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Risk of Coronary Events in Atrial Fibrillation

It has been established that cardiovascular events due to coronary heart disease are highly prevalent in the population of patients with atrial fibrillation. In this review, pathophysiologic mechanisms explaining this association are detailed along with supporting epidemiological evidence. Various methods for the prediction and prevention of coronary events in atrial fibrillation are discussed, including modification of shared risk factors, antithrombotic therapy and selection of the optimal direct oral anticoagulant in terms of favourable influence on ischemic cardiac outcomes.

Keywords Coronary heart disease; anticoagulants; prevention; myocardial infarction; arrhythmia

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Embolic stroke is often considered to be the most serious complication of atrial fibrillation (AF). For this reason, approaches to ensuring the early prevention of this condition have been extensively investigated in multiple studies [1–3]. This challenge can be successfully met by prescribing direct oral anticoagulants (DOAC), which offer an advantage over warfarin in terms of safety due to the lower risk of bleeding events – in particular, intracranial haemorrhages [4–7]. Although less attention has traditionally been paid to the prevention of other cardiovascular events (CVE) in patients with AF, recent data demonstrates the importance of studying these risks. In particular, in a meta-analysis that studied the causes of death in the population of patients (n=71,683) who had undergone anticoagulant therapy in 4 major randomised controlled trials (RCT) of DOACs vs. warfarin, it was established that the largest number (46%) of the 6,206 deaths (9% of the total population, 4.72% annually) were due to cardiac disease, while embolic and haemorrhagic events were the cause of only 5.7% and 5.6% of deaths, respectively [8]. This demonstrated the need for an in-depth study and discussion of approaches to the prevention of coronary events in the AF patient population [9].

Epidemiological associations between coronary heart disease and atrial fibrillation

While atrial fibrillation is the most frequently diagnosed type of chronic cardiac arrhythmia [1], coronary heart disease (CHD) is the most prevalent cardiovascular disease [10]. The prevalence of AF in the general population is 1–2% [11] while the percentage of patients with AF and various concomitant coronary pathologies varies 17 to 46.5% [12–15]. CHD is the second most frequent concomitant chronic disease in AF patients involved in the Medicare program (USA) [16]. According to epidemiological studies, CHD is one of the causes of AF [17], which can lead to progression of coronary pathology. In a prospective cohort study REGARDS (n=23,928), AF was independently associated with a nearly twofold increase in the risk of myocardial infarction (MI) in patients without a history of CHD over a 4.5-year follow-up period (relative risk (RR) 1.70 with a 95% confidence interval (CI) 1.26–2.30) [18]. A systemic review and meta-analysis of 27 epidemiological studies showed that AF is a risk factor (RF) for MI (10 studies; RR 1.39, 5% CI 1.05–1.85) for cardiovascular mortality (10 studies; RR 1.95, 95% CI 1.51–2.51) [19]. According to some authors, AF is a more reliable predictor of cardiovascular death and MI in women than in men [18, 20, 21]. Although, this finding is additionally supported by the data of a meta-analysis of 30 cohort studies with long-term follow-up (n=4,371,714) performed by C. A. Emdin et al. [20], it was not confirmed in other patient cohorts [22]. Meanwhile, AF is also associated with an increased risk of sudden cardiac death [23].

In a pooled multifactorial analysis of the data from several prospective studies, which used methods of intravascular imaging in patients (n=4,966) having a diagnosed coronary pathology, AF vs. no AF was associated with an increased risk of MI (3.3% vs. 1.5%; RR 2.41, 95% CI 1.74–3.35; p<0,001) and a higher overall number of ischemic events (4.4% vs. 2.0%; RR 2.2, 95% CI 1.66–2.92; p<0.001) over a 2-year period [24].

