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ORIGINAL ARTICLE

Milvexian with Antiplatelet Therapy after Acute Coronary Syndrome Event

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ABSTRACT

BACKGROUND

Patients are at increased risk for recurrent ischemic events after an acute coronary syndrome event. Milvexian, an oral factor XIa inhibitor, may reduce the risk of major adverse clinical events with minimal bleeding risk.

METHODS

In this phase 3, randomized, placebo-controlled trial, we evaluated the efficacy and safety of milvexian when added to standard antiplatelet therapy within 7 days after an acute coronary syndrome event. Patients were assigned in a 1:1 ratio to receive oral milvexian (25 mg twice daily) or matched placebo. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or ischemic stroke as evaluated in a time-to-event analysis. The principal safety outcome was Bleeding Academic Research Consortium (BARC) type 3c or 5 bleeding (intracranial or intraocular bleeding that compromises vision or fatal bleeding).

RESULTS

After a planned interim analysis that was based on 556 adjudicated efficacy end points, the trial was terminated for futility. A total of 14,194 patients had been enrolled, with 7094 assigned to receive milvexian and 7100 to receive placebo. After a median follow-up of 12.2 months, a primary efficacy outcome event had occurred in 384 patients (5.4%) in the milvexian group and in 365 patients (5.1%) in the placebo group (hazard ratio, 1.05; 95% confidence interval, 0.91 to 1.21; $P=0.50$). BARC type 3c or 5 bleeding occurred in 23 patients (0.3%) in the milvexian group and in 22 patients (0.3%) in the placebo group ($P=0.88$).

CONCLUSIONS

Among patients with a recent acute coronary syndrome event, milvexian did not decrease the risk of cardiovascular death, myocardial infarction, or ischemic stroke but did not increase the risk of intracranial or fatal bleeding, as compared with placebo. (Funded by Janssen Research and Development and Bristol Myers Squibb; LIBREXIA ACS ClinicalTrials.gov number, NCT05754957.)

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*A complete list of the committees and investigators in the LIBREXIA ACS trial is provided in the Supplementary Appendix, available at NEJM.org.

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AMONG PATIENTS WITH MYOCARDIAL infarction, the risk of recurrent events remains high despite modern pharmacotherapy, including dual antiplatelet therapy, high-dose statins, and the latest generation of drug-eluting stents.^{1,2} Although pharmacotherapy often focuses on platelets, thrombin generation and factor XI levels remain elevated for months after an acute coronary syndrome event, and persistently elevated levels of thrombin generation and factor XI are associated with an increased risk of major adverse cardiovascular events.³⁻⁷ Among patients with either acute or chronic coronary artery disease, the addition of low-dose rivaroxaban to dual or single antiplatelet therapy has been shown to reduce the risk of major adverse cardiovascular events, including death, but was associated with an increased risk of bleeding.⁸⁻¹⁰

Factor XIa inhibition has been considered as an anticoagulant option with a reduced bleeding risk in patients receiving antiplatelet agents because although factor XI is involved in the intrinsic pathway of pathologic thrombus formation, it is not integral to physiologic hemostasis.¹¹ Mendelian randomization studies have shown a lower risk of venous and arterial thrombosis in patients who have a low factor XI level than in those with a normal level, with little or no increased risk of spontaneous bleeding.^{12,13}

Milvexian (JNJ-70033093; BMS-986177) is an oral, reversible, high-affinity inhibitor of factor XIa, a serine protease involved in the intrinsic pathway of the coagulation cascade.¹⁴ We conducted a phase 3 trial involving patients with a recent, cardiac biomarker-positive acute coronary syndrome event to evaluate whether milvexian would reduce the risk of major adverse cardiovascular events without increasing the risk of major bleeding when added to standard care.

METHODS

TRIAL OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled trial at 893 sites in 44 countries. The trial was designed by members of the executive committee and the sponsors, Janssen Research and Development and Bristol Myers Squibb. The trial design has been published previously.¹⁵ The trial protocol, which includes the statistical analysis plan, is available with the full text of this article at NEJM.org.

The first two authors, who were coauthors of the executive and steering committees, were responsible for oversight of the trial conduct and for the preparation of the first draft of the manuscript, which was reviewed by all the coauthors. The executive committee included the principal investigators and other recognized leaders in the fields of myocardial infarction, hematology, and biostatistics, as well as representatives of the sponsors. A complete list of the members of the executive and steering committees is provided in the Supplementary Appendix, available at NEJM.org.

