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ORIGINAL RESEARCH

Total Cardiovascular and Limb Events and the Impact of Polyvascular Disease in Chronic Symptomatic Peripheral Artery Disease

Michael Szarek (iD), PhD; Connie Hess, MD MHS; Manesh R. Patel (iD), MD; W. Schuyler Jones (iD), MD; Jeffrey S. Berger (iD), MD, MS; Iris Baumgartner, MD; Brian Katona (iD), PharmD; Kenneth W. Mahaffey, MD; Lars Norgren (iD), MD, PhD; Juuso Blomster, MD; Frank W. Rockhold (iD), PhD; Judith Hsia (iD), MD; F. Gerry R. Fowkes, MBChB, PhD; Marc P. Bonaca (iD), MD, MPH

BACKGROUND: Peripheral artery disease (PAD) is associated with heightened risk for major adverse cardiovascular and limb events, but data on the burden of risk for total (first and potentially subsequent) events, and the association with polyvascular disease, are limited. This post hoc analysis of the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial evaluated total cardiovascular and limb events among patients with symptomatic PAD, overall and by number of symptomatic vascular territories.

METHODS AND RESULTS: In the EUCLID trial, patients with symptomatic PAD (lower extremity revascularization >30 days before randomization or ankle-brachial index ≤0.80) were randomized to treatment with ticagrelor or clopidogrel. Relative effects on total events (cardiovascular death; nonfatal myocardial infarction and ischemic stroke; acute limb ischemia, unstable angina, and transient ischemic attack requiring hospitalization; coronary, carotid, and peripheral revascularization procedures; and amputation for symptomatic PAD) were summarized by hazard ratios (HRs), whereas absolute risks were estimated by incidence rates and mean cumulative functions. Among 13 885 randomized patients, 7600 total cardiovascular and limb events occurred during a median 2.7 years of follow-up, translating to 60.0 and 62.5 events per 100 patients through 3 years for the ticagrelor and clopidogrel groups, respectively (HR, 0.96; 95% CI, 0.89–1.03; P=0.27). Among 1393 patients with disease in 3 vascular territories, event accrual rates through 3 years for the ticagrelor and clopidogrel groups were 87.3 and 97.7 events per 100 patients, respectively. Absolute risk reductions for ticagrelor relative to clopidogrel at 3 years were −0.2, 6.7, and 10.3 events per 100 patients for 1, 2, and 3 affected vascular territories, respectively ($P_{interaction}$=0.09).

CONCLUSIONS: Patients with symptomatic PAD have nearly double the number of total events than first events, with rates reflecting the number of affected vascular territories. These findings highlight the clinical relevance of quantifying disease burden in terms of total events and the need for long-term preventive treatments in high-risk patient populations.

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Key Words: clopidogrel ■ peripheral artery disease ■ polyvascular disease ■ ticagrelor ■ total events

Peripheral artery disease (PAD) is associated with increased risk for major adverse limb events (MALEs), including acute limb ischemia and amputation, and major adverse cardiovascular events (MACEs), including cardiovascular death, myocardial infarction, and stroke.[1] This increased risk when

CLINICAL PERSPECTIVE

What Is New?

- In the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial, the rate of total (first and potentially subsequent) cardiovascular and limb events was nearly double the number of first events over a median 2.7 years of follow-up.
- Event rates were higher among patients with symptomatic disease in multiple vascular territories (ie, a history of symptomatic coronary and/or cerebrovascular disease in addition to peripheral artery disease).

What Are the Clinical Implications?

- These findings reinforce the clinical importance of quantifying disease burden in terms of total events and the need for long-term preventive strategies in high-risk patient populations, including patients with polyvascular disease.

Nonstandard Abbreviations and Acronyms

EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
LER	lower extremity revascularization
MACE	major adverse cardiovascular event
MALE	major adverse limb event

evaluated in clinical trials is usually described in terms of first events, although it may be inferred that this would also translate to increased risk for total (ie, first and subsequent) events.

