European Heart Journal Supplements (2024) **26** (Supplement 1), i29–i34
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae013

Factor XI inhibition in patients with acute coronary syndrome

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KEYWORDS
Factor XI;
Milvexian;
Asundexian;
Abelacimab;
Acute myocardial infarction

A hypercoagulable condition is typical of patients with acute coronary syndrome and is a determining factor in the genesis of recurrent ischaemic events. Modern pharmacological therapies consisting of antiplatelets and anticoagulants derive their rationale for use on the pathophysiological mechanisms most commonly associated with myocardial infarction (MI); they have contributed to reducing the ischaemic risk of these patients, but left ample room for improvement. In particular, trials that have studied the association of an anticoagulant with antiplatelet drugs have provided promising results in terms of efficacy, but highlighted a significant bleeding risk. Evidence derived from experimental animal and epidemiological studies has shown how factor XI (FXI) deficiency is associated with a reduction in thrombotic events but with modest bleeding. These data added to the role that FXI plays in the coagulation cascade constituted an incipit for the pharmacological attempt to decouple thrombosis from haemostasis by means of the inhibition of this factor. The theoretical assumption that FXI inhibitor drugs may be able to reduce the ischaemic risk without significantly increasing the haemorrhagic risk makes these compounds a potential therapeutic aid for patients in secondary prevention after acute MI. To date, on these patients, we only have data from a Phase 2 trial, PACIFIC-AMI (Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2 433 334 in Patients Following an Acute Heart Attack). In this study, the primary endpoint—represented by the Bleeding Academic Research Consortium (BARC) composite of Type 2, 3, or 5 bleeding—showed no significant differences between the various doses of asundexian tested (10, 20, and 50 mg quoque die), and between these and placebo (asundexian all doses vs. placebo: hazard ratio, 0.98; 90% confidence interval, 0.71–1.35). The data on efficacy, however, showed neutral results, but it should be noted that the study did not have the adequate statistical power to evaluate this outcome. Valuable information could, therefore, derive in the future from the ongoing Phase 3 trial with milvexian, LIBREXIA-ACS (A Study of Milvexian in Participants After a Recent Acute Coronary Syndrome) and from any future studies that could be started by testing different molecules.

Introduction

Ischaemic heart disease represents one of the most relevant scenarios of the 21st century in terms of public health. This is corroborated by epidemiological data which attest to how this condition constitutes the main cause of death globally, especially in high-income countries.[1] This context includes acute coronary syndromes (ACSs), whose spectrum is made up of three distinct nosological entities, namely ST-segment elevation myocardial infarction (ST-segment myocardial infarction, STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. Although it is possible to distinguish different types of myocardial infarction (MI) on the basis of the underlying pathophysiological processes, in most cases, the

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predominant mechanism is represented by the erosion and/or rupture of an intracoronary atherosclerotic plaque.[2] This results in the phenomena of platelet adhesion, activation, and aggregation which, together with the triggering of the coagulation cascade, culminate in the formation of an intraluminal thrombus.[2,3]

While percutaneous myocardial revascularization often constitutes the initial therapeutic approach, pharmacological treatment plays a decisive role in the prevention of recurrent ischaemic events. The pathophysiological mechanisms previously mentioned justify the rationale for the use of antiplatelets and anticoagulants, which represent the cornerstone of the treatment of atherothrombotic cardiovascular diseases. Despite this, it must be underlined that thrombotic relapses remain common in patients with previous ACS, resulting in a worsening of the prognosis.[2] The persistence of a significant thrombotic risk has therefore led to the creation of new pharmacological combination strategies, as well as the development of new drugs with the aim of simultaneously reducing the haemorrhagic events that often afflict these patients.