All statistical analyses were independently performed by employees of the Baim Institute. The trial was approved by national regulatory agencies and institutional review boards or ethics committees at all participating sites. All the patients who were included in the analyses provided written informed consent.

An independent clinical events committee whose members were unaware of trial-group assignments adjudicated all suspected major adverse cardiovascular events and major adverse limb events using both events identified by the investigator and those identified in the adverse events database. A single independent data and safety monitoring committee that was composed of board-certified physicians who were not affiliated with the trial or the sponsors jointly oversaw all three phase 3 milvexian trials (Librexia ACS [ClinicalTrials.gov number, NCT05754957],¹⁵ Librexia AF [NCT05757869],¹⁶ and Librexia Stroke [NCT05702034]). The data and safety monitoring committee reported to the chair of the program executive council and the executive committee of each trial and was responsible for overseeing the safety of each trial individually, as well as the overall program safety on the basis of the totality of data. The trial actively promoted diversity in sex, race or ethnic group, geography, and expertise across all trial aspects, including but not limited to the trial leadership, site investigators, and planned participants.

PATIENTS

The patients who were eligible for enrollment included adults (≥ 18 years of age) who were evaluated within 7 days after an acute coronary syndrome event. The latter was defined as ST-segment elevation myocardial infarction [STEMI], type 1 non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina with cardiac bio-

marker positivity. All the patients had undergone cardiac catheterization with percutaneous coronary intervention (PCI) or were being treated conservatively with or without catheterization and had received standard antiplatelet therapy, as determined by the investigator. In addition, the patients needed to have at least two of the following risk-enhancing factors associated with an increase in the risk of recurrent ischemic events: an age of 65 years or older, diabetes mellitus, previous myocardial infarction, multivessel coronary artery disease, history of coronary-artery bypass grafting (CABG) before the index event, peripheral artery disease or cerebrovascular disease, conservative management (i.e., no PCI or CABG) after the index event, or high-risk angiographic features.¹⁷

Patients were excluded if they had type 2 myocardial infarction, nonobstructive coronary disease, a need for long-term anticoagulation or dialysis, a high bleeding risk, advanced liver disease, active cancer, previous ischemic stroke or transient ischemic attack, or a known factor XI deficiency. Full eligibility criteria are detailed in the Supplementary Appendix.

RANDOMIZATION AND TREATMENT

The patients were randomly assigned in a 1:1 ratio to receive milvexian (25 mg twice daily) or matching placebo. Randomization was stratified according to the intended strategy of background antiplatelet therapy selected by the investigator before randomization: dual antiplatelet therapy for more than 90 days (with or without de-escalation to single antiplatelet therapy), dual antiplatelet therapy for 90 days or less with de-escalation to single antiplatelet therapy, or single antiplatelet therapy from the time of randomization.

Randomization was scheduled to occur at least 4 hours after PCI or angiography and at least 24 hours after thrombolysis. The administration of milvexian or placebo was to begin as soon as possible after randomization but at least 6 hours after the administration of unfractionated heparin and 12 hours after the administration of low-molecular-weight heparin or glycoprotein IIb/IIIa receptor inhibitors. Background therapy was managed according to local guidelines, and changes in the antiplatelet regimen were recorded. The twice-daily 25-mg dose of milvexian was selected on the basis of data from previous phase 1 and 2 studies.¹⁸⁻²⁰

OUTCOMES

The primary efficacy outcome was the first occurrence of a composite of cardiovascular death, myocardial infarction, or ischemic stroke, as evaluated in a time-to-event analysis. The first major secondary outcome was a composite of cardiovascular death, myocardial infarction, ischemic stroke, major adverse limb event, or symptomatic venous thromboembolism. The principal safety outcome was type 3c or 5 bleeding (intracranial or intraocular bleeding that compromises vision or fatal bleeding) according to the criteria of the Bleeding Academic Research Consortium (BARC).²¹ A pharmacodynamic effect was assessed on the basis of an activated partial-thromboplastin time (aPTT) at trough level at 4 weeks.