A high rate of total cardiovascular and limb events and recurrent peripheral revascularization has been documented among patients who underwent recent lower extremity revascularization (LER),[2] but data on the burden of risk for total events in chronic stable symptomatic PAD, including those who have never had LER, and the possible association with polyvascular disease are limited. Furthermore, although analyses of total events have been reported for patients treated with ticagrelor[3] and clopidogrel[4] in the setting of acute coronary syndrome, the relative and absolute impacts of these treatments on total events among patients with PAD are unknown.

In the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial, patients with symptomatic PAD treated with ticagrelor or clopidogrel had similar rates of first cardiovascular death, nonfatal

myocardial infarction, or nonfatal stroke.[5] The current post hoc analysis compares the treatment groups in the EUCLID trial in terms of total disease burden, quantified by total cardiovascular and limb events observed during study follow-up, overall and in subgroups, including those defined by number of symptomatic affected vascular territories.

METHODS

The data, analytic methods, and study materials are not available to other researchers for purposes of reproducing the results or replicating the procedures.

Population

Details of the study design[6] and primary efficacy and safety results[5] have been published. The study was conducted at 821 sites in 28 countries; each site obtained relevant institutional review board and ethics approvals. Eligible patients provided written informed consent and were aged ≥50 years and had symptomatic PAD defined by either LER >30 days before randomization or ankle-brachial index (ABI) ≤0.80. Key exclusion criteria included planned long-term dual-antiplatelet therapy, requirement for aspirin, increased risk of bleeding, long-term anticoagulation treatment, or poor clopidogrel metabolizer status. Double-blind, double-dummy randomization in a 1:1 ratio to treatment with ticagrelor, 90 mg twice daily, or clopidogrel, 75 mg once daily, was performed, with 13 885 patients meeting study entry criteria. Follow-up visits were scheduled 2 and 6 months after randomization and every 6 months thereafter until a minimum of 1364 participants experienced a first primary end point event, after which surviving participants had a final end-of-study visit.

End Points

The primary efficacy outcome of the EUCLID trial was time to occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. Additional cardiovascular and limb events recorded in the trial were acute limb ischemia requiring hospitalization, unstable angina requiring hospitalization, and transient ischemic attack (TIA) requiring hospitalization; coronary, carotid, and peripheral revascularization procedures; amputation for symptomatic PAD; and noncardiovascular death. Definitions for each event have been published[5]; events in the primary efficacy outcome, acute limb ischemia, unstable angina, TIA, and noncardiovascular death were confirmed by central adjudication, whereas procedures and amputations were investigator reported and not subject to adjudication. Events included in the primary analysis of the present report were total (ie, first and potentially subsequent) primary end point events

(MACEs) and total other cardiovascular and limb events. Additional analyses of total events were by subcategory of event, as denoted in Table 1.

Statistical Analysis

We applied a marginal proportional hazards model that allows for the possibility of multiple cardiovascular and limb events within a given participant while treating non-cardiovascular death as a competing terminal event. For model convergence purposes, for a given patient, a maximum of 1 nonfatal event could occur on a given day. A robust sandwich variance estimate for the estimated SE of the log hazard ratio (HR) was applied to account for the dependence of event times within individual patients. Treatment effects on total cardiovascular and limb events are summarized by ticagrelor/clopidogrel HRs, corresponding 95% CIs, and P values. Treatment effects on additional categories of total events were estimated in separate models; cardiovascular deaths not included in a given category were also treated as competing terminal events. "On-treatment" sensitivity analyses excluded follow-up and events >2 days after permanent discontinuation of study treatment, consistent with conventions in other PAD studies.[7] Possible heterogeneity of relative treatment effects on total events for the PAD inclusion criterion (LER >30 days before randomization or ABI ≤0.80), by quartile of ABI, and for subgroups previously reported to have high event rates on the study primary efficacy outcome, including polyvascular disease, was assessed by the significance of interaction terms in marginal proportional hazards models. For polyvascular disease, an affected vascular territory was defined by the presence of PAD (based on the PAD inclusion criterion), coronary artery disease (history of myocardial infarction or coronary revascularization), or cerebrovascular disease (history of stroke, transient ischemic attack, carotid-artery stenosis, or carotid revascularization).