Guidelines on antithrombotic therapy in acute coronary syndromes

The 2023 guidelines of the European Society of Cardiology relating to ACS recommend dual antiplatelet therapy (DAPT) which involves the association of aspirin with a potent inhibitor of the P2Y12 platelet receptor, i.e. ticagrelor or prasugrel, for a standard period of 12 months, beyond which to continue chronically with aspirin [Class of Recommendation (COR) I, level of evidence (LOE) A]. In this regard, recent scientific evidence has introduced the possibility of using a P2Y12 receptor inhibitor as monotherapy for long-term treatment, in particular clopidogrel as an alternative to aspirin, by virtue of the possible superiority of the former over the latter in the prevention of adverse clinical events (COR IIb, LOE A).[4] The indication for the use of ticagrelor or prasugrel rather than clopidogrel in DAPT for patients with ACS, however, arises from two randomized Phase 3 trials which highlighted a lower rate of ischaemic events in favour of the first two drugs, although this was accompanied by a greater risk of haemorrhagic events. The greater safety guaranteed by clopidogrel, together with its ability to prevent thrombotic events—although to a lesser extent than the more potent P2Y12 inhibitors—determines the possibility of its use in DAPT in place of the latter in specific contexts. This is true, for example, if there are contraindications to the use of ticagrelor and prasugrel, or in the presence of intolerance to these compounds, or their unavailability (COR I, LOE C). It should, however, be underlined that the antiplatelet efficacy of clopidogrel is subject to considerable interindividual variability, which is attributable to polymorphisms associated with cytochrome P450 2C19.

However, the European ACS guidelines leave the possibility of adapting the therapy to the individual patient on the basis of risks and benefits. In this regard, in patients at high haemorrhagic but not ischaemic risk, it is possible to resort to de-escalation strategies consisting in reducing the duration of DAPT to 3 or 6 months (COR IIa, LOE A), or even to 1 month in particularly selected cases (COR IIb, LOE B), and then continue with a single antiplatelet agent (preferably a P2Y12 inhibitor); alternatively, it is possible to keep the duration of DAPT unchanged, however replacing ticagrelor/prasugrel with clopidogrel after the first month of therapy (COR IIb, LOE A).[5] On the other hand, for patients at high thrombotic but not haemorrhagic risk, when advantageous, it is possible to extend antithrombotic therapy beyond 12 months by combining aspirin with one of rivaroxaban (2.5 mg b.i.d.), prasugrel (10 mg q.d.; 5 mg q.d. if age ≥75 years or weight <60 kg), or ticagrelor (60 mg b.i.d. or 90 mg b.i.d., preferring the first option due to the lower risk of bleeding) (COR IIa, LOE A).

Finally, parenteral anticoagulant therapy (e.g. heparin) is recommended in all patients with ACS at the time of diagnosis (COR I, LOE A).

Evidence on the use of anticoagulant drugs currently on the market in addition to antiplatelet therapy in the secondary prevention of thrombotic risk

Although DAPT followed by aspirin monotherapy today constitutes the standard of care in the secondary prevention of MI, it is necessary to point out that this strategy is not able to eliminate the risk of recurrent ischaemic events which remains non-negligible for these patients.[6] The persistence of this risk has stimulated the scientific community to explore new pharmacological approaches through the combined use of antiplatelets and anticoagulants. This combination exploits the ability of these drugs to prevent thrombus formation by acting on distinct pathophysiological mechanisms.

Initial studies, conducted several decades ago, evaluated the efficacy and safety of vitamin K antagonists (VKAs)—particularly warfarin—in combination with aspirin. However, the results of these studies did not highlight a favourable risk–benefit ratio, leading to the early abandonment of this approach.[6]

The subsequent advent of the direct oral anticoagulants (DOACs) has renewed interest in the use of a combination strategy thanks to their better safety profile linked to the lower risk of bleeding and greater ease of handling compared with VKAs, not requiring the former to undergo laboratory monitoring of their anticoagulant efficacy. Numerous trials conducted in recent years have examined the use of DOACs in addition to antiplatelet therapy, both in chronic contexts—such as stable coronary heart disease and peripheral arterial disease—and in acute contexts—such as MI.[7] Among these, the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) study tested apixaban 5 mg b.i.d. in addition to DAPT in patients with ACS at high thrombotic risk, demonstrating that it significantly increased the bleeding risk without, however, reducing ischaemic events.[8] The results of the ATLAS-ACS 2 TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51) trial, however, showed that low doses of rivaroxaban (2.5 mg b.i.d.), when added to a clopidogrel-based DAPT, are

able to reduce the rate of ischaemic cardiovascular events at the cost, however, of a greater risk of major and intracranial bleeding.[9]

