]Original data from the RE-LY study [2]. [b]Results from reanalysis of the RE-LY study [6]

the acute phase of MI recommended for years in the ESC guidelines was based on the results of the meta-analysis published by Yusuf et al. in 1998 [40]. In 98 486 patients with MI, for whom ACE-Is were added to standard treatment (fibrinolysis, heparin, nitrates), a significant reduction in 30-day mortality by 0.5% was observed. In this group, the therapeutic benefit estimated by the NNT (number needed to treat) was 1/200. This is the same order of magnitude as NNH for dabigatran. All NOACs are recommended in the same class [41, 42], though differences between them may have an impact on the efficacy of dual (DAT) or triple (TAT) antithrombotic therapy. In patients with ACS or CCS and sinus rhythm, SAPT is recommended after stent implantation due to similar efficacy with significantly fewer bleeding complications as compared to DAPT [43–45]. Some investigators expressed the opinion that in AF patients treated with NOACs, premature discontinuation of DAPT in favor of SAPT after stent implantation may increase the risk of ischemic complications [46]. In the discussion on the adequate treatment of this group of patients (TAT vs. DAT), the focus was primarily on selecting the optimal antiplatelet therapy, assuming that all NOACs were of similar effectiveness. In our meta-analysis, we have demonstrated the varying efficacy of this class of drugs [31]. When comparing TAT vs. DAT in the PIONEER AF PCI [26], RE-DUAL PCI [27], ENTRUST AF PCI [29], and AUGUSTUS [28] studies, Gargiulo et al. [46] showed a significant reduction in bleeding complications in patients treated with DAT with an alarming increase in the risk of ischemic complications for MI (RR, 1.22; 95%, CI 0.99–1.52) and ST (RR, 1.59; 95% CI, 1.01–2.50) (Figures 3A and 4A). Gargiulo et al. [46] did not consider the diverse effect of NOACs, and by incorporating the results of the AUGUSTUS study into the meta-analysis, they chose a scheme comparing TAT vs. DAT (Figure 5B). With this division, for treated and untreated with aspirin (aspirin+ vs. aspirin–) in each studied group, one half of patients took apixaban, and the other half took warfarin (Figure 5B). According to our meta-analysis (Table 1), the protective effect of apixaban is 5 to 10 times stronger compared to dabigatran 150 mg and 110 mg. Assuming, in line with the research assumption of our meta-analysis, the division: NOACs vs. warfarin (Figure 5A), regardless of antiplatelet therapy (SAPT or DAPT), and excluding the results of the RE-DUAL PCI study [27], we found no increased risk of MI and ST. In Figures 3B and 4B, the results of the calculations are presented. After the above correction, the RR of MI was 0.96 (95% CI,