Mean cumulative functions were used to estimate, by treatment group, accrual of total cardiovascular events, total acute cardiovascular and limb events, and total procedures over time in the presence of competing deaths.[8] Possible heterogeneity of absolute risk reductions for selected subgroups was assessed by quantitative interactions based on mean cumulative function estimates at 3 years after randomization.[9]

Continuous variables are expressed as median (quartile 1–quartile 3), whereas categorical variables are expressed as counts and percentages. Incidence rates were calculated as number of events per 100 patient-years of follow-up. For all analyses, P<0.05, 2 tailed, was considered statistically significant, with no adjustment for multiple testing.

Table 1. Categories of Total Events

Event	Ticagrelor (n=6930)	Clopidogrel (n=6955)	Total (n=13 885)
Total cardiovascular and limb events	3710	3890	7600
Acute cardiovascular and limb events	1546	1544	3090
Cardiovascular death*,†	390	378	768
Sudden cardiac, myocardial infarction, or ischemic stroke	182	190	372
Other cardiovascular	57	64	121
Undetermined	151	124	275
Nonfatal myocardial infarction†	430	422	852
Nonfatal ischemic stroke†,‡	151	177	328
Acute limb ischemia§	151	139	290
Unstable angina	372	374	746
Transient ischemic attack	52	54	106
Procedures	2164	2346	4510
Coronary revascularization‖	489	491	980
Carotid revascularization‖	109	123	232
Peripheral revascularization‖	1323	1480	2803
Amputation for symptomatic PAD§,‖	243	252	495
Noncardiovascular death	266	283	549

Values are given as number. PAD indicates peripheral artery disease.
*Includes deaths adjudicated to have an undetermined cause.
†Included in major adverse cardiovascular events.
‡Includes strokes adjudicated to not be primarily hemorrhagic (ie, primarily ischemic or uncertain type).
§Included in major adverse limb events.
‖Investigator reported; not subject to adjudication by independent committee.

All analyses were conducted according to intention to treat, with the exception of the on-treatment analyses described above. Although the primary analysis included events through the primary analysis censoring date (May 19, 2016), to maximize the number of events available for analysis, the current report included all events through the last patient's last visit (September 26, 2016). The first author had full access to all the data in the study and takes responsibility for their integrity and the data analysis. Analyses were performed in SAS 9.4 and R 3.5.

RESULTS

Duration of Follow-Up and Total Events by Type and Ordinal Number

Patients were followed up for a median of 2.7 (2.5–2.9) years; selected baseline characteristics of the study population by treatment group are presented in Table S1. The types and counts of total cardiovascular and limb events and noncardiovascular deaths after randomization by treatment assignment are shown in Table 1. There were over twice as many total MACEs (cardiovascular death, nonfatal myocardial infarction, and ischemic stroke; 1948 events) than total MALEs (acute limb ischemia and amputation for symptomatic PAD; 785 events). Total revascularization procedures, however, were the most frequent event (4510 events) with the largest component peripheral revascularizations (2803) followed by coronary revascularizations (980).

Table 2 summarizes the distributions of cardiovascular and limb events and noncardiovascular deaths by event number. The total number of cardiovascular and limb events (7600, consisting of 3090 total acute cardiovascular and limb events and 4510 total procedures) was nearly double the number of first events (3878, consisting of 1858 first acute cardiovascular and limb events and 2020 first procedures), and 13.2% of the total study population (1829 patients) experienced >1 event. A similar number of total acute cardiovascular and limb events occurred in each treatment group (1546 for ticagrelor, and 1544 for clopidogrel), whereas there were numerically fewer total procedures in the ticagrelor group (2164) than in the clopidogrel group (2346). In addition, competing noncardiovascular death was relatively infrequent in both groups (266 for ticagrelor, and 283 for clopidogrel). Among 3090 total acute cardiovascular and limb events and 4510 total procedures, 1147 (37.1%) and 1454 (32.2%), respectively, occurred >2 days after the patients' last dose of ticagrelor or clopidogrel study treatment.

Figure 1 displays the rates of second events by type of first nonfatal event. Patients who experienced a first nonfatal acute cardiovascular or limb event were at higher risk of subsequent events relative to patients who experienced a first procedure, regardless of randomized treatment. Similar to the overall results, there was a higher rate of procedures as a second event than acute cardiovascular and limb events. Figure S1 shows these rates, where first and second events restricted to MACEs (nonfatal for first) or MALEs. Overall, patients with a first nonfatal MACE had a higher second event rate than patients with a first MALE. In addition, most second events among patients with a first nonfatal MACE were also MACEs, whereas most second events among patients with a first MALE were also MALEs.

