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ORIGINAL RESEARCH

Caffeinated Beverage Intake, Dyspnea With Ticagrelor, and Cardiovascular Outcomes: Insights From the PEGASUS-TIMI 54 Trial

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BACKGROUND: A proposed cause of dyspnea induced by ticagrelor is an increase in adenosine blood levels. Because caffeine is an adenosine antagonist, it can potentially improve drug tolerability with regard to dyspnea. Furthermore, association between caffeine and cardiovascular events is of clinical interest.

METHODS AND RESULTS: This prespecified analysis used data from the PEGASUS TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial, which randomized 21 162 patients with prior myocardial infarction to ticagrelor 60 mg or 90 mg or matching placebo (twice daily). Baseline caffeine intake in cups per week was prospectively collected for 9694 patients. Outcomes of interest included dyspnea, major adverse cardiovascular events (ie, the composite of cardiovascular death, myocardial infarction, or stroke), and arrhythmias. Dyspnea analyses considered the pooled ticagrelor group, whereas cardiovascular outcome analyses included patients from the 3 randomized arms. After adjustment, caffeine intake, compared with no intake, was not associated with lower rates of dyspnea in patients taking ticagrelor (adjusted hazard ratio (HR), 0.91; 95% CI, 0.76–1.10; *P*=0.34). There was no excess risk with caffeine for major adverse cardiovascular events (adjusted HR, 0.78; 95% CI, 0.63–0.98; *P*=0.031), sudden cardiac death (adjusted HR, 0.98; 95% CI, 0.57–1.70; *P*=0.95), or atrial fibrillation (adjusted odds ratio, 1.07; 95% CI, 0.56–2.04; *P*=0.84).

CONCLUSIONS: In patients taking ticagrelor for secondary prevention after myocardial infarction, caffeine intake at baseline was not associated with lower rates of dyspnea compared with no intake. Otherwise, caffeine appeared to be safe in this population, with no apparent increase in atherothrombotic events or clinically significant arrhythmias.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01225562.

Key Words: arrhythmias ■ caffeine ■ cardiovascular outcomes ■ dyspnea ■ ticagrelor

Ticagrelor is a potent reversible $P2Y_{12}$ inhibitor that reduces ischemic risk in patients with acute coronary syndromes[1] and in those who need long-term secondary prevention after myocardial infarction (MI).[2] Dyspnea associated with ticagrelor has been described as an adverse event of mild to moderate intensity that is generally self-limited and not associated with any adverse cardiovascular or pulmonary impact.[3,4] The potential adverse impact of dyspnea, however, is that it may affect drug adherence, particularly when initiated in stable asymptomatic patients.[5] Therefore, strategies to improve drug tolerability and reduce discontinuation due to dyspnea may be clinically useful.

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CLINICAL PERSPECTIVE

What Is New?

- We observed that caffeine ingestion was not associated with lower rates of dyspnea induced by ticagrelor.
- Even in patients at high risk following myocardial infarction, such as those included in the PEGASUS TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial, no increased risk of recurrent myocardial infarction, stroke, sudden cardiac death, major adverse limb events, or clinically meaningful arrhythmias was apparent with caffeine.

What Are the Clinical Implications?

- Despite the possible link between adenosine and dyspnea on ticagrelor, our data do not support a recommendation of drinking caffeine to alleviate this adverse reaction.
- High-risk patients with prior myocardial infarction, including those with polyvascular disease who chose to take caffeine, do not appear to be at heightened risk of cardiovascular events.
- Although several studies, including this one, observed an inverse association between caffeine and cardiovascular risk, these observations should be viewed as hypothesis generating; randomized trials would be necessary to confirm a benefit.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
ENT-1	equilibrative nucleoside transporter 1
HR	hazard ratio
MI	myocardial infarction
MACE	major adverse cardiovascular events
MALE	major adverse limb events
PEGASUS	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
TIMI	Thrombolysis in Myocardial Infarction

Although it is well documented that dyspnea while taking ticagrelor is not associated with disturbed heart or lung function, its exact mechanism remains unclear. Ticagrelor has been shown to inhibit ENT-1 (equilibrative nucleoside transporter 1) in red blood cells and thus decrease adenosine reuptake.[6,7] Therefore, it is hypothesized that higher adenosine exposure due to ticagrelor could account for dyspnea and for other drug-related adverse events, such as ventricular pauses and gout.[8] In contrast, other reports have challenged whether inhibition of adenosine uptake could lead to increase in adenosine blood levels of clinical relevance.[9,10] In the HIGH-TECH (Hunting for the Off-Target Properties of Ticagrelor on Endothelial Function in Humans) trial, investigators did not find increased levels of plasma adenosine among patients experiencing dyspnea while on ticagrelor.[10] Consequently, other pathways involved in dyspnea may exist as alternative explanations for this adverse event, for example, a direct effect of ticagrelor on $P2Y_{12}$ receptors from inhibitory neuron fibers that convey dyspnea signaling.[11,12]

Caffeine and theophylline are adenosine antagonists that can block adenosinergic A_{1A} receptors involved in the mediation of dyspnea by pulmonary C-fibers.[13,14] In healthy volunteers, ticagrelor enhanced dyspnea intensity during adenosine infusion, an effect that was decreased by intravenous theophylline.[15] If dyspnea induced by ticagrelor is mostly caused by adenosine, then it is plausible that caffeine intake may also attenuate the intensity of this adverse event and improve drug tolerability.

Because of its stimulant effects, the potential risks and benefits of caffeine in high-risk patients with coronary artery disease (CAD) continue to be debated. Some reports have raised concerns about higher risk of sudden death with coffee intake by individuals with prior CAD.[16] Conversely, other reports have observed an inverse association between coffee intake and cardiovascular risk.[17] To date, there has not been an evaluation of caffeinated beverage intake and adjudicated cardiovascular outcomes in a large, well-characterized, multinational cohort of high-risk patients with prior MI receiving current optimal medical therapy.

We sought to investigate 2 hypotheses: (1) that the risk of dyspnea with ticagrelor would be affected by baseline intake of caffeinated beverages and (2) that caffeine intake would not be associated with any excess risk of major adverse cardiovascular events (MACE) or arrhythmias in a high-risk population of patients with prior MI.

METHODS

Population and Variables Selection

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions. The study protocol and enrollment criteria from PEGASUS TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to

Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) have been published previously.[18] Briefly, 21 162 patients with prior MI between 1 and 3 years (median: 1.7 years) after the index event were randomized to double-blinded ticagrelor (60 or 90 mg twice daily) or matching placebo. To be included, patients had to have at least 1 additional high-risk feature: age ≥65 years, >1 MI beyond the index event, diabetes mellitus, chronic kidney disease with creatinine clearance <60 mL/min, or multivessel CAD at baseline. The intention-to-treat database comprised all randomized patients. The trial safety database, which comprised 20 942 patients, included any patient who took at least 1 dose of the study drug.

While the trial was still recruiting new participants, data supporting a possible relationship between adenosine and dyspnea due to ticagrelor and the potential inhibitory effect of caffeine were described.[15] Based on this new information, a hypothesis that caffeine intake at randomization would be associated with the risk of dyspnea with ticagrelor was prespecified. At that time, study sites were instructed to prospectively collect information regarding caffeine consumption at the baseline visit through a dedicated page in the study case report form. This information was collected prospectively as ingestion of any caffeinated beverage (including coffee, tea, and soda drinks) in cups per week. Therefore, the present analysis included 9694 of 21 162 randomized participants for whom baseline caffeine intake was collected. Analyses of dyspnea included patients from the safety database, and cardiovascular outcomes were analyzed from the intention-to-treat database.