STATISTICAL ANALYSIS

We determined that the enrollment of approximately 16,000 patients would provide the trial with a power of 90% to determine a 20% relative risk reduction (hazard ratio, 0.80) in the first occurrence of a primary-outcome event for efficacy (cardiovascular death, myocardial infarction, or ischemic stroke) in the milvexian group as compared with the placebo group at a two-sided significance level of 0.05. It was estimated that a primary-outcome event would occur in 875 patients in both groups on the basis of the beta spent during the interim review.^{22,23} We estimated the number of patients with one or more primary-outcome events using East 6.5 software. If a patient had multiple events, only the first event was counted toward the determination of the primary efficacy outcome. Given the results of recent studies involving patients with acute coronary syndrome, the estimated cumulative event rates in the placebo group were modeled to be 1.6% at 1 month, 3.8% at 6 months, and 5.0% at 12 months.

Efficacy analyses were performed according to the intention-to-treat principle and included data from all the patients who had undergone randomization, regardless of treatment received from randomization until the trial end date. Bleeding analyses included all the patients who had undergone randomization and received at least one dose of milvexian or placebo; bleeding events were counted from randomization to 2 days after the last dose. Nonbleeding adverse events were analyzed after the administration of the first dose of milvexian or placebo.

Unless stated otherwise, all statistical tests were interpreted at a nominal two-sided significance level of 0.05 and all confidence intervals at a nominal two-sided level of 95%. A stratified Cox regression model was used to estimate the hazard ratio and 95% confidence interval for the treatment effect on the primary-outcome events, and the cumulative incidence was summarized by the Kaplan–Meier method. Event rates are reported per 100 person-years. As a supplementary estimand to account for competing risks, the subdistribution hazard for the primary outcome was estimated with a Fine–Gray model. Because the results for the primary outcome were not significant, no multiplicity adjustment was performed for the testing of key secondary outcomes. Thus, the widths of the confidence intervals should not be used to infer treatment effects. A pharmacodynamic assessment was planned in a subgroup of 1000 patients at baseline and at trough at week 4 to assess the increase from baseline in the aPTT. The percent change from baseline between groups was assessed by means of a two-sided Mood’s median test.

One interim analysis for futility only was planned with a nonbinding stopping rule and O’Brien–Fleming approach (with a futility boundary of a hazard ratio of approximately 0.95 or conditional power of approximately 5%) when one or more primary-outcome events had occurred in approximately 60% of the patients (525 of 875). Because the trial was not designed to stop for superiority and the futility stopping rule was nonbinding, the type I error rate was not adjusted.^{22,23} Additional details regarding the statistical methods are provided in the Supplementary Appendix and the statistical analysis plan in the protocol.

RESULTS

PATIENTS

From April 2023 through November 2025, a total of 14,194 patients were randomly assigned to receive milvexian (7094 patients) or placebo (7100 patients) and were included in the intention-to-treat analysis (Fig. S1 in the Supplementary Appendix). Milvexian was discontinued in 1419 patients and placebo was discontinued in 1397 patients, for a total of 2816 patients in both groups (19.8%). The outcome assessment was not performed in 128 patients in the milvexian group and in 134 in the placebo group (total, 262

patients [1.8%]). Vital status at the trial end date was obtained in all but 10 patients.

The clinical and demographic characteristics of the patients were well balanced between the trial groups at baseline (Table 1 and Table S1). The mean age of the patients was 63.2 years, and 78.1% were men. The type of index myocardial infarction was STEMI in 4085 participants (57.6%) in the milvexian group and 4067 (57.3%) in the placebo group. Most of the patients had undergone revascularization during the index hospitalization and were receiving guideline-directed medical therapy.

The representativeness of the patients as compared with others at risk for recurrent ischemic events after an acute coronary syndrome event is shown in Table S2. Although the type and duration of antiplatelet therapy were selected by the investigators, 95.2% of the patients were receiving dual antiplatelet therapy at baseline (including 59.8% who were receiving potent P2Y₁₂ inhibitors). A total of 86.1% of the patients were still receiving dual antiplatelet therapy at the 1-year visit (Fig. S2).

EFFICACY

On the basis of the results of the prespecified interim analysis, the data and safety monitoring committee recommended halting the trial for futility. The recommendation was accepted by the chair of the program executive committee and a small group of representatives of the sponsor who were aware of the unblinded results on November 13, 2025, with the trial end date declared on November 14, 2025. The main results of the interim efficacy and safety analyses are presented in Table S3.