Treatment Effects on Total Cardiovascular and Limb Events and Procedures

Figure 2 displays ticagrelor/clopidogrel treatment HRs and 95% CIs and number of events per 100 patient-years by treatment group for total cardiovascular and limb events, overall and by event type. There was no significant difference between the treatment groups in the risk of total cardiovascular and limb events, with event rates per 100 patient-years of 20.5 and 21.3 for the ticagrelor and clopidogrel groups, respectively (HR, 0.96; 95% CI, 0.89–1.03; *P*=0.27). There were also no differences when acute cardiovascular or limb events (HR, 1.01; 95% CI, 0.92–1.11; *P*=0.88) or procedures (HR, 0.93; 95% CI, 0.85–1.01; *P*=0.08) were analyzed separately, although ticagrelor treatment was associated with a nominally lower risk of total peripheral revascularizations (HR, 0.90; 95% CI, 0.81–1.00; *P*=0.0484). Similarly, there were no differences in total MACEs (event rates per 100 patient-years of 5.4 and 5.4 for the ticagrelor and clopidogrel groups, respectively; HR, 1.00; 95% CI, 0.90–1.11; *P*=1.00) or total MALEs (event rates per 100 patient-years of 2.2 and 2.1 for the ticagrelor and clopidogrel groups, respectively; HR, 1.01; 95% CI, 0.84–1.22; *P*=0.91). Figure S2 contains the mean cumulative functions for total cardiovascular and limb events by treatment group, with separate panels for total acute cardiovascular and limb events and for total procedures. The accrual of events was at a relatively constant rate over time, with an estimated 60.0 and 62.5 events per 100 patients after 3 years of follow-up in the ticagrelor and clopidogrel groups, respectively.

Table S2 summarizes treatment HRs and 95% CIs and incidence rates by treatment group for on-treatment sensitivity analyses of total events. Results were generally similar to the intention-to-treat results, although there was a nominally lower risk of total procedures with ticagrelor treatment (HR, 0.90; 95% CI, 0.81–0.99; *P*=0.0260) primarily because of lower risk of total peripheral revascularizations (HR, 0.87; 95% CI, 0.78–0.98; *P*=0.0192).

Table 2. Distribution of First and Subsequent Acute Cardiovascular Events, Procedures, and Noncardiovascular Death

Event	Ticagrelor (n=6930)	Clopidogrel (n=6955)	Total (n=13 885)
First cardiovascular and limb event	1924	1954	3378
Acute cardiovascular and limb event	943	915	1858
Cardiovascular death	252	238	490
Nonfatal*	691	677	1368
Procedure†	981	1039	2020
Noncardiovascular death	183	200	383
Second cardiovascular and limb event	891	938	1829‡
Acute cardiovascular and limb event	284	269	553
Cardiovascular death	72	59	131
Nonfatal*	212	210	422
Procedure†	607	669	1276
Noncardiovascular death	47	39	86
Third cardiovascular and limb event	408	453	861
Acute cardiovascular and limb event	166	161	327
Cardiovascular death	32	37	69
Nonfatal*	134	124	258
Procedure†	242	292	534
Noncardiovascular death	14	28	42
Fourth and subsequent cardiovascular and limb events	487	545	1032
Acute cardiovascular and limb events	153	199	352
Cardiovascular death	34	44	78
Nonfatal*	119	155	274
Procedures†	334	346	680
Noncardiovascular death	22	16	38
Total cardiovascular and limb events	3710	3890	7600
Acute cardiovascular and limb events	1546	1544	3090
Cardiovascular death	390	378	768
Nonfatal*	1156	1166	2322
Procedures†	2164	2346	4510
Noncardiovascular death	266	283	549

Values are given as number.

*Includes nonfatal myocardial infarction, nonfatal ischemic stroke, acute limb ischemia, unstable angina, and transient ischemic attack.

†Includes coronary revascularization, carotid revascularization, peripheral revascularization, and amputation for symptomatic peripheral artery disease.