The primary analysis for this article was the incidence of dyspnea among patients assigned to ticagrelor during the trial, with additional analyses for drug discontinuation due to dyspnea and for dyspnea according to different intensities. Dyspnea was reported by study sites using standard safety reporting processes, with dyspnea intensity reported as mild, moderate, or severe, according to the site investigator's assessment. As has been reported previously, dyspnea was considered to have led to drug discontinuation when it was the main cause of study drug withdrawal, and this definition excluded discontinuation in the setting of an efficacy event.[5]

The cardiovascular outcome analyses considered MACE (the composite of cardiovascular death, MI, or stroke) and its individual components, all-cause mortality, death due to CAD, sudden cardiac death, clinically relevant arrhythmias, major bleeding as defined by Thrombolysis in Myocardial Infarction (TIMI), and major adverse limb events (MALE). All deaths, bleeding, and cardiovascular events, except arrhythmias and MALE, were independently adjudicated by a clinical events committee whose members were unaware of study drug assignment but not necessarily blinded to information regarding caffeine intake. Arrhythmias were site-reported using standard safety reporting. Event terms were searched for arrhythmias of special interest including atrial fibrillation or flutter, ventricular tachycardia or fibrillation, and other tachyarrhythmias. Narratives from the serious adverse events were reviewed independently by 2 authors (R.H.M.F., M.P.B.) to ascertain whether arrhythmias consistent with one of those categories were present, with disagreements resolved by consensus. MALE, the composite of acute limb ischemia or peripheral revascularization for ischemia, were prospectively collected and blindly reviewed, as defined previously.[19]

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges and were compared with the Mann–Whitney test. Categorical variables are presented as absolute counts and percentages and were compared using the χ^2 test.

The primary population of interest for dyspnea outcomes comprised patients in the pooled ticagrelor group from the safety database, with additional sensitivity analyses done separately for the 60- and 90-mg dosing and placebo groups. For cardiovascular outcomes and arrhythmias, we considered patients from the intention-to-treat database. Our primary analysis compared patients who did not drink any caffeinated beverage with those who drank any amount. Additional analyses were done according to quantitative intake considering quartiles of caffeine ingestion. Cox proportional hazard models were used to model the association between this binary caffeine variable and the following outcomes: dyspnea, MACE, MI, stroke, sudden cardiac death, death due to coronary heart disease, cardiovascular death, TIMI major bleeding, and MALE. Logistic regression was used for the end points of atrial fibrillation or flutter and any tachyarrhythmia.

Adjustment for confounders was performed using multivariable Cox or logistic regression models that controlled for all variables with a standardized mean difference between caffeine drinkers and nondrinkers of >5%. The final model was then adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel CAD, history of percutaneous coronary intervention, type of qualifying MI (ST-segment–elevation myocardial infarction versus non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min per 1.73 m^2, smoking, region of the world, and use of

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline.

All tests were 2-tailed, and no adjustment was made for multiplicity. $P<0.05$ was considered statistically significant. SAS software v9.4 (SAS Institute) and R v3.5.3 (R Foundation for Statistical Computing) were used for the statistical analyses.

Compliance With Ethical Standards

This trial conformed to the recommendations of the Helsinki Declaration and Good Clinical Practice norms on medical research in humans. The study protocol was approved by all institutional review boards of participating sites before starting enrollment. All patients signed an informed consent form before participation.

Role of the Funding Source

The PEGASUS TIMI 54 trial received grant funding from AstraZeneca. The current analyses received no sources of external funding. The TIMI Study Group has an independent copy of the trial databases. The authors wrote all drafts of the article and take full responsibility for its content integrity and data analysis. The corresponding author had full access to the data and had final responsibility to submit it for publication.

RESULTS

Descriptive Statistics: Baseline Caffeine Intake

A total of 9694 participants were included in this analysis, of whom 9568 form the safety database. Median caffeinated beverage intake was 10 cups per week (interquartile range: 4–21). A total of 8406 patients reported drinking at least 1 cup of caffeinated beverage per week, whereas 1288 patients drank no caffeine. Caffeine intake was significantly associated with region of the world, with the highest in western Europe

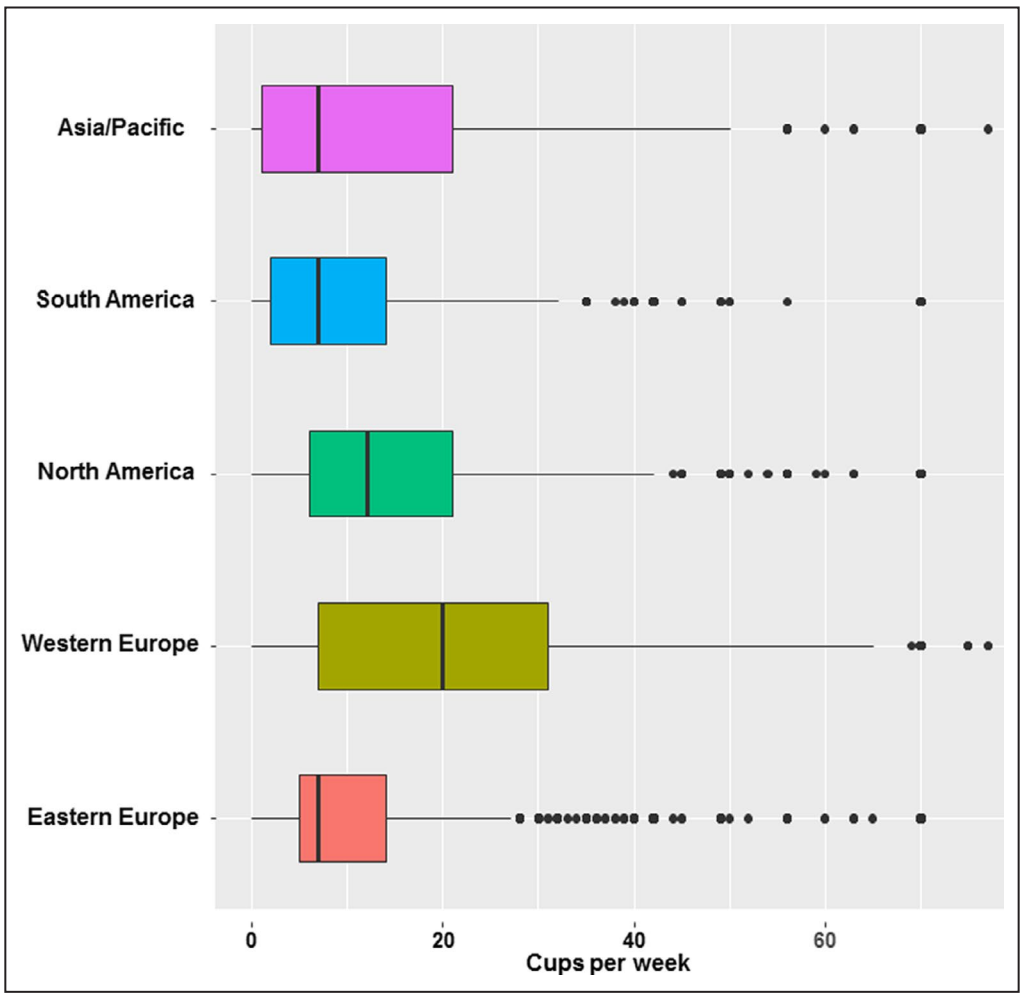

Figure 1. Median caffeinated beverages consumption in cups per week according to regions of the world.