In theory, therefore, the use of a DOAC in addition to antiplatelet therapy can lead to a benefit on thrombotic risk, but this effect—as demonstrated by the abovementioned trials—could be strictly dependent on the specific drug used[8-10] and from the type of MI. In fact, DOACs might be more effective in the case of STEMI rather than NSTEMI.[11] Currently, rivaroxaban at a dosage of 2.5 mg b.i.d. is the only drug in its category to have been approved in association with an antiplatelet, in particular aspirin, in stable coronary artery disease and peripheral arterial disease in the absence of high bleeding risk, as well as in ACS.[12-14]

The data made available by the APPRAISE-2 and ATLAS-ACS 2 TIMI 51 trials, therefore, reiterate how the attempt to safely associate an anticoagulant with DAPT still remains largely unrealistic today. Therefore, the possible future availability of new anticoagulants characterized by a low intrinsic risk of bleeding could pave the way for a wider range of treatments, confirming, expanding, and strengthening the current indications for this pharmacological combination.

New currents of research: the role of factor XI

Despite the previously mentioned pharmacological advantages of DOACs compared with VKAs, it is imperative to reiterate that the bleeding problem persists even with their use, especially in patients suffering from specific comorbidities such as, for example, advanced stages of chronic kidney disease. Furthermore, these anticoagulants are not indicated in significant clinical contexts, such as in patients with mechanical valve prostheses.

Evidence deriving from experimental animal and epidemiological studies demonstrate that congenital deficiency of factor XI (FXI) (commonly known as C haemophilia or Rosenthal disease) is associated with a lower risk of thrombotic events and with a modest risk of bleeding, especially associated with dental, surgical, or trauma interventions.[15] On the contrary, high levels of FXI lead to an increased thrombotic risk.[15]

Factor XI is a zymogen that can be converted by other coagulation factors into a serine protease which represents its active form (FXIa).[16] It plays a crucial role in the coagulation contact pathway which recognizes various factors among its activation triggers such as, for example, contact with foreign materials such as extracorporeal circuits, vascular catheters, mechanical valves.[17] At a molecular level, however, the main culprits are exogenous polyanions, capable of inducing the self-activation of factor XII, which represents the main activator of FXI.[15] The latter, in turn, initiates a series of biochemical reactions that culminate in the conversion of prothrombin into thrombin, an enzyme capable of retroactivating FXI through a positive feedback mechanism, fuelling the coagulation process. The retroactivation of FXI by thrombin is also the basis of the activation of this factor following the triggering of the tissue factor pathway.[17] The latter is typically initiated by damage to the vascular wall and is involved in the process of haemostasis with the main aim of stopping bleeding through the formation of a haemostatic plug.[15] In pathological thrombosis, FXI plays an important role in amplifying the growth and development phenomena of the thrombus.[17]