‡Represents the number of patients with >1 event during the study.

Subgroup analyses for total cardiovascular and limb events are shown in Figure S3; none of the relative tests of heterogeneity was significant. Patients with prior peripheral revascularization, a history of coronary artery disease (including stent implantation), or disease in multiple vascular territories had especially high event rates, regardless of randomized treatment assignment. Subgroup results for total MACEs and total MALEs are summarized in Tables S3 and S4. Across treatment groups, patients with a history of coronary artery disease or multiple affected vascular territories were at markedly higher risk of MACEs, whereas patients with prior peripheral revascularization were at elevated risk of MALEs. In addition, risk of MACEs increased with increasing numbers of affected vascular territories,

whereas this was not the case for MALEs. There was significant heterogeneity in the relative treatment effects on MALEs across quartiles of ABI, where risk was numerically lower for ticagrelor among patients with ABI in the lowest 2 quartiles, whereas the risk for clopidogrel was numerically lower among patients with ABI in the highest 2 quartiles ($P_{interaction}$=0.0472).

Mean cumulative functions for total cardiovascular and limb events by number of affected vascular territories and treatment group are presented in Figure 3. Absolute risk was associated with the number of affected vascular territories, with estimated rates of 87.3 and 97.7 events per 100 patients at 3 years for the ticagrelor and clopidogrel groups, respectively, among 1393 patients with disease in 3 vascular territories. The
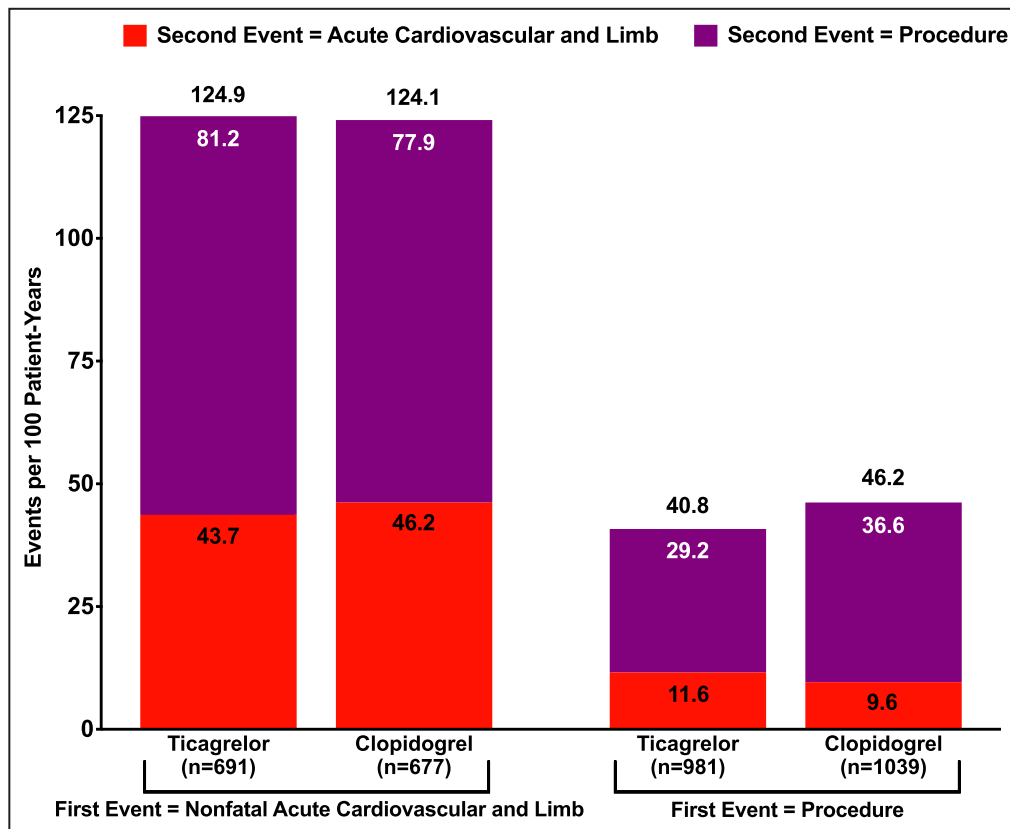
Figure 1. Rates of second events by type of first nonfatal event.
Values above bars are the sum of the rates of acute cardiovascular and limb events and procedures as a second event. Values within bars are the rates of acute cardiovascular and limb events or the rates of procedures as a second event.

absolute risk reductions for ticagrelor relative to clopidogrel at 3 years were −0.2, 6.7, and 10.3 events per 100 patients for 1, 2, and 3 affected vascular territories, respectively ($P_{interaction}$=0.09).