Table 1. Baseline Characteristics According to Baseline Caffeine Intake (Intention-to-Treat Database, N=9694)

	No Caffeine (n=1288)	Any Caffeine (n=8406)	*P* Value
Age, y	66 (59–72)	65 (58–71)	<0.001
Female sex	362 (28.1)	1872 (22.3)	<0.001
White race	939 (72.9)	7259 (86.4)	<0.001
BMI, kg/m^2	27.3 (24.5–30.5)	27.8 (25.1–31.1)	<0.001
Hypertension	994 (77.2)	6532 (77.7)	0.70
Hypercholesterolemia	815 (63.3)	6616 (78.7)	<0.001
Current smoker	148 (11.5)	1521 (18.1)	<0.001
Diabetes mellitus	470 (36.5)	2583 (30.7)	<0.001
Prior HF	205 (15.9)	1570 (18.7)	0.019
Multivessel CAD	766 (59.6)	5297 (63.0)	0.019
History of PCI	1026 (79.7)	7140 (84.9)	<0.001
>1 prior MI	196 (15.2)	1368 (16.3)	0.36
PAD	59 (4.6)	451 (5.4)	0.27
Years since qualifying MI	1.65 (1.19–2.25)	1.58 (1.17–2.23)	0.087
STEMI as qualifying MI	704 (54.8)	4560 (54.3)	0.79
Aspirin	1286 (99.8)	8397 (99.9)	0.97
Statin	1184 (91.9)	7833 (93.2)	0.11
β-Blocker	1053 (81.8)	6939 (82.5)	0.51
ACEI or ARB	999 (77.6)	6784 (80.7)	0.009
eGFR <60 mL/min/1.73 m^2 (MDRD)	303 (24.2)	1779 (21.4)	0.027
COPD	78 (6.1)	606 (7.2)	0.15
Asthma	49 (3.8)	308 (3.7)	0.86
Region			<0.001
Asia/Pacific	295 (22.9)	886 (10.5)	
Eastern Europe	248 (19.3)	2245 (26.7)	
North America	200 (15.5)	1858 (22.1)	
South America	247 (19.2)	1043 (12.4)	
Western Europe	298 (23.1)	2374 (28.2)	

Values are median (interquartile range) or n (%) unless otherwise specified. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

and the lowest in Asia (Table S1 and Figure 1). The countries with highest caffeine intake were Turkey, the Netherlands, and the United Kingdom, and those with the lowest intake were China, Peru, and Spain (Table S2).

Predictors of Caffeinated Beverage Intake

Table 1 shows baseline characteristics by caffeine consumption (caffeine drinkers versus nondrinkers). Among other differences, patients who drank caffeine at baseline were younger and more often male and white and had higher body mass index and higher prevalence of hypercholesterolemia, smoking, multivessel CAD, and heart failure but lower prevalence of diabetes mellitus. Table S3 shows the same characteristics considering the safety population.

Risk of Dyspnea With Ticagrelor

The risk of dyspnea due to ticagrelor has been described previously.[5] There was a significant increase in dyspnea compared with placebo use with both ticagrelor doses. This increase was consistent for the incidence of any dyspnea throughout trial follow-up and for dyspnea leading to drug discontinuation (Figure 2). Rates of dyspnea reporting had wide variability among regions of the world, with western Europe and North America being more likely to report dyspnea than South America, eastern Europe, and Asia/Pacific (Table S4).

Relationship Between Caffeine Intake and Dyspnea in Patients Taking Ticagrelor

At univariate analysis, in the pooled ticagrelor group, caffeine drinkers had similar rates of dyspnea compared with nondrinkers and numerically lower rates

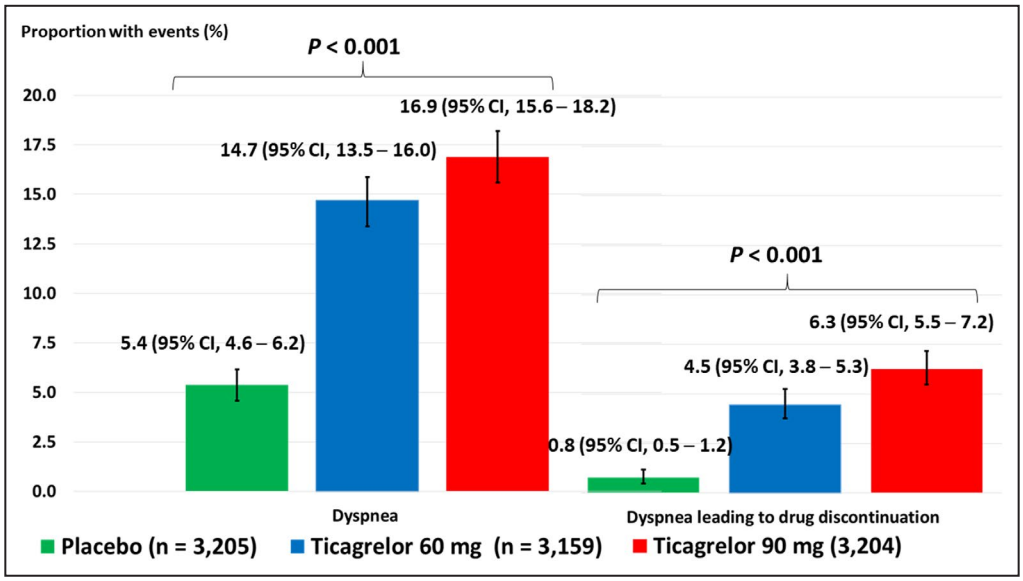

Figure 2. Proportion of patients with dyspnea according to randomized groups.
P values are shown for comparison of proportions across the 3 groups for each adverse event.

of drug discontinuation due to dyspnea. After adjustment, caffeine intake was not associated with lower rates of overall dyspnea (adjusted hazard ratio [HR], 0.91; 95% CI, 0.76–1.10; *P*=0.34). Similarly, there was no association with lower rates of mild dyspnea (adjusted HR, 0.97; 95% CI, 0.76–1.24; *P*=0.78; Table 2). Although there was a significant association between drinking caffeine and lower rates of drug discontinuation due to dyspnea (adjusted HR, 0.72; 95% CI, 0.53–0.98; *P*=0.035), there was no significant association with lower rates of moderate dyspnea (adjusted HR, 0.84; 95% CI, 0.63–1.14; *P*=0.27) or moderate to severe dyspnea (adjusted HR, 0.82; 95% CI, 0.62–1.08; *P*=0.16; Table 2 and Figure 3). Table S5 shows the same results for each separate ticagrelor dose and for the placebo group. Table S6 shows those results stratified by regions of higher versus lower caffeine intake.

Caffeine Intake and Cardiovascular Events

In the overall trial population, caffeine intake was independently associated with a lower incidence of the composite of cardiovascular death, MI, or stroke and with a lower risk of recurrent myocardial infarction compared with not drinking caffeine (Figure 4). Moreover, there was no significant association of drinking caffeine with the incidence of any tachyarrhythmia, atrial fibrillation or flutter, or sudden cardiac death (Figure 5 and Table 3). Although there was a significant association with lower rates of MACE and recurrent MI, there was no significant association between drinking caffeine and lower rates of TIMI major bleeding. In addition, there appeared to be an association between drinking caffeine and numerically lower rates of MALE; however, the numbers did not reach statistical significance,

Table 2. Association Between Caffeine Intake at Baseline and Dyspnea Adverse Events in Patients Taking Ticagrelor, Pooled Dose Groups (n=6363)

	No Caffeine Intake (n=830), n (%)	Any Caffeine Intake (n=5533), n (%)	Adjusted HR (95% CI)	*P* Value
Any dyspnea	131 (15.8)	874 (15.8)	0.91 (0.76–1.10)	0.34
Mild dyspnea	77 (9.3)	545 (9.8)	0.97 (0.76–1.24)	0.78
Moderate dyspnea	52 (6.3)	328 (5.9)	0.84 (0.63–1.14)	0.27
Severe dyspnea	9 (1.1)	55 (1.0)	0.85 (0.41–1.74)	0.65
Moderate or severe dyspnea	60 (7.2)	367 (6.6)	0.82 (0.62–1.08)	0.16
Dyspnea leading to drug discontinuation	54 (6.5)	288 (5.2)	0.72 (0.53–0.98)	0.035

Adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel coronary artery disease, history of percutaneous coronary intervention, type of qualifying myocardial infarction (ST-segment–elevation myocardial infarction vs non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min/1.73 m^2, smoking, region of the world, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. HR indicates hazard ratio.