The marginal role played by FXI in haemostasis has encouraged the pharmacological attempt to dissociate this process from thrombosis through the inhibition of this factor. This rationale has therefore led to the development and identification of compounds capable of inhibiting this molecule. Based on their biochemical characteristics, they can be classified as antisense oligonucleotides, monoclonal antibodies, small synthetic molecules, natural peptides, and aptamers. With the exception of the last two categories, all the others have already been the subject of human studies.[17] Research areas include mainly, but not exclusively, the prevention of venous thrombo-embolism after major orthopaedic surgery, end-stage chronic kidney disease, atrial fibrillation, non-cardioembolic stroke, and ACS.[18] In particular, in the context of the prevention of venous thrombo-embolism in patients undergoing total knee arthroplasty, Phase 2 trials have highlighted a good safety profile as well as a promising efficacy of the tested compounds compared with enoxaparin.[17] Even in patients with atrial fibrillation, FXI inhibitors have shown in Phase 2 trials to be safe drugs,[17] so much so that the AZALEA-TIMI 71 study [Safety and Tolerability of Abelacimab (MAA868) vs. Rivaroxaban in Patients With Atrial Fibrillation] was stopped early due to the finding of a significant reduction in bleeding events with the monoclonal antibody abelacimab compared with rivaroxaban. However, the question of efficacy remains, which needs to be demonstrated by a Phase 3 study. This is even more important considering that, according to the drug's manufacturer, one such study of the oral FXI inhibitor asundexian, titled OCEANIC-AF (A Study to Learn How Well the Study Treatment Asundexian Works and How Safe it is Compared to Apixaban to Prevent Stroke or Systemic Embolism in People With Irregular and Often Rapid Heartbeat, and at Risk for Stroke) was discontinued early due to the lack of efficacy. Similarly, in patients with non-cardioembolic stroke, the evidence deriving from Phase 2 trials gives rise to hope regarding the safety of these drugs without, however, being conclusive on their effectiveness.[19]

The use of FXI inhibitors in ACS is based on the pathophysiological mechanisms mentioned previously. To date, only one Phase 2 trial is completed on patients in secondary prevention for MI (NCT04304534), while a Phase 3 study is currently underway (NCT05754957), respectively, with asundexian and milvexian, both small synthetic molecules. The pharmacological characteristics of these two compounds are summarized in *Table 1*.[17]

The PACIFIC-AMI trial

The PACIFIC-AMI (Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2 433 334 in Patients Following an Acute Heart Attack) trial is a Phase 2, randomized, double-blind, multicentre study that evaluated the pharmacodynamics, safety, and efficacy of three different doses of asundexian (10, 20,

Table 1 Clinical pharmacology of asundexian and milvexian

Drug	Mechanism of action	Route of administration	Time to reach peak drug concentration	Half-life	Elimination	Drug interactions
Asundexian	Inhibition of FXIa	Oral	~1–4 h	14–21 h	Renal metabolism (limited)	No
Milvexian	Inhibition of FXIa	Oral	~3 h	11–18 h	Hepatic (CYP450) and renal	CYP450 3A4 inhibitors

CYP450, cytochrome P450; FXIa, factor XI activated.

and 50 mg q.d., respectively) compared with placebo in addition to DAPT in patients in secondary prevention after an ACS.[20] A total of 1601 patients were randomized into four different groups (1:1:1:1), each made up of ~400 individuals, within 5 days of hospitalization but, in any case, after any percutaneous coronary intervention (PCI), which was performed in 99.3% of cases. In particular, patients aged ≥45 years with acute MI (except Types 4a and 5), candidates for DAPT with aspirin plus ticagrelor/prasugrel or clopidogrel, regardless of the need for myocardial revascularization, were included in the study. On the other hand, subjects suffering from haemorrhagic diathesis, active bleeding, or with a history of major bleeding in the 6 months preceding randomization were excluded, as well as those suffering from liver disease, chronic kidney disease in Stage 4 or 5, haemodynamically unstable, or requiring long-term full-dose anticoagulant therapy. The population was characterized by an average age of 68 years, predominantly made up of white male subjects, with a high prevalence of systemic arterial hypertension and diabetes. Of them, 80% were receiving treatment with ticagrelor or prasugrel. The rate of STEMI and NSTEMI was balanced. The primary safety endpoint was the number of participants with a composite Bleeding Academic Research Consortium (BARC) Type 2, 3, or 5, and the primary efficacy endpoint was the number of participants with a composite of cardiovascular death, recurrent MI, stroke (ischaemic or haemorrhagic), or stent thrombosis. The average duration of follow-up was 368 days.