DISCUSSION

The current analyses reveal several novel aspects on the accrual of events in patients with chronic symptomatic PAD that, to our knowledge, have not been previously reported. The total event rates were high overall, driven by a high rate of peripheral revascularization and acute coronary events and procedures (nonfatal myocardial infarction, unstable angina, and coronary revascularization). The risk of a second event was exceptionally high among patients with a first nonfatal acute cardiovascular or limb event, with a second event rate of >100 events per 100 patient-years of follow-up that was essentially 3 times higher than that for patients who had a procedure as a first event. In addition, patients with a first nonfatal MACE were more likely to have a MACE than a MALE as a second event, whereas the converse was true for patients with a first MALE. Finally, the present report highlights the relationship of total events and

risk according to symptomatic vascular territories, demonstrating the importance of polyvascular disease as a marker of atherosclerosis burden and atherothrombotic risk among patients with chronic symptomatic PAD.

Extending on previous findings from the EUCLID trial, the current analyses found no significant differences between treatment groups in total MACEs, which was similar to the primary findings of the trial.[5] More important, a substantial fraction of total events, 2601 of 7600, occurred in patients >2 days after their last dose of ticagrelor or clopidogrel study treatment. This likely reduced the ability to find differences between treatment groups in the risk of total events, although on-treatment analyses revealed a nominal difference in total procedures.