In 6.4–7.9% of the reported cases, the occurrence of MI also leads to AF, while the frequency of subclinical episodes may be as high as 32% [25, 26]. According to the data of a meta-analysis of 43 studies (n=278,854), AF is associated with a 1.5-fold increase in the risk of mortality in MI [27]. In a large population study

(n=6,384), incident AF was rather a frequent (10.8%) and occasionally lethal complication of MI, associated with a more than twofold increase in the risk of stroke and hospital mortality, as well as heart failure and cardiogenic shock [28]. Finally, subclinical atherosclerosis of coronary arteries can be found in 74% of AF patients [29], while an increased likelihood of AF has been reported in patients with increased coronary calcium [30].

Pathophysiological mechanisms and risk factors

Mechanisms of mutual influence of coronary pathology and AF, as well as shared RFs for both diseases, have been proposed to explain the association between different forms of CHD and AF. S. Kralev et al. [13] found a higher incidence of stenosis of the right coronary artery responsible for blood supply to the atria as compared to the left coronary stenosis in AF patients (n=261) (62% vs. 26%, respectively; p=0.001). Despite the potential role of involvement of the right coronary and circumflex arteries, a retrospective analysis of the data from another study that included 3,220 patients with CHD and AF revealed the presence of atherosclerotic plaques in the right coronary artery only in 43% of the patients, with two thirds of those patients developing stenotic lesions in the area after the origin of atrial branches [31]. In a single-centre study, L. J. Motloch et al. [32] reported an association between AF in CHD patients (n=796), disease severity and the number of coronary vessels involved; however, again no evidence was found to support a hypothesis for the predominant build-up of atherosclerotic plaques in the right coronary artery.

Other authors report a lower extent and a slower progression of atheroma in AF patients with concomitant CHD, which suggests that a leading role is played by non-atherosclerotic mechanisms of CHD pathogenesis [24]. One of the possible causes is systemic inflammation causing a predisposition to the build-up and rupture of atherosclerotic plaques, as well as leading to the development of AF in which increased serum concentrations of inflammatory markers and cytokines are measured [33–35]. Elevated levels of inflammatory biomarkers (e.g. interleukin-6, C-reactive protein and 15th growth/differentiation factor) in AF patients have been associated with recurrent arrhythmic attacks, MI and lethal outcomes [36].

Additional potential mechanisms leading to coronary events may also include an increased activity of blood coagulation system and coronary micro-emboli [37]. In a cohort study, only 2.9% of 1,776 MI patients showed signs of coronary emboli, with 73% of these emboli being AF related [38]. However, the number of potentially embolic MIs is low; the role of atherothrombotic process may additionally be less important [21] due to the predominant prevalence of MI without ST-segment elevation in this population.

AF has also been found to be associated with impaired coronary blood flow and decreased myocardial perfusion [39], as well as with endothelial dysfunction [40]. Additionally, a role may be played by increased myocardial oxygen demand and oxidative stress due to tachyarrhythmia [41]. In patients with frequent ventricular contractions, type 2 MI due to increased myocardial oxygen demand cannot be excluded [42].

The large number of patients with concomitant AF and CHD can be explained by shared RFs for these conditions [9].

Age

In a Rotterdam population-based study (n=6,808), the prevalence of AF was found to increase from 0.7% in the 55–59 year age group to 17.8% in patients aged 85 years and older [43]. Similarly, the incidence of MI in patients older than 80 years was reported to be 4–5 times as high as in the 40–59 year age group [44]. According to the Framingham Heart Study, age is the most important RF for AF as compared to other known parameters; the same holds true for CHD [45].

The role of age can be explained by a gradual replacement of cardiomyocytes with connective tissue, which alters the electric properties of the tissues. This leads to changes in the structure and function of ion channels in the atria, with the effect of reduced transmembrane calcium currents and increased potassium concentrations. Furthermore, the effect of reduced sinoatrial automatism in parallel with the impulse generation by the cells in region of the pulmonary vein ostia and coronary sinus is observed [46].