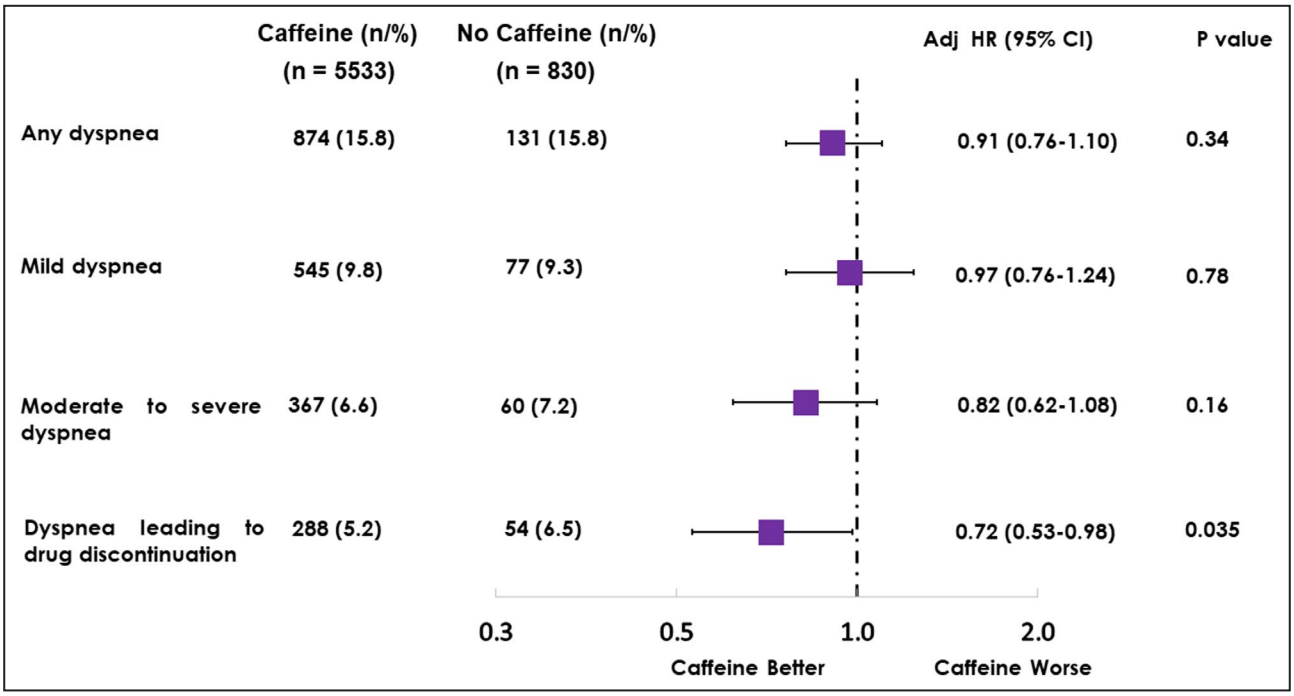

Figure 3. Association between dyspnea and baseline caffeine intake in the pooled ticagrelor group (n=6363).
Adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel coronary artery disease history of percutaneous coronary intervention, type of qualifying myocardial infarction (ST-segment–elevation myocardial infarction vs non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min per 1.73 m^2, smoking, region of the world, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. Adj HR indicates adjusted hazard ratio.

probably because of smaller numbers of events than MACE (Table 3).

Quantitative Caffeine Intake

The risk of dyspnea with both ticagrelor doses (60 and 90 mg) compared with placebo were analyzed according to strata of caffeine intake (by quartiles). Overall, there did not appear to be any effect modification with caffeine intake on the risk of dyspnea with either dose of ticagrelor (Figure 6). Moreover, when analyses for dyspnea and cardiovascular outcomes were performed according to quartiles of caffeine intake, results were consistent with the main analysis comparing any versus no intake (Table S7).

DISCUSSION

The current study describes important findings. First, caffeinated beverages are routinely ingested by high-risk patients with prior MI, but this habit is highly correlated with region and comorbidities. Second, compared with no caffeine intake, caffeine intake was not associated with lower rates of dyspnea in patients with prior MI taking ticagrelor for secondary prevention, and the increase in dyspnea with ticagrelor versus placebo, at both doses, was not modified by baseline caffeine intake Third, caffeine does not appear to be associated with higher risk of ischemic cardiovascular events or clinically important arrythmias in patients with previous MI and high-risk features.

Overall, we found that the majority of patients (>75%) in the almost 10 000-patient cohort consumed at least 1 cup of caffeinated beverage per week. We observed important regional variation, and the overall patterns matched those described in other studies.[20,21] Moreover, similar to prior reports, caffeine intake was associated with smoking and obesity.[17]

When ticagrelor first became available, dyspnea was a troubling side effect. Even though it was shown to be benign, it may prompt patients to stop treatment prematurely. Adenosine exposure has been postulated as a possible cause of this dyspnea, and ticagrelor has been shown to reduce adenosine uptake by red blood cells and to increase plasma concentrations.[6] However, mechanistic studies linking this increase in adenosine to dyspnea have shown conflicting results. In a study with healthy volunteers, van den Berg et al[22] could not find any increase in ex vivo adenosine reuptake at relevant plasma concentrations of ticagrelor. In addition, the STEEL-PCI (Study of Two Doses of Ticagrelor in Percutaneous Coronary

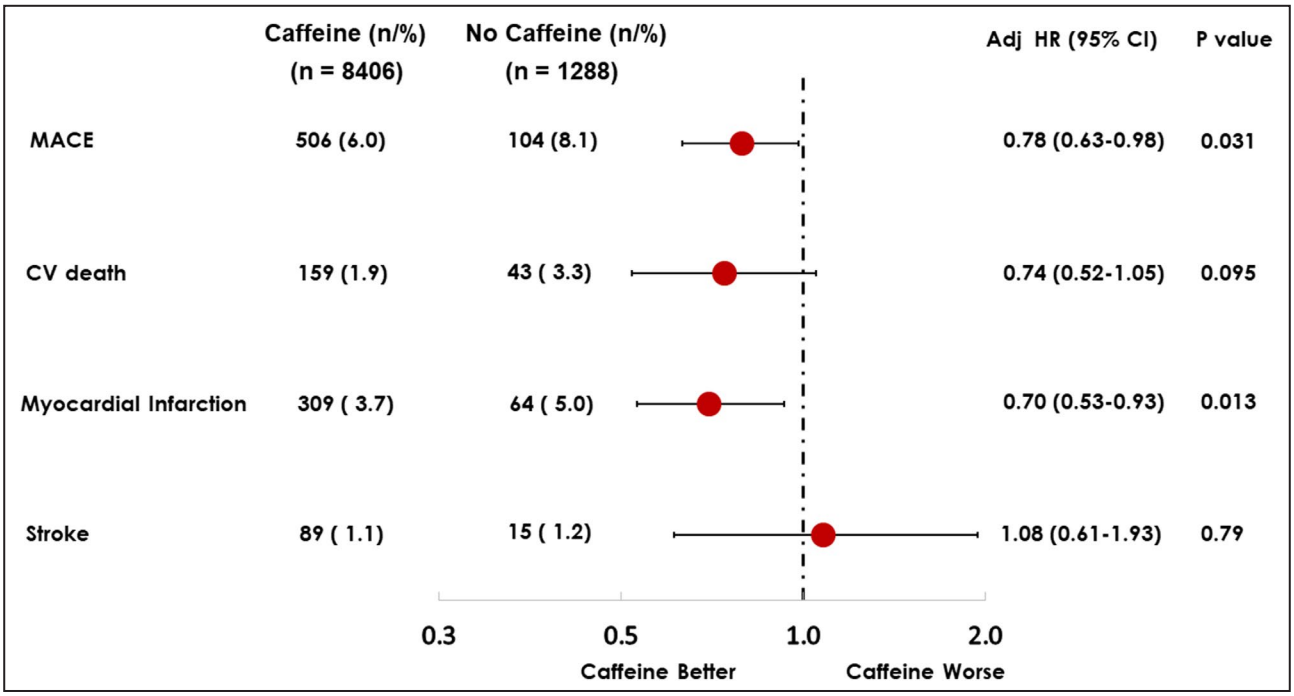

Figure 4. Association between major adverse cardiovascular events (MACE) and its components and baseline caffeine intake in the overall population (N=9694).
MACE was defined as the composite of cardiovascular (CV) death, myocardial infarction, or stroke. Adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel coronary artery disease, history of percutaneous coronary intervention, type of qualifying myocardial infarction (ST-segment–elevation myocardial infarction vs non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min per 1.73 m^2, smoking, region of the world, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. Adj HR indicates adjusted hazard ratio.