The risk of events in both treatment groups was related to the extent of the patients' cardiovascular disease at baseline, as defined by number of affected vascular territories. Patients with established coronary disease at baseline had total event rates that were markedly higher than patients without this history, consistent with prior reports from the study for first primary events[10] and other studies that included subsets of patients with coronary and peripheral
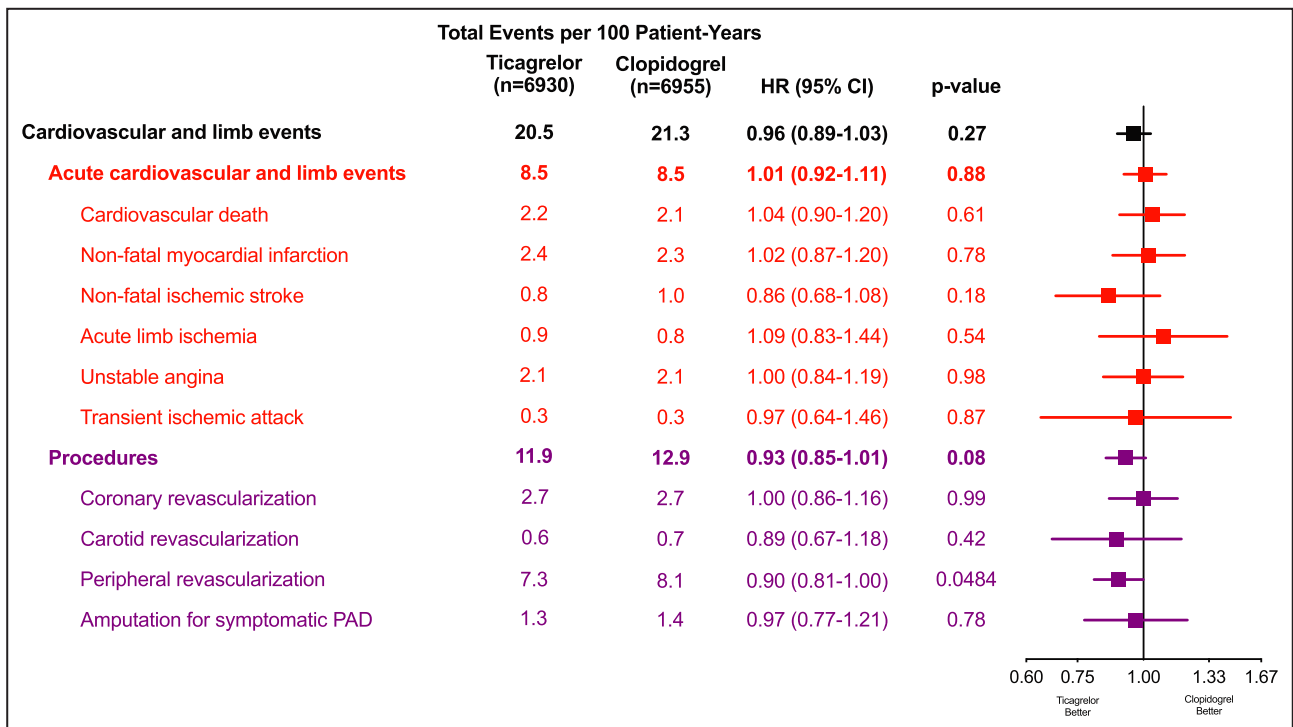
Total Events per 100 Patient-Years				
	Ticagrelor (n=6930)	Clopidogrel (n=6955)	HR (95% CI)	p-value
Cardiovascular and limb events	**20.5**	**21.3**	**0.96 (0.89-1.03)**	**0.27**
Acute cardiovascular and limb events	**8.5**	**8.5**	**1.01 (0.92-1.11)**	**0.88**
Cardiovascular death	2.2	2.1	1.04 (0.90-1.20)	0.61
Non-fatal myocardial infarction	2.4	2.3	1.02 (0.87-1.20)	0.78
Non-fatal ischemic stroke	0.8	1.0	0.86 (0.68-1.08)	0.18
Acute limb ischemia	0.9	0.8	1.09 (0.83-1.44)	0.54
Unstable angina	2.1	2.1	1.00 (0.84-1.19)	0.98
Transient ischemic attack	0.3	0.3	0.97 (0.64-1.46)	0.87
Procedures	**11.9**	**12.9**	**0.93 (0.85-1.01)**	**0.08**
Coronary revascularization	2.7	2.7	1.00 (0.86-1.16)	0.99
Carotid revascularization	0.6	0.7	0.89 (0.67-1.18)	0.42
Peripheral revascularization	7.3	8.1	0.90 (0.81-1.00)	0.0484
Amputation for symptomatic PAD	1.3	1.4	0.97 (0.77-1.21)	0.78

0.60 0.75   1.00   1.33 1.67

Ticagrelor Better   Clopidogrel Better

Figure 2. **Treatment effects on total cardiovascular and limb events and procedures by event type.**
Hazard ratios (HRs), 95% CIs, and *P* values from marginal proportional hazards models with death not included in a given end point treated as a competing terminal event. PAD indicates peripheral artery disease.

disease.[11–14] Furthermore, relative to patients with only peripheral disease (ie, 1 affected vascular territory), patients with 2 affected territories had an ≈50% higher event rate, whereas patients with 3 affected territories had an event rate that was more than double. The total event rate among patients with only peripheral disease appeared to be considerably higher, however, than previous findings among patients with only documented cerebrovascular disease at baseline.[15] In terms of treatment differences, based on cumulative event rates at 3 years, patients with a greater extent of disease had nominally lower event rates with ticagrelor
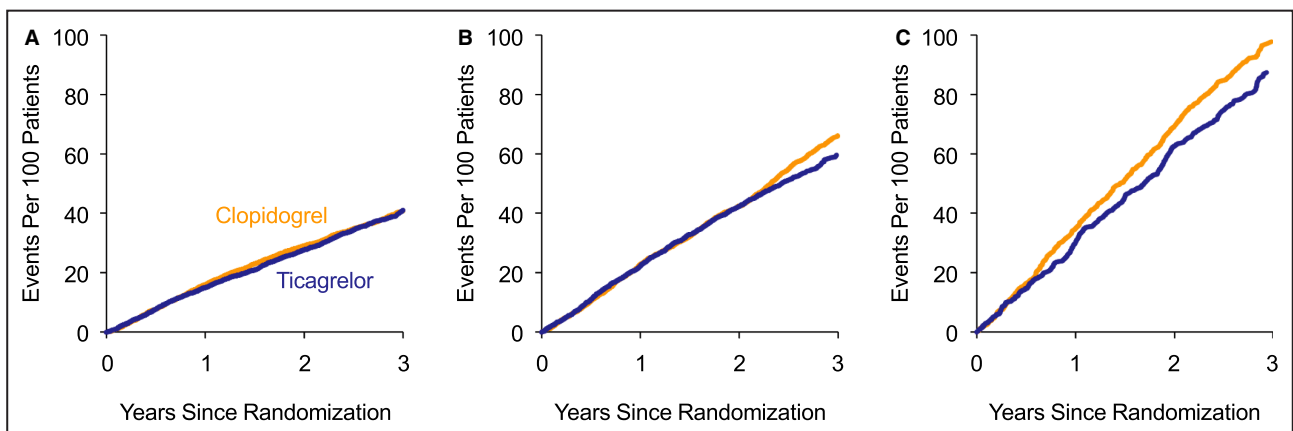