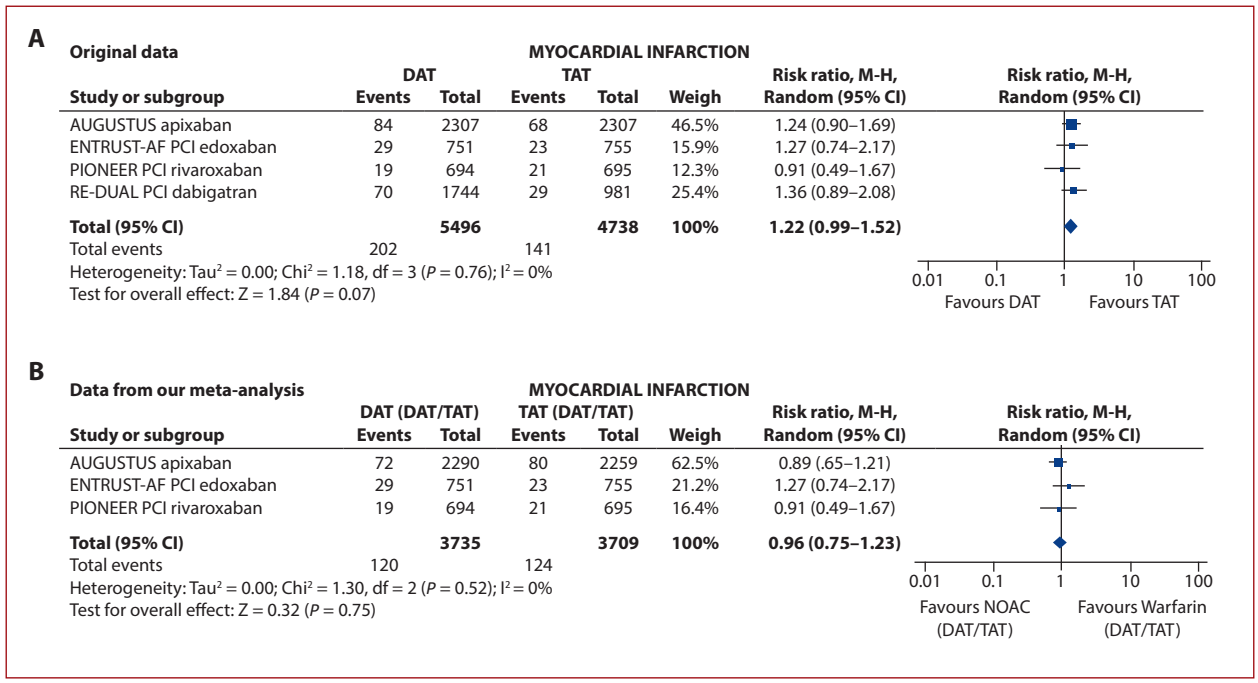

Figure 3. Ischemic endpoints: myocardial infarction reconstruction of Gargiulo et al. [46] data according to our meta-analysis design

[a]Data from Gargiulo et al. [46]. [b]Data from our meta-analysis
Abbreviations: DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; other — see Figure 1

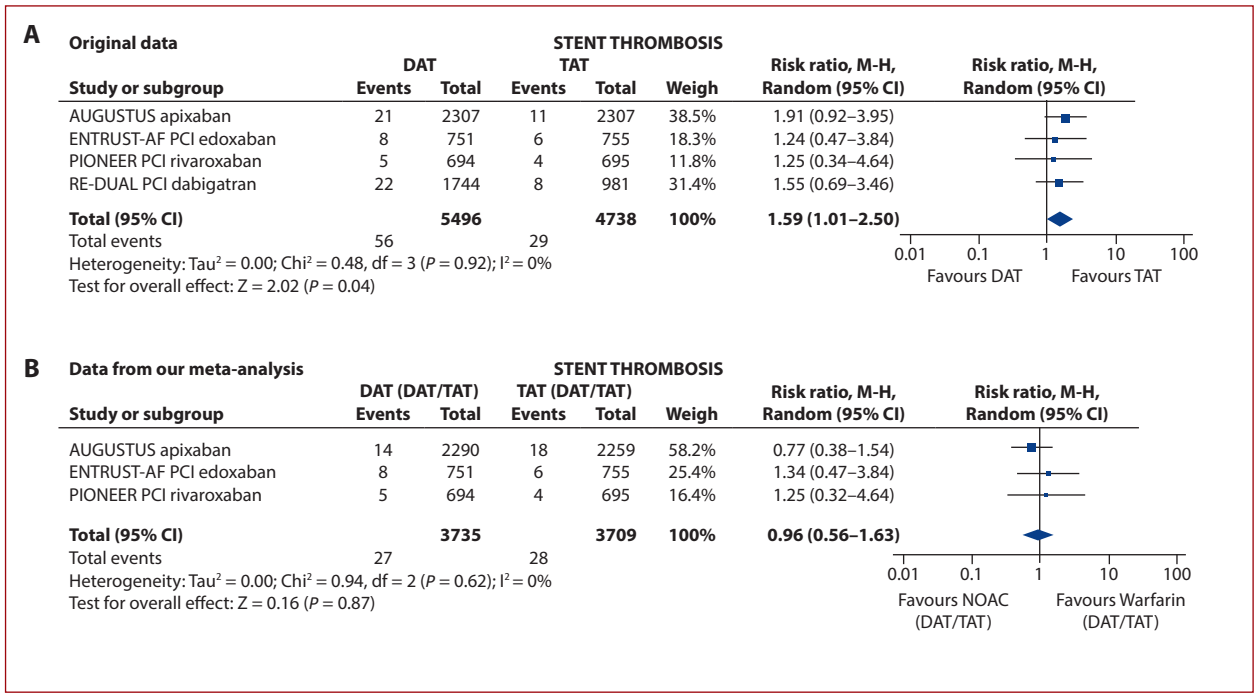

Figure 4. Ischemic endpoints: stent thrombosis — reconstruction of Gargiulo et al. [46] data according to our meta-analysis design