Arterial hypertension

Arterial hypertension (AH) predisposes patients to first and recurrent AF attacks [1, 17], while uncontrolled BP increases the risk of both strokes and haemorrhages in AF patients [1, 47]. Due to the high prevalence of elevated blood pressure, a large number of AF and MI cases are related to A, with an AH-related extra population risk for these conditions estimated at 13.5 and 18%, respectively [48, 49]. Each increase of blood pressure by 5 mm Hg in AF patients receiving an antihypertensive therapy is associated with a 5% increase in the risk of MI (95% CI 1.00–1.11; p=0.04) [50].

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In terms of pathophysiology, AH leads to atrial enlargement and dysfunction, which, together with left ventricular hypertrophy and its diastolic dysfunction, increases the likelihood of development of AF [51]. Alteration of the electric properties of atrial tissues and activation of the renin-angiotensin-aldosterone system are also considered to play a role in the development of AF in AH patients [52].

Obesity

Obesity is currently becoming one of the main RFs for cardiovascular disease, including AF and CHD [53]. An additional obesity-related population risk is estimated at 13.5% for AF [49] and about 20% for MI [48].

The likelihood of AF increases with severity of obesity. [54] Each increase of the body weight index by 5 kg/m^2 is associated with a 10–29% increase of the incidence of AF attacks following cardiosurgical interventions and ablation [55–58]. An increase in the pericardial adipose tissue, which is biologically active, also seems to be a significant factor [59]. Shortening of the effective refractory period of the left atrial cells seen in obese patients may be an additional factor contributing to a predisposition to arrhythmia [60].

Other shared RFs

Other shared RFs for AF and CHD include male sex [49], carbohydrate metabolism disorders (in particular, uncontrolled diabetes mellitus (DM)) [48, 61] and obstructive sleep apnoea [62, 63]. Smoking is a less important factor [48, 64], while dyslipidaemia, by contrast, seems to be of little significance in the development of AF [49, 65].

Determination of probability of coronary events in atrial fibrillation

The identification of AF patients at the highest risk of MI and other coronary events is of particular interest. In patients receiving an anticoagulant therapy, the key RFs for cardiovascular death were male sex (Odds Ratio (OR) 1.24, 95% CI 1.13–1.37), older age (mean difference 3.2 years, 95% CI 1.6–4.8), a history of heart failure (OR 1.75, 95% CI 1.25–2.44), permanent or persistent AF (OR 1.38, 95% CI 1.25–1.52), DM (OR 1.37, 95% CI 1.11–1.68), as well as lower creatinine clearance (– 9.9 mL/min, 95% CI 11.3–8.4) [8]. A subgroup analysis of the data from the ROCKET-AF study found that cardiovascular death was reported more frequently in a subgroup of AF patients with heart failure (HF) (n=9,033, 63.7% of the study population, 3.53% per annum) as compared to patients without HF (1.75% per annum): RR 1.65, 95% CI 1.37–1.98; p<0.01 [66]. DM (n=9,033, 40% of the study population) was also associated with an increased probability of both cardiovascular death (3.24% per annum vs. 2.63% per annum; RR 1.35, 95% CI 1.16–1.57; p=0,0001) and MI (1.35% per annum vs. 0.75% per annum; RR 1.70, 95% CI 1.31–2.20; p<0.0001) [67].

On the basis of data obtained from a prospective cohort study (n=1,019), a special 2MACE scale was developed for predicting major CVEs in AF patients, including MI, revascularisation of coronary arteries and death. The factors considered in the 2MACE scoring system include metabolic syndrome (2 points), age ≥75 years (1 point), a history of MI or myocardial revascularisation (1 point), congestive heart failure associated with a left ventricular ejection fraction < 40% (1 point), thromboembolic events (1 point). Validation on a cohort of AF patients receiving an effective anticoagulant therapy confirmed the good discrimination power of this scoring system: the risk of a major CVE in patients with the 2MACE score ≥3 was about 4 times as high as in patients with a lower score (RR 3.92, 95% CI 2.41–6.40; p<0.001) [68]. Subsequently, the predictive capability of the 2MACE was confirmed on other populations (n=2,630): the risk of non-embolic events in patients with the score ≥3 was 2.4–3.5 times as high as that in patients having a lower score [69].