Intervention) study did not detect any effect of ticagrelor 60 or 90 mg on adenosine uptake in patients with stable CAD, raising the question of whether therapeutic concentrations of ticagrelor are sufficient to affect adenosine metabolism to a clinically relevant extent.[9] Finally, the HI-TECH study aimed to analyze possible pleiotropic effects from ticagrelor in a population with acute coronary syndromes. The investigators could not find any association between dyspnea with ticagrelor use and adenosine plasma levels; however, ticagrelor plasma concentrations were significantly higher in those patients experiencing dyspnea.[10] These findings suggest that adenosine exposure does not account for most dyspnea induced by ticagrelor and raise the possibility of other explanations for this adverse reaction, for example, a direct $P2Y_{12}$ inhibitory effect on the central nervous system.[11]

In our study, caffeine intake was not associated with lower rates of dyspnea on ticagrelor, but surprisingly, there appeared to be an association with lower rates of drug discontinuation due to dyspnea. If adenosine were the predominant pathway involved in ticagrelor-induced dyspnea, then we would expect to observe consistently lower rates of overall dyspnea among caffeine drinkers and not only an effect on the decision to stop the drug prematurely. Together with the fact that severe and moderate dyspnea intensities were not lower with caffeine, this may suggest that lower rates of drug discontinuation due to dyspnea could be explained by play of chance, bias (eg, knowing that caffeine could potentially reduce dyspnea could have made the study investigators stop the study drug less frequently among caffeine drinkers), or other unknown uncontrolled confounder. The null association between caffeine drinking and dyspnea while taking ticagrelor in our study is in accordance with the results from the HI-TECH study and reinforces that other alternative explanations may exist for dyspnea induced by ticagrelor besides increase in adenosine exposure.[10,11]

Other reports have described improvements in dyspnea with ticagrelor when intravenous theophylline or aminophylline was used,[15,23] although one was a single case report and the other evaluated dyspnea induced during adenosine infusion (and not necessarily caused only by ticagrelor). That caffeine could achieve the same effect is plausible, considering that, like theophylline derivatives, caffeine blocks adenosine-mediated effects.[14] This hypothesis was of sufficient importance to drive a randomized trial that would rigorously investigate the impact of caffeine on dyspnea related to ticagrelor.[24] Unfortunately, the trial enrolled only 23 patients out of a calculated sample size of 416. However, none of the randomized patients

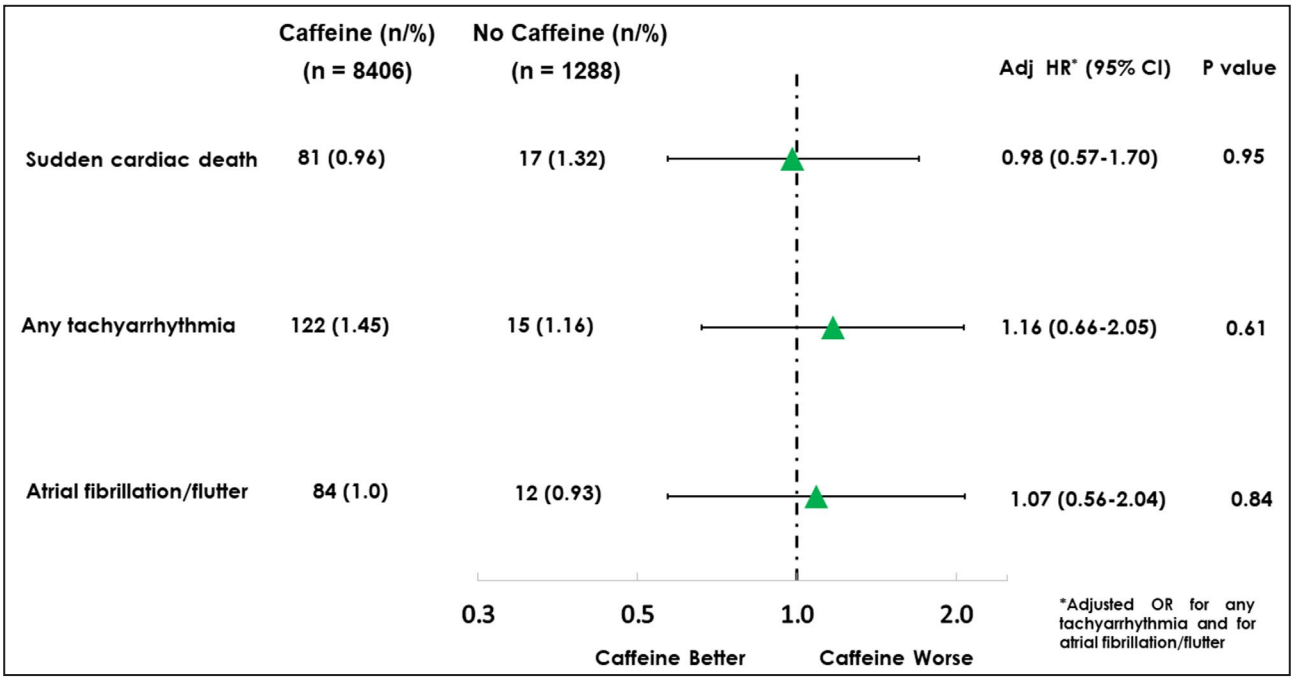

Figure 5. Association between clinically meaningful arrhythmias (reported as serious adverse events) and baseline caffeine intake in the overall population (N=9694).
Adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel coronary artery disease, history of percutaneous coronary intervention, type of qualifying myocardial infarction (ST-segment–elevation myocardial infarction vs non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min per 1.73 m^2, smoking, region of the world, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. Adj HR indicates adjusted hazard ratio; and OR, odds ratio.

benefited from the administration of caffeine 200 mg twice a day (a higher amount than is usually found in a single cup of coffee, which is 60–90 mg), and the results of a preliminary questionnaire survey among 180 patients with ticagrelor-induced dyspnea revealed that caffeine failed to improve dyspnea in 153 of 173 patients who responded.[25]

Table 3. Association Between Caffeine Intake at Baseline and Cardiovascular Outcomes (N=9694)

	No Caffeine Intake (n=1288, n (%)	Any Caffeine Intake (n=8406), n (%)	Adjusted HR* (95% CI)	*P* Value
Cardiovascular death, MI, or stroke	104 (8.07)	506 (6.02)	0.78 (0.63–0.98)	0.031
Cardiovascular death	43 (3.34)	159 (1.89)	0.74 (0.52–1.05)	0.095
MI	64 (4.97)	309 (3.68)	0.70 (0.53–0.93)	0.013
Stroke	15 (1.16)	89 (1.06)	1.08 (0.61–1.93)	0.79
All-cause death	58 (4.50)	262 (3.12)	0.84 (0.63–1.13)	0.26
CHD death	25 (1.94)	98 (1.17)	0.84 (0.52–1.34)	0.46
Sudden cardiac death	17 (1.32)	81 (0.96)	0.98 (0.57–1.70)	0.95
Any tachyarrhythmia	15 (1.16)	122 (1.45)	1.16 (0.66–2.05)	0.61
Atrial fibrillation/flutter	12 (0.93)	84 (1.00)	1.07 (0.56–2.04)	0.84
Noncardiovascular death	15 (0.99)	102 (0.96)	1.11 (0.64–1.93)	0.72
MALE	6 (0.39)	36 (0.41)	0.66 (0.28–1.59)	0.36
TIMI major bleeding	11 (0.92)	101 (1.35)	1.46 (0.77–2.76)	0.25

Adjusted for age, sex, race, body mass index, hypercholesterolemia, heart failure, diabetes mellitus, presence of multivessel coronary artery disease, history of percutaneous coronary intervention, type of qualifying myocardial infarction (ST-segment–elevation myocardial infarction vs non–ST-segment–elevation myocardial infarction), glomerular filtration rate <60 mL/min/1.73 m^2, smoking, region of the world, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. CHD indicates coronary heart disease; HR, hazard ratio; MALE, major limb adverse events (the composite of acute limb ischemia or peripheral revascularization for ischemia); MI, myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*For the end points atrial fibrillation/flutter and any tachyarrhythmia, odds ratios are reported with corresponding 95% CI.