Asundexian demonstrated the effective inhibition of FXIa with a dose-dependent action, reducing FXIa activity to levels >90% at the 50 mg dose. However, the primary safety endpoint (*Figure 1*) occurred in 30 (7.59%), 32 (8.06%), and 42 (10.45%) patients treated with asundexian 10, 20 and 50 mg, respectively, and in 36 patients (9.02%) in the control group [asundexian all doses vs. placebo: hazard ratio (HR), 0.98; 90% confidence interval (CI), 0.71–1.35], thus not highlighting significant differences in terms of bleeding between the study drug and the placebo. No fatal bleeding was recorded in any group (i.e. BARC Type 5). Furthermore, even with regard to other adverse reactions, no significant differences were found between the various doses of asundexian and the placebo.

The efficacy endpoint (*Figure 2*) concerned 27 (6.8%), 24 (5.99%), and 22 (5.47%) patients, respectively, treated with asundexian 10, 20, and 50 mg, and 22 patients (5.49%) of the control group (asundexian 20 and 50 mg vs. placebo: HR, 1.05; 90% CI, 0.69–1.61). Although these events involved a smaller number of subjects in absolute terms as the drug dose used increased, it should be noted that no significant differences in terms of efficacy were identified between the various doses of asundexian, and between these and the placebo. Furthermore, there was a numerically greater decrease in the primary efficacy outcome among patients with STEMI compared with those with NSTEMI, as well as among those who received ticagrelor or prasugrel rather than clopidogrel.

In conclusion, although PACIFIC-AMI demonstrated the notable safety of asundexian even at the highest doses, it should be underlined that the study did not include subjects at high risk of bleeding, who theoretically represent the main target population for the use of this new category of anticoagulants. On the other hand, the results relating to the efficacy of the drug were not conclusive, but this should not cause concern, as the study did not have sufficient statistical power to adequately analyse this aspect, as its design focused on safety evaluation and determination of the best dose to apply in future studies. To date, no Phase 3 study with asundexian in patients with ACS has been announced.

The LIBREXIA-ACS trial

At the time of writing this manuscript, only one trial is underway on the use of FXI inhibitor anticoagulants in patients with ACS. Specifically, it is LIBREXIA-ACS (A Study of Milvexian in Participants After a Recent Acute Coronary Syndrome), a Phase 3, multicentre, randomized, double-blind, placebo-controlled study, started in April 2023. The primary objective of this trial is to demonstrate the efficacy and safety of milvexian as an adjunct to standard-of-care antiplatelet therapy. Overall, it aims to recruit a cohort of ~16 000 patients within 7 days of the onset of the index ACS, regardless of the use of the coronary angiography study and any PCI. Adult patients for whom laboratory investigations have highlighted an increase in the blood concentration of myocardial damage biomarkers above the upper reference limit and who have at least two of the following risk factors will be included in the study: age ≥65 years, diabetes mellitus, multivessel coronary artery disease, history of peripheral arterial disease or cerebrovascular disease, history of previous MI, history of previous coronary artery bypass graft (CABG), and high-risk angiographic features. On the other hand, patients with Type 2 and 4a MI, with high risk of bleeding, requiring anticoagulant therapy for other indications, and those candidates for CABG or staged PCI after randomization are excluded. The primary endpoint