After the final data accrual, an analysis of the intention-to-treat population was performed with a median follow-up of 12.2 months (interquartile range, 6.28 to 17.61). At that point, a primary efficacy outcome event had occurred in 384 patients (5.4%) in the milvexian group and in 365 patients (5.1%) in the placebo group (hazard ratio, 1.05; 95% confidence interval (CI), 0.91 to 1.21; $P=0.50$) (Fig. 1 and Table 2). Results appeared to be consistent across all prespecified subgroups, with the exception that women in the milvexian group appeared to have a higher risk of a primary-outcome event than those in the placebo group (Fig. S3).

The individual components of the primary and secondary outcomes are shown in Table 2. The

Table 1. Key Characteristics of the Patients at Baseline.*

Characteristic	Milvexian (N = 7094)	Placebo (N = 7100)
Age		
Mean — yr	63.1±10.6	63.2±10.5
≥65 yr — no. (%)	3545 (50.0)	3559 (50.1)
Male sex — no. (%)	5542 (78.1)	5543 (78.1)
Geographic region — no. (%)		
Asia	1570 (22.1)	1572 (22.1)
Western Europe	1424 (20.1)	1419 (20.0)
Eastern Europe	1783 (25.1)	1785 (25.1)
North America	454 (6.4)	460 (6.5)
South America	1355 (19.1)	1354 (19.1)
Other	508 (7.2)	510 (7.2)
Medical history — no. (%)		
Diabetes	3014 (42.5)	3154 (44.4)
Previous myocardial infarction other than index event	1606 (22.6)	1569 (22.1)
Previous coronary revascularization	1808 (25.5)	1726 (24.3)
Hypertension	5181 (73.0)	5083 (71.6)
Type of index myocardial infarction — no. (%)		
STEMI	4085 (57.6)	4067 (57.3)
NSTEMI	2615 (36.9)	2644 (37.2)
Unstable angina with elevated cardiac biomarkers	393 (5.5)	389 (5.5)
PCI performed for index myocardial infarction — no. (%)	6516 (91.9)	6496 (91.5)
Medications — no. (%)		
Aspirin	6884 (97.0)	6893 (97.1)
P2Y12 inhibitor or other antiplatelet agent	6885 (97.1)	6880 (96.9)
Statin	6607 (93.1)	6628 (93.4)

* Plus-minus values are means ±SD. NSTEMI denotes non-ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation MI.

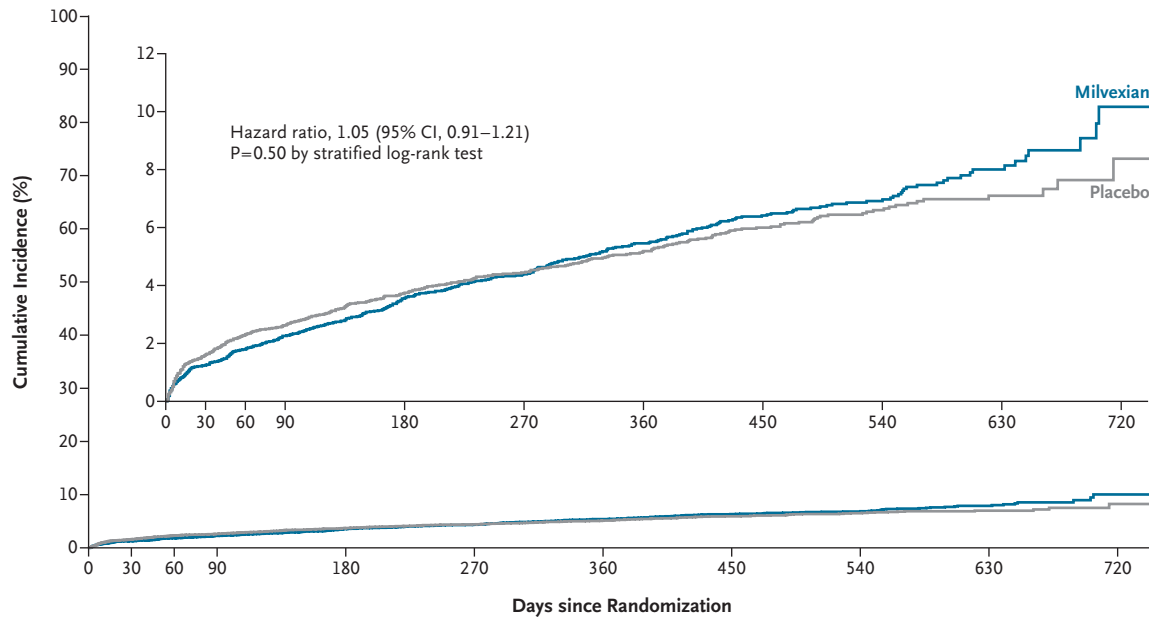
aPTT was similar at baseline in the two groups (25.7 seconds in 443 patients in the milvexian group and 25.3 seconds in 433 patients in the placebo group). The mean increase in the trough aPTT at 4 weeks was 1.59 times as high as the baseline value in the milvexian group and 1.03 times as high as the baseline value in the placebo group.