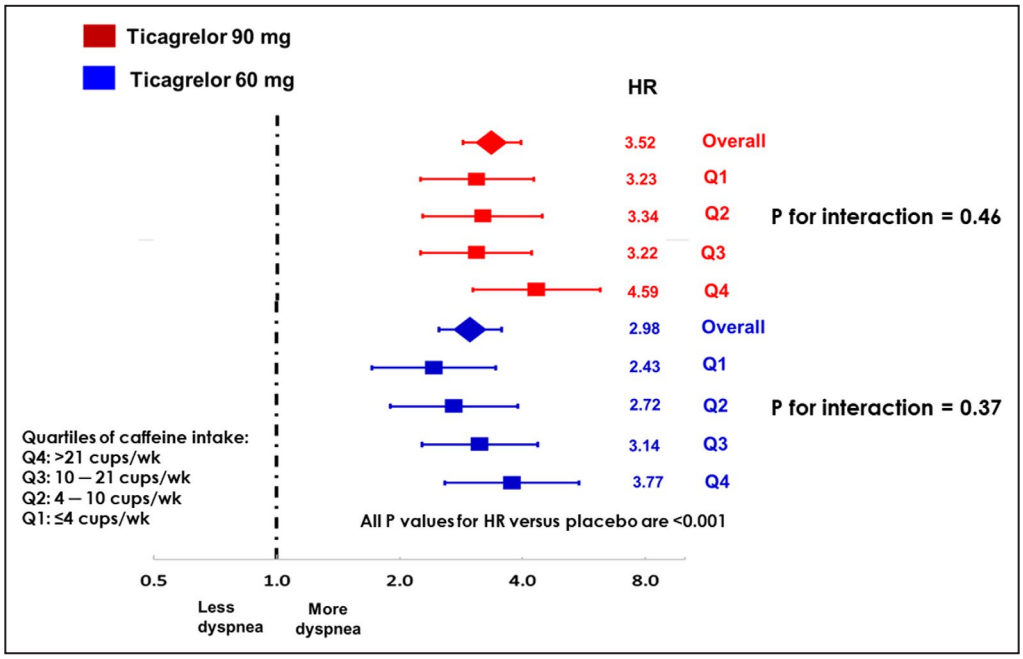

Figure 6. Hazards for dyspnea with ticagrelor vs placebo stratified by quartiles of caffeine intake.
HR indicates hazard ratio; and Q, quartile.

This current analysis in almost 10 000 high-risk patients with prior MI did not find any association between caffeinated beverage intake and higher rates of cardiovascular events. Other studies in patients with prior MI have similarly found no suggestion of harm from coffee or other caffeine sources when prospective cohort reports were considered; however, many of these studies were limited to a single country, were not representative of modern medical therapy, or had lower risk cohorts.[17,26–28] Our findings of lower rates of MACE are reassuring because they likely exclude an excess risk of cardiovascular atherothrombotic events with the ingestion of caffeine, even considering a population with prior MI and high-risk features such as those patients enrolled in the PEGASUS TIMI 54 trial. If one considers the upper boundary of the 95% CI for the adjusted HR for MACE with caffeine in our study, a 30% increase in the relative risk can be ruled out. This margin of noninferiority is in accordance with what has been used in trials with antidiabetic drugs.[29] The limb outcomes, although not significantly lower, were directionally consistent with overall MACE and MI reductions. In addition, drinking caffeine was associated with numerically higher rates of TIMI major bleeding. Caffeine is known to decrease platelet aggregation by upregulation of the adenosine A_2 receptor on platelets, so those observations could have biological plausibility.[30] This hypothesis should be investigated in future randomized event-driven studies.

We did not find any association between caffeine consumption and clinically relevant arrhythmias. Regarding atrial fibrillation, such concerns have been raised in the past,[31] although more recent reports have been reassuring.[32] However, no data specifically in the particular group of patients with prior MI has been published to date. Regarding potentially fatal arrhythmias, extremely high doses of intravenous caffeine can provoke malignant ventricular arrhythmias in experimental models,[33] and high coffee intake has been associated with sudden cardiac death in prior reports.[16] In our data, incidence of sudden cardiac death was not higher with caffeine. Despite the apparent absence of higher risk of arrhythmias with caffeine intake in our study, given the small number of events and the wide CIs (for which the upper boundary of the CI for the adjusted HR does not exclude an acceptable risk of 1.3), we cannot completely rule out such a risk. Moreover, we cannot exclude the possibility that drinks with high caffeine concentrations are harmful to patients with CAD because we have not specifically addressed this type of beverage.

Study Limitations

This study has several important limitations. First, caffeine intake was recorded only at baseline, so it is possible that caffeine ingestion could have changed during trial follow-up. Second, we could not ascertain caffeine intake from all patients from the trial because this hypothesis was raised after enrollment started. Nevertheless, baseline clinical characteristics were

well matched between those from the main trial population and the almost 10 000 patients included in this analysis.[2] Nevertheless, it is not known whether the implementation of this substudy while the trial was ongoing could have influenced our results. For example, knowing the hypothesis that caffeine intake could mitigate dyspnea induced by ticagrelor may have influenced site investigators to stop the study drug less commonly among caffeine drinkers than among nondrinkers, thus explaining a spurious association between caffeine drinking and lower rates of drug discontinuation due to dyspnea but without any association between drinking caffeine and overall dyspnea rates. Third, we did not collect detailed information regarding each type of caffeinated beverage. It is well known that the concentrations of caffeine, as well as roasting properties and other characteristics, differ substantially among different beverages, so we cannot be sure that our results would be applicable to different sources of caffeine. Fourth, dyspnea was investigator-reported and not centrally adjudicated, and sites were not required to perform extensive diagnostic workup to rule out other potential causes. Finally, even with adjusted models, the findings should be viewed as only hypothesis-generating given the nonrandomized design of the analysis and the lack of adjustment for multiplicity. Especially regarding the lower rates of MACE with caffeine, future randomized studies should clarify this question because in an observational study, uncontrolled unknown confounders may explain most of the association.

CONCLUSIONS

In high-risk patients with prior MI taking ticagrelor for secondary prevention, intake of caffeinated beverages at baseline compared with no intake was not associated with lower rates of dyspnea due to ticagrelor. Caffeine consumption in the range occurring in this cohort appeared to be safe, with no excess of ischemic cardiovascular events, arrhythmias, or sudden cardiac death. These findings do not support a recommendation of drinking caffeine to improve drug tolerability related to dyspnea, and they challenge the hypothesis that dyspnea induced by ticagrelor is mediated mainly by adenosine.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S7