[a]Data from Gargiulo et al. [46]. [b]Data from our meta-analysis
Abbreviations: DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; other — see Figures 1 and 3

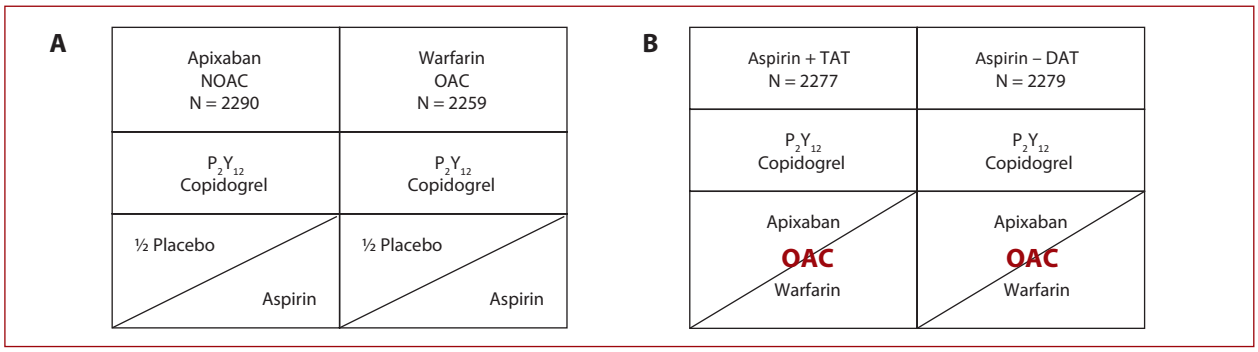

Figure 5. Scheme used for analysis in our meta-analysis (**A**) and by Gargiulo et al. [46] (**B**)

Abbreviations: see Figure 4

0.75–1.23) (Figure 3B), and the RR of ST was 0.96 (95% CI, 0.56–1.63) (Figure 4B), i.e., they were not statistically significant. Our calculations show that optimization of TAT or DAT should include not only the antiplatelet component but also the type of anticoagulant. Some clinicians believe that adding ticagrelor to dabigatran, instead of clopidogrel, partially reduces the risk of MI [47]. This concept was even presented in the last European Heart Rhythm Association guidelines [42]. Its weakness is the small number (n = 327) of patients treated with this strategy [47] and the increased risk of bleeding complications when using the recommended dose of dabigatran 2 × 150 mg with ticagrelor. To minimize bleeding, de-escalation from ticagrelor to clopidogrel was recommended after six months of treatment [42]. It is known that the use of NOACs is a significant factor in increasing the risk of bleeding complications [48]. In AF patients undergoing PCI, the need to add antiplatelet therapy additionally increases that risk. During the annual follow-up of patients with an increased risk of bleeding complications, bleeding complications in patients treated with SAPT were found in 4.9%, with DAPT — in 8.9%, with NOACs + SAPT — in 9.1%, and with NOACs + DAPT — in 11.7% [48].

In our opinion, we should choose NOACs that do not increase the MI risk and are sufficiently effective together with clopidogrel without combining with potent antiplatelet drugs (ticagrelor, prasugrel) to reduce bleeding complications. Among NOACs, FXa inhibitors (rivaroxaban and apixaban) should be recommended as the first choice option, especially in AF patients with coexisting ischemic heart disease.

SUMMARY

Each NOAC was associated with a different risk of MI. There is evidence suggesting that dabigatran at both daily doses might be associated with a higher risk of MI, compared to warfarin and FXa inhibitors. Furthermore, FXa inhibitors should be considered the first-line NOACs in patients with AF and coronary artery disease. Further research is needed to clarify this issue.

Article information

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