The role of add-on antiplatelet therapy in patients with AF and stable CHD

Although a major study of antiplatelet therapy in a special cohort of patients with AF and stable CHD has yet to be carried out [70], the OLTAT observational study (n=606, mean age 73.4 years), which compared patients with AF and CHD receiving an anticoagulant as monotherapy and in combination with an antiplatelet drug, found that the use of antiplatelet drugs as add-on therapy was associated with an increased incidence of clinically meaningful bleeding events (28.3% vs. 18.5%; RR 1.8, 95% CI 1.2–2.8; p=0,005) and overall mortality (29.5% vs. 20.8%; RR 1.4, 95% CI 1.0–2.2; p=0.049), as well as a similar incidence of ischemic events (30.9% vs. 26.8%; RR 1.1, 95% CI 0.8–1.5; p=0.58) [71].

In a cohort of patients recorded in a major Danish registry (n=8,700, mean follow-up period – 3.3 years) having AF and chronic CHD and a history of MI or percutaneous coronary intervention reported earlier than 12 months prior to inclusion, the risk of MI, coronary death and embolic events was comparable in patients on DOAC as monotherapy (14% of the patients) and in those who received DOAC + acetylsalicylic acid (ASA) (26% of the patients) or DOAC + clopidogrel

(RR 1.12, 95% CI 0.94–1.34 and RR 1.53, 95% CI 0.93–2.52, respectively) while the use of ASA and P2Y12 receptor inhibitors as add-on therapy to DOAC was associated with an increase in the risk of bleeding events by 50% (RR 1.50; 95% CI 1.23–1.82) and 84% (RR 1.85; 95% CI 1.11–3.06), respectively [72].

An analysis of the data of 2,347 patients with AF and stable CHD included in the REACH registry over a 4-year period of follow-up showed that the overall rate of cardiovascular death, MI and stroke was significantly lower in those patients who received DOAC in combination with an antiplatelet therapy than in patients on warfarin as monotherapy (RR 0.85, 95% CI 0.64–1.14; p=0.27) at a marginal increase in the risk of bleeding events (RR 1.87, 95% CI 0.99–3.50; p=0.051) [73].

Based on the results of the above studies, it is currently recommended that antithrombotic therapy in patients with AF and CHD be confined to DOAC-only therapy, since the use of antiplatelet drugs as add-on therapy can be associated with an increased risk of bleeding events without any significant benefit in terms of efficacy [74].

Data from the AFIRE multicentre prospective open RCT having a follow-up period of about 2 years on 2,236 Japanese patients with AF and angiographically verified CHD, which compared rivaroxaban as monotherapy (at a dose of 15 mg approved for Asian countries) and a dual therapy regimen that included an antiplatelet drug (ASA or P2Y12 receptor inhibitor) as add-on therapy, confirm the efficacy and safety of rivaroxaban in this patient population. However, this trial was not performed for other DOACs: the anticoagulant-only group showed lower rates of both major bleedings (1.62% per annum vs. 2.76% per annum; p=0.01) and ischemic events (death, systemic embolic events, MI, stroke, unstable angina requiring revascularisation (4.14% per annum vs. 5.75% per annum; p<0.001 for 'non-inferiority' comparison and p=0.02 for 'superiority' comparison), as well as a lower all-cause death rate (1.85% per annum vs. 3.37% per annum; RR 0.59, 95% CI 0.39–0.89), as compared to a dual therapy approach with rivaroxaban and an antiplatelet drug [75].