REFERENCES

1. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
3. Storey RF, Bliden KP, Patil SB, Karunakaran A, Ecob R, Butler K, Teng R, Wei C, Tantry US, Gurbel PA; ONSET/OFFSET Investigators. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol*. 2010;56:185–193.
4. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, Steg PG, Khurmi NS, Emanuelsson H, Cooper A, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J*. 2011;32:2945–2953.
5. Bonaca MP, Bhatt DL, Oude Ophuis T, Steg PG, Storey R, Cohen M, Kuder J, Im K, Magnani G, Budaj A, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. *JAMA Cardiol*. 2016;1:425–432.
6. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, Gariboldi V, Condo J, Thuny F, Frere C, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. *J Am Coll Cardiol*. 2014;63:872–877.
7. Armstrong A, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. *J Cardiovasc Pharmacol Ther*. 2014;19:209–219.
8. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014;63:2503–2509.
9. Orme RC, Parker WAE, Thomas MR, Judge HM, Baster K, Sumaya W, Morgan KM, McMellon HC, Richardson JD, Grech ED, et al. Study of two dose regimens of ticagrelor compared with clopidogrel in patients undergoing percutaneous coronary intervention for stable coronary artery disease (STEEL-PCI). *Circulation*. 2018;138:1290–1300.
10. Ortega-Paz L, Brugaletta S, Ariotti S, Akkerhuis KM, Karagiannis A, Windecker S, Valgimigli M; HI-TECH Investigators. Adenosine and ticagrelor plasma levels in patients with and without ticagrelor-related dyspnea. *Circulation*. 2018;138:646–648.
11. Cattaneo M, Faioni EM. Why does ticagrelor induce dyspnea? *Thromb Haemost*. 2012;108:1031–1036.
12. Unterberger U, Moskvina E, Scholze T, Freissmuth M, Boehm S. Inhibition of adenylyl cyclase by neuronal P2Y receptors. *Br J Pharmacol*. 2002;135:673–684.
13. Burki NK, Lee LY. Blockade of airway sensory nerves and dyspnea in humans. *Pulm Pharmacol Ther*. 2010;23:279–282.
14. Smits P, Lenders JW, Thien T. Caffeine and theophylline attenuate adenosine-induced vasodilation in humans. *Clin Pharmacol Ther*. 1990;48:410–418.
15. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, Gan LM. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. *J Am Coll Cardiol*. 2013;61:723–727.
16. de Vreede-Swagemakers JJ, Gorgels AP, Weijenberg MP, Dubois-Arbouw WI, Golombeck B, van Ree JW, Knottnerus A, Wellens HJ. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. *J Clin Epidemiol*. 1999;52:601–607.
17. Mukamal KJ, Hallqvist J, Hammar N, Ljung R, Gémes K, Ahlbom A, Ahnve S, Janszky I. Coffee consumption and mortality after acute myocardial infarction: the Stockholm Heart Epidemiology Program. *Am Heart J*. 2009;157:495–501.
18. Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, Held P, Jensen EC, Sabatine MS. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. *Am Heart J*. 2014;167: 437–444.e5.
19. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol*. 2016;67: 2719–2728.
20. Michaud DS, Gallo V, Schlehofer B, Tjønneland A, Olsen A, Overvad K, Dahm CC, Teucher B, Lukanova A, Boeing H, et al. Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr*. 2010;92:1145–1150.
21. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev*. 1999;51:83–133.
22. van den Berg TN, El Messaoudi S, Rongen GA, van den Broek PH, Bilos A, Donders AR, Gomes ME, Riksen NP. Ticagrelor does not inhibit adenosine transport at relevant concentrations: a randomized cross-over study in healthy subjects in vivo. *PLoS One*. 2015;10: e0137560.
23. Conte L, Pugliese NR, Giannoni A. Reversal of ticagrelor-induced arrhythmias and Cheyne-Stokes respiration with aminophylline infusion. *J Cardiovasc Pharmacol*. 2017;70:290–292.
24. Lindholm D, Storey RF, Christersson C, Halvorsen S, Grove EL, Braun OÖ, Varenhorst C, James SK. Design and rationale of TROCADERO: a TRial Of Caffeine to Alleviate DyspnEa Related to ticagrelOr. *Am Heart J*. 2015;170:465–470.
25. Lindholm D, James S, Andersson J, Braun OÖ, Heller S, Henriksson P, Lauermann J, Öhagen P, Varenhorst C. Caffeine and incidence of dyspnea in patients treated with ticagrelor. *Am Heart J*. 2018;200:141–143.
26. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Caffeinated coffee consumption and mortality after acute myocardial infarction. *Am Heart J*. 2004;147:999–1004.
27. Silletta MG, Marfisi R, Levantesi G, Boccanelli A, Chieffo C, Franzosi M, Geraci E, Maggioni AP, Nicolosi G, Schweiger C, et al. Coffee consumption and risk of cardiovascular events after acute myocardial infarction: results from the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial. *Circulation*. 2007;116:2944–2951.
28. van Dongen LH, Mölenberg FJ, Soedamah-Muthu SS, Kromhout D, Geleijnse JM. Coffee consumption after myocardial infarction and risk of cardiovascular mortality: a prospective analysis in the Alpha Omega Cohort. *Am J Clin Nutr*. 2017;106:1113–1120.

29. Hiatt WR, Kaul S, Smith RJ. The Cardiovascular Safety of Diabetes Drugs — Insights from the Rosiglitazone Experience. *N Eng J Med*. 2013;369:1285–1287.
30. Varani K, Portaluppi F, Gessi S, Merighi S, Ongini E, Belardinelli L, Borea PA. Dose and time effects of caffeine intake on human platelet adenosine A(2A) receptors : functional and biochemical aspects. *Circulation*. 2000;102:285–289.
31. Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. *Europace*. 2005;7:211–220.
32. Mostofsky E, Johansen MB, LundbyeChristensen S, Tjønneland A, Mittleman MA, Overvad K. Risk of atrial fibrillation associated with coffee intake: findings from the Danish Diet, Cancer, and Health study. *Eur J Prev Cardiol*. 2016;23:922–930.
33. Strubelt O, Diederich KW. Experimental treatment of the acute cardiovascular toxicity of caffeine. *J Toxicol Clin Toxicol*. 1999;37: 29–33.

SUPPLEMENTAL MATERIAL

Table S1. Caffeine consumption in cups per week according to regions of the world.

Region	**Count (%)**	**Median intake (IQR)**
Asia/Pacific	1,181 (12.2)	7 (1 to 21)
Eastern Europe	2,493 (25.7)	7 (5 to 14)
North America	2,058 (21.2)	12 (6 to 21)
South America	1,290 (13.3)	7 (2 to 14)
Western Europe	2,672 (27.6)	20 (7 to 30)
Overall	9,694 (100)	10 (4 to 21)

Table S2. Caffeine consumption in cups per week according to participating countries.

Country	Count (%)	Median intake (IQR)
Argentina	251 (2.6)	5 (0 to 7)
Australia	94 (1.0)	20 (10 to 28)
Belgium	249 (2.6)	21 (14 to 35)
Brazil	481 (5.0)	10 (7 to 15)
Bulgaria	221 (2.3)	5 (2 to 7)
Canada	761 (7.9)	14 (7 to 21)
Chile	167 (1.7)	5 (2 to 12)
China	283 (2.9)	0
Colombia	268 (2.8)	7 (3 to 14)
Czech Republic	323 (3.3)	7 (3.5 to 14)
France	152 (1.6)	12 (5.75 to 14.25)
Germany	435 (4.5)	15 (7 to 28)
Hungary	283 (2.9)	7 (3 to 14)
Italy	195 (2.0)	7 (5 to 14)

Japan	544 (5.6)	17.5 (7 to 28)
Netherlands	717 (7.4)	31 (21 to 42)
Norway	50 (0.5)	24 (14 to 35)
Peru	123 (1.3)	1 (0 to 3)
Philippines	164 (1.7)	3 (1 to 7)
Poland	563 (5.8)	14 (7 to 21)
Romania	217 (2.2)	5 (1 to 7)
Russian Federation	372 (3.8)	14 (7 to 21)
Slovakia	145 (1.5)	7 (3 to 7)
South Africa	188 (1.9)	14 (7 to 22)
South Korea	96 (1.0)	3 (1 to 7)
Spain	335 (3.5)	0 (0 to 4.5)
Sweden	141 (1.4)	15 (9.25 to 25)
Turkey	111 (1.1)	40 (21 to 49)
Ukraine	258 (2.7)	7 (5 to 14)
United Kingdom	210 (2.2)	30 (21 to 42)
United States	1,297 (13.4)	7 (4 to 16)
OVERALL	9,694	10 (4 to 21)

Table S3. Baseline characteristics according to baseline caffeine intake (safety database, n = 9,568).