SAFETY

BARC type 3c or 5 bleeding occurred in 23 patients (0.3%) in the milvexian group and in 22 patients (0.3%) in the placebo group (hazard ratio, 1.04; 95% CI, 0.58 to 1.87; $P=0.88$) (Table 3). The risk of bleeding appeared to be similar in the two

groups with respect to BARC type 3b, BARC type 3c, BARC type 5, severe or life-threatening bleeding according to GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) criteria, major bleeding according to ISTH (International Society on Thrombosis and Haemostasis) criteria, or major bleeding not related to CABG according to TIMI (Thrombolysis in Myocardial Infarction) criteria.

Clinically relevant nonmajor bleeding (BARC type 2) occurred in 363 patients (5.2%) in the milvexian group and in 318 patients (4.5%) in the placebo group (hazard ratio, 1.14; 95% CI, 0.98 to 1.33). Additional adverse events and serious adverse events are shown in Table 3.

**No. at Risk**

Milvexian	7094	6726	6409	6158	5305	4367	3541	2642	1648	684	103
Placebo	7100	6715	6383	6134	5284	4368	3545	2639	1657	687	109

Figure 1. Primary Efficacy Outcome.

Shown is the cumulative incidence of the primary outcome (a composite of cardiovascular death, myocardial infarction, or ischemic stroke) in the milvexian group and the placebo group. After a planned interim analysis that was based on 556 adjudicated efficacy end points, the trial was terminated for futility. After a median follow-up of 12.2 months, a primary-outcome event had occurred in 384 patients (5.4%) in the milvexian group and in 365 patients (5.1%) in the placebo group. Although the longest follow-up was more than 2 years, the Kaplan–Meier plot was truncated when the number at risk in either group was less than 25. The inset graph shows the same data on an expanded y axis.

DISCUSSION

Despite contemporary antiplatelet therapy, statins, and advanced stent technologies, patients with cardiac biomarker–positive acute coronary syndromes remain at high risk for recurrent ischemic events.^{1,24} In the current trial, we found that milvexian was not superior to placebo with respect to a composite of cardiovascular death, myocardial infarction, or ischemic stroke when added to standard antiplatelet therapy after an acute coronary syndrome event.

There are several potential explanations for the lack of benefit observed with milvexian. Although data obtained from mendelian randomization indicate reductions in ischemic stroke and venous thromboembolism in patients with a low factor XI level, evidence for a reduction in myocardial infarction is less robust. As with the current phase 3 findings regarding milvexian, a

small phase 2 trial²⁵ that compared asundexian (at a dose of 50 mg daily), another oral factor XIa inhibitor, with placebo in patients with acute myocardial infarction also showed no benefit; however, that trial was markedly underpowered to assess efficacy. In contrast, in the phase 3 OCEANIC-STROKE (Oral Factor Eleven A Inhibitor Asundexian as Novel Antithrombotic Stroke) trial²⁶ involving patients with acute noncardioembolic ischemic stroke or high-risk transient ischemic attack who were receiving standard antiplatelet therapy, the 50-mg dose of asundexian resulted in a significantly lower risk of recurrent stroke than placebo. Together, these findings suggest that the role of factor XI may vary across vascular beds. Whereas factor XI may drive intravascular thrombus expansion in smaller arteries, such as those in the brain, it may be less important in larger arteries, such as those in the heart.

Table 2. Primary and Key Secondary Efficacy Outcomes.