The effect of direct oral anticoagulants on the risk of MI

In view of the high prevalence of coronary events due to AF and the established close epidemiological and pathophysiological association between AF and different clinical forms of CHD, a drug lowering the risk of CVEs – including MI – would be an optimal choice when selecting an anticoagulant for the prevention of thromboembolic events. Previously, it was shown that warfarin may reduce the risk of MI in AF patients without CHD (a meta-analysis of 8 RCTs, n=10 thousand) since its use was associated with an insignificant decrease of the risk of coronary events (RR 0.69, 95% CI 0.47–1.01; p=0.058) [76]. Although a direct comparison between different DOACs is impossible, some suggestions on the comparative efficacy and safety of individual drugs in this group can be made on the basis of the available data.

Results of RCTs

When considering the prescription of a drug to a particular patient, it is important to establish whether this patient meets the inclusion criteria and thus has characteristics similar to those of the population of the pivotal RCT that provided the necessary evidence for the drug marketing approval. Therefore, it is necessary to determine which anticoagulant was most extensively studied in the population of patients with AF and CHD, as well as to perform an analysis of the study result heterogeneity for subgroups defined based on the concomitant coronary pathology.

In an open RCT that compared two doses of dabigatran with warfarin (RE-LY, n=18,113), 3,005 (16.6%), subjects had a history of MI at the time of enrolment in the study [4]. The key findings of the RE-LY study were similar regardless of whether these patients had a history of coronary events (n=5,650, including effort angina) or did not have such a history (p=0.45 for interaction of the primary endpoint): the rates of ischemic strokes and systemic embolism in the subjects assigned to receive dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d. or warfarin were 1.55%, 1.46% and 1.93% respectively. In other subjects, the rates of the above events were 1.53%, 0.95% and 1.61%, respectively. For other endpoints, no heterogeneity was found [77].

In the ARISTOTLE study (n=18,201), which compared apixaban and warfarin, only 2,585 (14.2%) subjects had a history of MI and 6,639 (36.5%) subjects had CHD [6]. The rate of stroke and systemic embolism in the subjects with a coronary pathology was 1.47% in the group of apixaban 5 mg b.i.d. and 1.55% in the warfarin group. In a subgroup of patients without CHD, the above outcomes were reported in 1.15% and 1.63% of cases, respectively [78].

Finally, in the ROCKET-AF trial designed as a double-blind RCT (n=14,264), which evaluated the efficacy of rivaroxaban, a history of MI reported in 2,468 (17.3%) patients did not influence the primary endpoint (stroke and systemic embolism, p=0.805 for interaction). In a subgroup of AF patients having a history of MI,

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the primary endpoint was achieved in 4.18% of the rivaroxaban 20 mg group and in 4.56% of the warfarin group vs. 3.72% and 4.26%, respectively, in patients not having a history of MI [5]. These findings were subsequently confirmed in a pre-specified intention-to-treat analysis (p=0.2522 for interaction) [79]. Therefore, the proportion of patients with a history of MI was a little higher in the ROCKET-AF study than in similar studies of dabigatran and apixaban. Furthermore, RCTs of rivaroxaban included the most numerous groups of patients with concomitant pathologies that are considered RFs for coronary events. To illustrate, in the ROCKET-AF, RE-LY and ARISTOTLE populations, HF was reported in 63%, 32% and 35% of the total study populations, respectively, and similar proportions were found for patients with a history of cerebral ischemic events (55%, 20% and 19%, respectively), DM (40%, 23% and 25%, respectively), as well as for subjects older than 75 years (44%, 40% and 31%, respectively) [4–6]. Therefore, it can be said that patients included in RCTs of rivaroxaban were at a higher risk of coronary events as compared to those patients who were treated with other DOACs.

Of course, no less important is the influence of the drugs on the probability of ischemic events, particularly MI, which was an outcome included in the secondary endpoint in the above RCTs. In this respect, quite alert signals were obtained in the RE-LY study in which the rate of MI was found to be 0.53% per annum in the warfarin group and higher in both dabigatran groups (the difference was statistically significant in the second case): 0.72% per annum in the 110 mg group (RR 1.35, 95% CI 0.98–1.87; p=0.07) and 0.74% per annum in the 150 mg group (RR 1.38, 95% CI 1.00–1.91; p=0.048) [4]. Although a subsequent analysis that included clinically asymptotic MIs found that the differences between the groups are insignificant, the tendency to a higher risk of MI in patients on dabigatran was revealed again: the rates of all MIs in the warfarin, dabigatran 100 mg b.i.d. and dabigatran 150 mg b.i.d. were 0.64; 0.82 (p=0.09) and 0.81% per annum (p=0.12), respectively [77].