	No caffeine (n = 1,253)	**Caffeine (n = 8,315)**	**P-value**
Age in years	66 (59 to 72)	65 (58 to 71)	< 0.001
Female sex	351 (28.0%)	1,847 (22.2%)	< 0.001
White race	914 (72.9%)	7,184 (86.4%)	< 0.001
BMI in kg/m^2	27.3 (24.5 to 30.5)	27.8 (25.1 to 31.1)	< 0.001
Hypertension	967 (77.2%)	6,455 (77.6%)	0.75
Hypercholesterolemia	793 (63.3%)	6546 (78.7)	< 0.001
Current smoker	144 (11.5%)	1,503 (18.1%)	< 0.001
Diabetes mellitus	459 (36.6%)	2,550 (30.7)	< 0.001
Prior HF	205 (16.4%)	1558 (18.7%)	0.047
Multi-vessel CAD	742 (59.2%)	5,243 (63.1%)	0.010
History of PCI	995 (79.4%)	7,058 (84.9%)	< 0.001
> 1 prior MI	192 (15.3%)	1,350 (16.2%)	0.44
PAD	57 (4.5%)	446 (5.4%)	0.26
Years since qualifying MI	1.65 (1.20 to 2.25)	1.58 (1.17 to 2.23)	0.060

STEMI as qualifying MI	686 (54.8%)	4,513 (54.4%)	0.80
Aspirin	1,252 (99.9%)	8,306 (99.9%)	1.00
Statin	1,151 (91.9%)	7,757 (93.3%)	0.072
Beta-blocker	1,023 (81.6%)	6,866 (82.6%)	0.44
ACE inhibitor or ARB	971 (77.5%)	6,714 (80.7%)	0.008
eGFR < 60 ml/min/1.73 m^2 (MDRD)	295 (24.0%)	1,755 (21.3%)	0.033
COPD	75 (6.0%)	591 (7.1%)	0.16
Asthma	46 (3.7%)	302 (3.6%)	1.00
Region			< 0.001
Asia/Pacific	287 (22.9%)	875 (10.5%)	
Eastern Europe	245 (19.6%)	2,228 (26.8%)	
North America	197 (15.7%)	1,836 (22.1%)	
South America	245 (19.6%)	1,036 (12.5%)	
Western Europe	279 (22.3%)	2,340 (28.1%)	

Values are median (IQR) or n(%) unless otherwise specified; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction

Table S4. Adverse event reporting according to different regions of the world.

	Eastern Europe	Western Europe	North America	South America	Asia / Pacific	P
N	2473	2619	2033	1281	1162	
Dyspnea	163 (6.6%)	402 (15.3%)	386 (19.0%)	123 (9.6%)	103 (8.9%)	<0.001
TIMI minor bleeding	34 (1.4%)	96(3.7%)	75 (3.7%)	41 (3.2%)	72 (6.2%)	<0.001
Renal event	27 (1.1%)	54 (2.1%)	58 (2.9%)	44 (3.4%)	13(1.1%)	<0.001
Bradyarrhtythmia	38(1.5%)	32 (1.2%)	26 (1.3%)	23 (1.8%)	6 (0.5%)	0.057
Gout	11 (0.4%)	60 (2.3%)	24 (1.2%)	10 (0.8%)	15 (1.3%)	<0.001

Table S5. Association between caffeine intake at baseline and dyspnea adverse events in patients taking ticagrelor 60 mg (N = 3,159), ticagrelor 90 mg (N = 3,204) and placebo (N = 3,205). Adjusted hazard ratios for drinking caffeine versus not drinking caffeine

	Placebo		**Ticagrelor 60 mg**		**Ticagrelor 90 mg**	
	Adj HR (95% CI)	**p-value**	**Adj HR (95% CI)**	**p-value**	**Adj HR (95% CI)**	**p-value**
Any dyspnea	0.89 (0.56-1.40)	0.61	0.86 (0.66-1.13)	0.29	0.97 (0.74-1.26)	0.81
Mild Dyspnea	1 (0.57-1.75)	1.00	0.84 (0.60-1.18)	0.32	1.12 (0.77-1.61)	0.55
Moderate or Severe Dyspnea	1.20 (0.47-3.07)	0.71	0.86 (0.56-1.32)	0.49	0.80 (0.55-1.16)	0.24
Dyspnea leading to drug discontinuation	0.51 (0.19-1.39)	0.19	0.71 (0.44-1.14)	0.16	0.72 (0.49-1.08)	0.11

CI = confidence interval; HR = hazard ratio. Adjusted for: age, sex, race, weight, hypercholesterolemia, heart failure (HF), diabetes, presence of multivessel CAD, history of PCI, type of qualifying MI (STEMI versus NSTEMI), GFR < 60 ml/min/1.73m2, smoking and region of the world.

Table S6. Associations between caffeine intake and dyspnea on ticagrelor stratified by regions.

		Adjusted HR (95 % CI)	**P-value**	**P-interaction**
Dyspnea	US/W. Europe	1.11 (0.86-1.45)	0.42	0.015
	Other regions	0.70 (0.54-0.91)	0.009	
Mild dyspnea	US/W. Europe	1.38 (0.96-1.98)	0.079	0.0007
	Other regions	0.60 (0.43-0.83)	0.0024	
Moderate or severe dyspnea	US/W. Europe	0.80 (0.55-1.16)	0.24	0.72
	Other regions	0.89 (0.59-1.33)	0.56	

Dyspnea leading to drug discontinuation	US/W. Europe	0.77 (0.51-1.15)	0.20	0.69
	Other regions	0.68 (0.44-1.04)	0.077	

CI = confidence interval; HR = hazard ratio Adjusted for: age, sex, race, weight, hypercholesterolemia, heart failure (HF), diabetes, presence of multivessel CAD, history of PCI, type of qualifying MI (STEMI versus NSTEMI), GFR < 60 ml/min/1.73m2, and smoking.

Table S7. Dyspnea and cardiovascular outcomes according to quartiles* of caffeine intake.

	Q2 vs Q1 adj HR (95% CI); p-value	Q3 vs Q1 adj HR (95% CI); p-value	Q4 vs Q1 adj HR (95% CI); p-value
Dyspnea	0.93 (0.78-1.10); 0.41	0.96 (0.82-1.13); 0.64	1.12 (0.95-1.34); 0.18
Dyspnea leading to drug discontinuation	1.09 (0.82-1.47); 0.53	0.92 (0.69-1.24); 0.59	0.98 (0.71-1.35); 0.89
CV death, MI or stroke	0.82 (0.67-1.01); 0.068	0.64 (0.51-0.81); <0.001	0.78 (0.61-1.01); 0.058
CV death	0.64 (0.45-0.90); 0.011	0.53 (0.36-0.79); 0.002	0.50 (0.30-0.84); 0.009
Non-CV death	1.26 (0.76-2.07); 0.37	1.14 (0.68-1.91); 0.62	0.85 (0.45-1.61); 0.62
MI	0.88 (0.67-1.15); 0.35	0.65 (0.48-0.87); 0.003	0.76 (0.56-1.05); 0.094
Stroke	1.01 (0.60-1.70); 0.96	0.76 (0.44-1.38); 0.39	1.28 (0.69-2.35); 0.43
CHD death	0.63 (0.39-0.99); 0.044	0.62 (0.38-1.00); 0.051	0.44 (0.22-0.87); 0.019
Sudden cardiac death	0.62 (0.37-1.04); 0.072	0.65 (0.38-1.11); 0.11	0.48 (0.22-1.03); 0.059

Any tachyarrhythmia	1.29 (0.81-2.06); 0.29	0.79 (0.47-1.32); 0.36	1.16 (0.67-2.00); 0.60
Atrial fibrillation/flutter	1.30 (0.74-2.27); 0.37	0.81 (0.43-1.50); 0.50	1.29 (0.67-2.48); 0.46
All-cause mortality	0.79 (0.60-1.05); 0.11	0.71 (0.52-0.96); 0.025	0.60 (0.41-0.89); 0.011
TIMI major bleeding	1.17 (0.69-1.99); 0.57	1.35 (0.80-2.29); 0.26	0.99 (0.52-1.89); 0.98
MALE	0.75 (0.32-1.74); 0.50	0.68 (0.29-1.59); 0.37	0.77 (0.31-1.95); 0.59

*Quartiles of caffeine intake: Q4: > 21 cups/wk; Q3: 10-21 cups/wk; Q2: 4-10 cups/wk; Q1: ≤ 4 cups/wk;

Number of events and event rates at 2 years (in %) estimated by Kaplan-Meier method a; CHD = coronary heart disease; CV = cardiovascular; ICH = intracranial hemorrhage; MALE = major adverse limb events; MI = myocardial infarction; TIMI = thrombolysis in myocardial infarction. Adjusted for: age, sex, race, weight, hypercholesterolemia, heart failure (HF), diabetes, presence of multivessel CAD, history of PCI, type of qualifying MI (STEMI versus NSTEMI), GFR < 60 ml/min/1.73m2, and smoking.