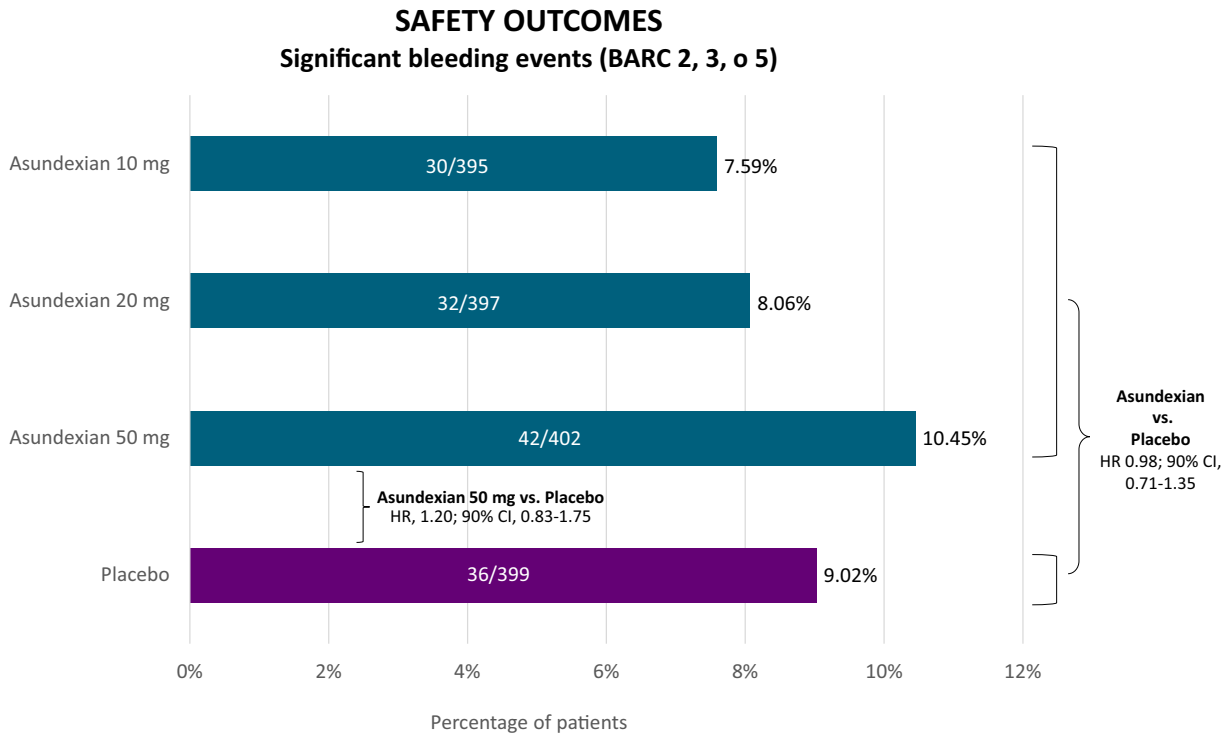

Figure 1 Safety outcomes. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.