In the ARISTOTLE study, MI occurred in 90 patients in the apixaban group and 102 patients in the warfarin group (0.53 and 0.61% per annum, respectively; RR 0.88, 95% CI 0.66–1.17; p=0.37), although the numerical difference in favour of apixaban did not achieve statistical significance [6].

In the ROCKET-AF study, MI was reported less frequently in the rivaroxaban group than in patients on warfarin while on treatment (0.9% per annum vs. 1.1% per annum, respectively; RR 0.81, 95% CI 0.63–1.06; p=0.12); however, the difference was again insignificant. An ad hoc analysis depending on a history of coronary events showed that the effect of rivaroxaban was generally homogenous (p=0.2626 for interaction); here, the drug caused a significant reduction of the rate of recurrence of similar outcomes in patients with a history of MI (1.42% per annum vs. 2.35% per annum, respectively; RR 0.61, 95% CI 0.37–0.99). In the intention-to-treat sample, rivaroxaban also decreased the overall rate of CVEs (cardiovascular death, MI, unstable angina) (RR 0.86, 95% CI 0.73–1.00; p=0.05) [79].

Results of meta-analyses

The RCT findings indicative of a risk of MI associated with some drugs were further investigated in a number of meta-analyses. Each such meta-analysis included a large number of studies of DOACs in different patient populations. In particular, one of the early meta-analyses, which included 7 RCTs (30,514 patients who were for the most part RE-LY subjects) of the effects of dabigatran for prevention of thromboembolic events in AF patients, as well as considering the treatment and prevention of venous thromboembolism (VTE), found an association between the therapy and increased risk for MI or acute coronary syndrome (ACS) as compared to controls (RR 1.33, 95% CI 1.03–1.71; p=0.05); moreover, this association held firm after the exclusion of short-term studies from the analysis (p=0.03), as well as following the inclusion of reconsidered RE-LY data (p=0.05) [80].

In a later meta-analysis by J. Douxfils et al. [81] (12 RCTs, 40,195 patients), treatment with dabigatran was associated with an increased risk of MI (OR 1.34, 95% CI 1.08–1.65; p=0.007); here, moreover, the risk was even higher when compared to warfarin (OR 1.41, 95% CI 1.11–1.80; p=0.005). Although these findings refer mostly to dabigatran 150 mg b.i.d., no evidence was obtained to support the expectation that therapies involving a lower dose of dabigatran are safer and associated with a lower risk of MI [81].

In a meta-analysis of 9 RCTs of rivaroxaban, which included 53,827 patients with different indications (VTE, AF, ACS) for anticoagulant therapy, treatment with this drug was characterised by a significant decrease in the risk of MI as compared to controls treated with warfarin, enoxaparin or placebo (RR 0.82, 95% CI 0.72–0.94; p=0.004). Furthermore, the prescription of rivaroxaban was associated with a decreased risk of cardiovascular death (RR 0.84, 95% CI 0.72–0.97; p=0.02) [82].

In a similar analysis (12 studies; n=54,054) of another factor X inhibitor, apixaban and comparators (warfarin,

enoxaparin, ASA, placebo) did not differ significantly in terms of their influence on the rate of MI (RR 0.90, 95% CI 0.77–1.05; p=0.17) and cardiovascular death (RR 0.88, 95% CI 0.72–1.06; p=0.18) [83].

These meta-analyses have common limitations comprising the inclusion of phase II trials and those studies that included patients at a low risk of CVEs, a lack of information on the onset of the analysed outcomes and access to baseline data of individual patients, as well as the impossibility of distinguishing between ACS and MI in a number of papers and performing a pre-specified analysis of these endpoints and specific definitions, which would allow their occurrence to be verified.