Outcome	Milvexian (N = 7094)		Placebo (N = 7100)		Hazard Ratio (95% CI)
	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	
Primary outcome					
Cardiovascular death, myocardial infarction, or ischemic stroke	384 (5.4)	5.60 (5.06–6.19)	365 (5.1)	5.33 (4.81–5.90)	1.05 (0.91–1.21)*
Cardiovascular death	110 (1.6)	1.54 (1.28–1.86)	112 (1.6)	1.57 (1.30–1.89)	0.98 (0.75–1.28)
Myocardial infarction	249 (3.5)	3.61 (3.19–4.09)	236 (3.3)	3.43 (3.02–3.89)	1.05 (0.88–1.26)
Ischemic stroke	60 (0.8)	0.85 (0.66–1.10)	46 (0.6)	0.66 (0.49–0.88)	1.30 (0.89–1.91)
Key secondary outcomes					
Cardiovascular death, myocardial infarction, ischemic stroke, major adverse limb event, or symptomatic venous thromboembolism	402 (5.7)	5.87 (5.32–6.47)	386 (5.4)	5.65 (5.11–6.24)	1.04 (0.90–1.20)
Death from any cause, myocardial infarction, or ischemic stroke	430 (6.1)	6.27 (5.70–6.89)	408 (5.7)	5.95 (5.40–6.56)	1.05 (0.92–1.21)
Cardiovascular death	110 (1.6)	1.54 (1.28–1.86)	112 (1.6)	1.57 (1.30–1.89)	0.98 (0.75–1.28)
Death from any cause	158 (2.2)	2.21 (1.89–2.59)	164 (2.3)	2.30 (1.97–2.68)	0.96 (0.77–1.20)

* P=0.50 for the primary-outcome comparison.

Although it is possible that the 25-mg twice-daily dose of milvexian administered in the current trial was too low, this factor is unlikely to explain the findings for several reasons. First, the antithrombotic efficacy of this dose of milvexian was shown in the phase 2 AXIOMATIC-TKR (Antithrombotic Treatment with Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events in Total Knee Replacement) trial,¹⁸ which compared milvexian dose regimens with enoxaparin for thromboprophylaxis after total knee replacement. Second, as compared with placebo in the phase 3 OCEANIC-STROKE trial, the same total daily dose of asundexian reduced the risk of recurrent stroke in patients with acute noncardioembolic ischemic stroke or high-risk transient ischemic attack.²⁶ On the basis of factor XIa inhibitory constants, milvexian is more potent than asundexian,²⁷ so at equimolar concentrations, milvexian prolongs the aPTT to a greater extent than asundexian.²⁸ The trough aPTT in the current trial was increased by a factor of 1.59 in the milvexian group as compared with baseline values, a finding that is consistent with biologic activity that is similar to the steady-state

trough in healthy volunteers who had received asundexian (50 mg daily)²⁹ and the highest dose of abelacimab (150 mg) at day 30 after a single injection in a study of venous thromboembolism prevention.³⁰ Likewise, the mild excess of clinically relevant nonmajor bleeding is also consistent with a biologic effect and very similar to results reported in the OCEANIC-STROKE trial (hazard ratio, 1.11; 95% CI, 0.92 to 1.34).²⁶ It is also possible that differences between the acute coronary syndrome and stroke populations may reflect differences in disease biology.

Despite current guideline recommendations for early de-escalation of antiplatelet therapy in patients with acute coronary syndrome, most patients in the current trial received dual antiplatelet therapy for up to 12 months, and much of this treatment included ticagrelor or prasugrel, which are more potent P2Y₁₂ inhibitors than clopidogrel. It is therefore possible that the potent background antiplatelet therapy minimized the potential benefit of milvexian, even though the planned duration of dual antiplatelet therapy at randomization did not appear to influence outcomes. The benefit of the 25-mg twice-daily dose of milvexian,