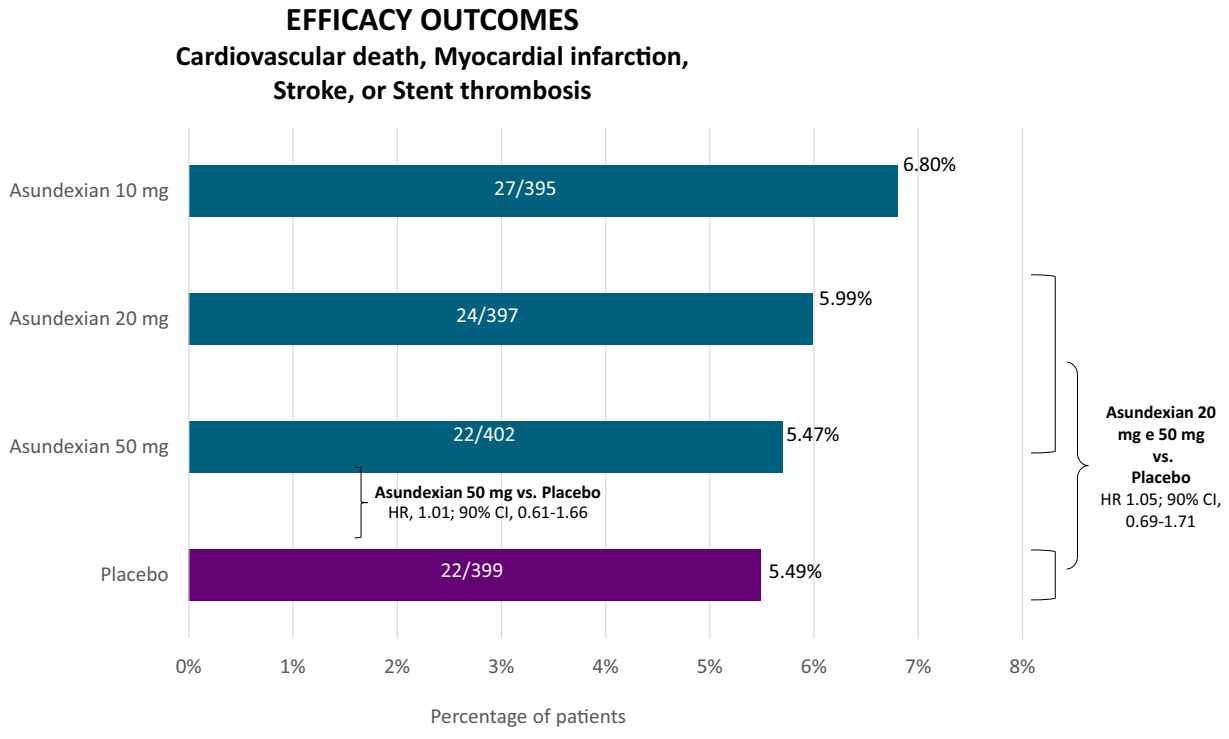

Figure 2 Effectiveness outcomes. CI, confidence interval; HR, hazard ratio.

of the study is the time until the first occurrence of major adverse cardiovascular events, i.e. the composite of cardiovascular death, MI, ischaemic stroke, for a period of up to 3 years and 6 months.

Future perspectives

Currently, evidence regarding the use of new FXI inhibitor anticoagulants in ACS patients is limited. Data emerging

from the PACIFIC-AMI clinical trial are promising regarding the safety of asundexian, but require further confirmation through a large Phase 3 trial, which should target the 50 mg dose and include a more heterogeneous population, including patients at high risk of bleeding. This study would certainly have the burden of demonstrating the effectiveness of this compound. The manufacturing company's plans, also in the light of the results of the OCEANIC-AF study, are not publicly known.

In the meantime, the results relating to milvexian in the LIBREXIA-ACS trial are awaited with interest, for which, however, we will have to wait until 2026 to have a complete picture, barring unexpected surprises.

The future could open the doors to new studies on FXI inhibitor molecules not yet explored in this clinical setting. Furthermore, the considerable pharmacological variability of these compounds could prove to be of crucial importance, allowing an adaptation of the anticoagulant treatment to the specific needs of each patient. For example, the use of drugs with a short half-life and rapid onset of action (including, in particular, the monoclonal antibody xisomab 3G3) could prove advantageous in the perioperative period, while compounds with a long half-life could promote greater adherence in long-term therapies (as in the case of abelacimab and the antisense oligonucleotide IONIS-FXI-RX).

In conclusion, studies on the use of FXI inhibitor anticoagulants in ACS are still in an embryonic stage; however, they suggest a potential that, if confirmed, could result in a significant improvement in prognosis for these patients through the reduction of recurrent ischaemic events with an acceptable risk of bleeding.

Conclusions

Despite the progress made thanks to modern pharmacological strategies, the thrombotic risk in patients suffering from ACS remains high. In this scenario, FXI inhibitors stand as a promising aid that could soon be added to the currently available antithrombotic armamentarium, making it possible to combine an anticoagulant with DAPT without leading to a significant increase in the risk of bleeding. Although trials conducted in various clinical contexts confirm the safety of these drugs despite the powerful dose-dependent inhibition of FXI, the data on efficacy remain to date not adequately explored. PACIFIC-AMI is the only phase study 2 currently available on patients in secondary prevention after ACS. Data from the ongoing Phase 3 LIBREXIA-ACS trial and from any future studies conducted on different molecules could soon be added to the growing literature in the field.

Funding

None declared.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

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