Other meta-analyses were undertaken in attempt to compare the effects of different DOACs on coronary outcomes. The best known and largest of these was the study by K.-H. Mak et al. (n=138,948) published in 2012, which included all DOAC studies completed by that time. Apixaban was characterised by an insignificant decrease in the risk of MI/ACS (7 studies; RR 0.94, 95% CI 0.82–1.07; p=0.333). The therapy with rivaroxaban resulted in a significant decrease of these events (7 studies; RR 0.78, 95% CI 0.69–0.89; p<0.001), while direct thrombin inhibitors dabigatran (9 studies; RR 1.30, 95% CI 1.04–1.63; p=0.021) and ximelagatran used in the past (6 studies; RR 1.65, 95% CI 0.56–4.87; p=0.368) were associated with an increase in the risk of adverse events of CHD [84].

A later meta-analysis (27 RCTs, n=132,445) found that apixaban insignificantly decreased the risk of ACS (9 studies; RR 0.89, 95% CI 0.78–1.03), rivaroxaban caused a significant decrease of this outcome (9 studies; RR 0.81, 95% CI 0.72–0.93), while dabigatran was associated with an increased risk of coronary events compared to controls (9 studies; RR 1.45, 95% CI 1.14–1.86) as well as in indirect comparison with factor X inhibitors (apixaban: RR 0.59, 95% CI 0.42–0.84; rivaroxaban: RR 0.52, 95% CI 0.37–0.72) in the studies in which similar therapies were given to the subjects [85]. Finally, in a network meta-analysis that included data from those 12 RCTs comparing DOACs with warfarin in different patient groups (n=100,524), A. Tornyos et al. [86] found that rivaroxaban was the safest drug in terms of the influence on the risk of MI (risk reduction by 44% as compared to dabigatran; RR 0.56, 95% CI 0.38–0.82), although other drugs were also superior to dabigatran (risk reduction by 41% for apixaban (RR 0.59, 95% CI 0.40–0.88) and 34% for vitamin K antagonists (RR 0.66, 95% CI 0.49–0.87) [86].

It should be noted that these meta-analyses have some limitations which include, above all, differences between study populations, designs (in particular, with regard to DOAC doses) and observation time, lack of the information on the treatment outcomes of individual patients, as well as difference in the outcome criteria between the studies included and the lack of necessary data in part of them. Nevertheless, the overall consistency between results of different studies is indicative of a favourable influence of rivaroxaban on the coronary prognosis in AF patients.

Use of DOACs in other CHD patient groups

The spectrum of additional indications and conditions, including different clinical forms of CHD for which a particular drug has been approved, can play a role for the selection of an optimal DOAC. In this context, rivaroxaban is clearly superior to other drugs of this anticoagulant class. Indeed, this factor X inhibitor was the first DOAC studied as part of a dual therapy in the cohort of AF patients who underwent a transcutaneous coronary intervention. In these subjects (n=2,124), the therapy with rivaroxaban 15 mg (10 mg case of patients with renal impairment) in combination with a P2Y12 receptor inhibitor led to a decrease in the risk of clinically meaningful bleedings from 26.7% to 16.8% (RR 0.59, 95% CI 0.47–0.46; p<0.001) as compared to the standard triple therapy (ASA, P2Y12 receptor inhibitor, warfarin) in the absence of any difference between the therapies in the rate of ischemic events (cardiovascular death, MI, stroke; 6,5% vs. 6%, respectively; RR 1.08, 95% CI 0.69–1.68; p=0.75) over 12 months [87].