Table 3. Safety Outcomes.*

Outcome	Milvexian (N = 7008)		Placebo (N = 7027)		Hazard Ratio (95% CI)
	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	
Principal safety outcome†					
BARC type 3c or 5 bleeding	23 (0.3)	0.37 (0.25–0.56)	22 (0.3)	0.36 (0.24–0.54)	1.04 (0.58–1.87)‡
Key secondary safety outcomes					
BARC type 3b, 3c, or 5 bleeding	62 (0.9)	1.01 (0.79–1.29)	64 (0.9)	1.04 (0.82–1.33)	0.97 (0.68–1.37)
Type 3b	40 (0.6)	0.65 (0.48–0.89)	42 (0.6)	0.68 (0.51–0.93)	0.95 (0.62–1.47)
Type 3c	14 (0.2)	0.23 (0.13–0.38)	16 (0.2)	0.26 (0.16–0.43)	0.87 (0.43–1.79)
Type 5	9 (0.1)	0.15 (0.08–0.28)	6 (0.1)	0.10 (0.04–0.22)	1.50 (0.53–4.21)
GUSTO severe or life-threatening bleeding event	27 (0.4)	0.44 (0.30–0.64)	23 (0.3)	0.37 (0.25–0.56)	1.17 (0.67–2.04)
ISTH major bleeding	105 (1.5)	1.71 (1.41–2.07)	102 (1.5)	1.67 (1.37–2.02)	1.03 (0.78–1.35)
Non–CABG-related TIMI major bleeding	49 (0.7)	0.80 (0.60–1.05)	46 (0.7)	0.75 (0.56–1.00)	1.06 (0.71–1.59)
BARC type 2 bleeding	363 (5.2)	6.11 (5.51–6.77)	318 (4.5)	5.34 (4.79–5.96)	1.14 (0.98–1.33)
Adverse events					
Any adverse event	3656 (52.2)	—	3583 (51.0)	—	—
Adverse event leading to treatment discontinuation	318 (4.5)	—	333 (4.7)	—	—
Serious adverse event	819 (11.7)	—	790 (11.2)	—	—
Adverse event leading to death	71 (1.0)	—	73 (1.0)	—	—

* In the safety analysis, the principal and key secondary safety outcomes include data that were obtained from randomization through 2 days after the administration of the last dose of milvexian or placebo. Data regarding adverse events were obtained from the time of administration of the first dose of milvexian or placebo through 2 days after the administration of the last dose, except for adverse events leading to death, which could be recorded at any time after randomization. CABG denotes coronary-artery bypass grafting, GUSTO Global Use of Strategies to Open Occluded Coronary Arteries, ISTH International Society of Thrombosis and Haemostasis, and TIMI Thrombolysis in Myocardial Infarction.

† The Bleeding Academic Research Consortium (BARC) scale defines type 2 as clinically overt, actionable bleeding that prompts medical evaluation, minor nonsurgical treatment, or hospitalization; type 3b as overt bleeding with a decrease in hemoglobin of 5g per deciliter or greater, cardiac tamponade, bleeding requiring surgical control, or bleeding treated with intravenous vasoactive drugs; type 3c as intracranial or intraocular bleeding that compromises vision; and type 5 as fatal bleeding.

‡ P = 0.88 for the between-group comparison.

when added to standard antiplatelet therapy after an acute ischemic stroke or high-risk transient ischemic attack, is being investigated in the LIBREXIA Stroke trial.

The potential treatment interaction according to sex was not adjusted for multiplicity and is most likely spurious given the numerous interactions tested, the lack of a qualitative difference on the Gail–Simon test, and the lack of a biologically plausible mechanism. These findings deserve exploration in future studies.

Of note, there was no detectable increase in major bleeding across the various bleeding categories among patients who received milvexian, even

though dual antiplatelet therapy was used in a majority of patients and a high proportion received potent P2Y₁₂ inhibitors (Fig. S2).

This trial has several limitations. Approximately 20% of the patients discontinued either milvexian or placebo, and some efficacy events occurred after the patients had stopped taking either one. Most patients received dual antiplatelet therapy for 1 year, and the number of patients was insufficient to assess efficacy among those receiving antiplatelet monotherapy. Because patients with atrial fibrillation who were receiving anticoagulation were excluded, no information is available regarding the role of milvexian in pa-

tients with atrial fibrillation receiving a stent, although another ongoing trial (LIBREXIA AF) is comparing a higher dose of milvexian (100 mg twice daily) with apixaban in patients with atrial fibrillation.

Among patients with acute coronary syndrome, the addition of milvexian to guideline-directed medical therapy did not reduce the risk of a composite outcome of cardiovascular death, myocardial infarction, or ischemic stroke but did not increase intracranial or fatal bleeding.

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