Rivaroxaban is the only DOAC for which a favourable effect in terms of better ACS prevention regardless of AF has been proved in clinical studies. In the ATLAS ACS 2-TIMI 51 trial designed as a double-blind, placebo-controlled RCT, rivaroxaban prescribed at 2.5 mg b.i.d or 5 mg b.i.d. (n=15,526) in addition to the standard therapy reduced the rate of ischemic events (cardiovascular death, MI, stroke) from 10.7 to 8.9% over 13 months (RR 0.84, 95% CI 0.74–0.96; p=0.008) [88]. A lower dose of rivaroxaban (2.5 mg b.i.d.) was found to be more effective (reduction of the overall mortality rate from 4.5 to 2.9% as compared to placebo; p=0.02) and safer (reduction of the rate of fatal bleedings from 0.4 to 0.1%; p=0.04). According to recommendations in international guidelines, rivaroxaban can be prescribed to patients with a history of a recent ACS demonstrating sinus rhythm (Class of Evidence IIb, Level B) provided that the risk of haemorrhagic events is low [89].

Finally, in the COMPASS trial, which comprised a major, double-blind RCT, prescription of rivaroxaban at the above dose in addition to ASA (100 mg/day) to

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patients with a verified diagnosis of stable CHD without AF (n=24,824) led to a decrease in the overall rate of MI, stroke and cardiovascular death as compared to placebo (4% vs. 6%, respectively; RR 0.74, 95% CI 0.65–0.86; p<0.001) and overall mortality rate (3% vs. 4%, respectively; RR 0.77, 95% CI 0.65–0.90; p=0.0012) at a less pronounced increase of major bleedings (3% vs. 2%, respectively; RR 1.66, 95% CI 1.37–2.03; p<0.001) [90].

Any attempts to use other DOACs available in the Russian Federation in patients with ACS and sinus rhythm failed to improve clinical outcomes. In the RE-DEEM trial comprising a double-blind, phase II study in patients (n=1,861) with a history of ACS treated with dabigatran at different doses (from 50 to 150 mg b.i.d.), a dose-dependent increase in the risk of major and clinically meaningful minor bleedings was observed, which was found to be 3.92 times as high as that of placebo for 110 mg b.i.d. (95% CI 1.72–8.95) and 4.27 times higher for 150 mg/day (95% CI 1.86–9.81) [91]. In a larger double-blind RCT, prescription of apixaban at 5 mg b.i.d. to these patients (n=7,392) was associated with an increase in the rate of major bleedings from 0.5 to 1.3% as compared to placebo (RR 2.59, 95% CI 1.50–4.46; p=0.001), including fatal and intracranial haemorrhages, without any benefit in terms of reduction in the risk of ischemic events (cardiovascular death, MI, stroke; 7.5% vs. 7.9%, respectively; RR 0.95, 95% CI 0.80–1.11; p=0.51); for this reason, the study was terminated early [92].

Discussion

The data presented in this paper are indicative of an inconsistent influence of different DOACs on coronary outcomes although all of them are of the same class. A relative superiority of rivaroxaban to other drugs of these class was also demonstrated in observational studies. Indeed, a recent analysis of the data from Danish registries for a population of 31,739 AF patients showed that the annual risk of MI was lower in patients treated with DOACs compared to warfarin (1.6%, 95% CI 1.3–1.8%), 1.2% for apixaban (95% CI 0.9–1.4%) and dabigatran (95% CI 1.0–1.5%) and even lower for rivaroxaban (1.1%, 95% CI 0.8–1.3%) [93].

Conclusion

To conclude, the strong epidemiological association between atrial fibrillation and different clinical forms of coronary heart disease can be explained by bidirectional pathophysiologic mechanisms and shared risk factors. Coronary events are one of the key causes of death in patients with atrial fibrillation. Antiplatelet drugs prescribed as an add-on therapy do not provide any additional benefits in terms of reduction of the risk of ischemic events in patients not having a history of acute coronary syndrome or coronary stent implantation who receive effective treatment with oral anticoagulants. Data from randomised clinical trials and meta-analyses that allow an indirect comparison of individual drugs may tip the scale in favour of rivaroxaban when selecting an optimal direct oral anticoagulant for AF patients at a high risk of myocardial infarction.

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