Figure 3. **Mean cumulative functions for total cardiovascular and limb events and procedures by number of affected vascular territories.**
A, One affected vascular territory. **B**, Two affected vascular territories. **C**, Three affected vascular territories. The estimated numbers of events per 100 patients in the ticagrelor and clopidogrel groups at 3 years were 40.9 and 40.7 among the subgroup with 1 affected vascular territory, 59.6 and 66.3 among the subgroup with 2 affected vascular territories, and 87.3 and 97.7 for among the subgroup with 3 affected vascular territories, respectively. Absolute risk reductions for ticagrelor relative to clopidogrel at 3 years were −0.2, 6.7, and 10.3 events per 100 patients for 1, 2, and 3 affected vascular territories, respectively (*P*interaction=0.09).

therapy relative to clopidogrel. Additional research is therefore needed to confirm if patients with PAD and more extensive cardiovascular disease might benefit from more potent antithrombotic therapy.

In the VOYAGER PAD (Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) study, patients with symptomatic PAD who underwent recent LER had annual total MACE and MALE rates of ≈5 and 4 per 100 patient-years of follow-up, respectively.[2] The current analyses found a similar rate for MACE but a lower rate for MALE, although the MALE rate was higher among the subset of patients with prior peripheral revascularization, mirroring previous findings on first acute limb ischemia event.[16] This difference in MALE rates between the 2 studies may be explained by the fact that the patients in the EUCLID trial had more "stable" PAD, in that they either had hemodynamic evidence of PAD or a previous revascularization >30 days before randomization, whereas all patients in VOYAGER PAD had a revascularization procedure only days before randomization.

The high proportion of total cardiovascular and limb events that were attributable to MALEs and peripheral revascularization in the EUCLID trial, 47.2% of the total, was consistent with other studies where patients were enrolled on the basis of established PAD and the majority did not have known disease in other vascular territories.[2] Furthermore, among procedures, there were nearly 3 times as many peripheral revascularizations than coronary revascularizations. In contrast, acute limb events and procedures have been reported to be a relatively small fraction of total events in patients with established coronary or cerebrovascular disease and either no or small fractions with disease in additional territories.[15,17–19] Therefore, although it has been previously documented that total event risk in the coronary or cerebrovascular territory is elevated if the given territory has established disease at baseline, the current results support extending this observation to the peripheral territory.

In the EUCLID trial, the number of TIA events (106) was relatively low relative to the number of nonfatal ischemic stroke events (328). This may be an artifact of the fact that TIA was primarily collected for the purposes of cardiovascular-related hospitalizations, rather than acute cerebrovascular events (along with ischemic stroke), and therefore hospitalizations may have been attributed to reasons other than TIA.

Limitations

A limitation of the analysis method is that although noncardiovascular deaths were treated as a competing event, cardiovascular deaths also removed 768 participants from the risk set for subsequent events. However, only 3.5% of participants (n=490) died because of cardiovascular causes before a first nonfatal cardiovascular event or procedure, so that the vast majority of participants were at risk for multiple events. In addition, the current analysis did not assign weights corresponding to severity to individual events, although results were also presented for MACEs and MALEs, which may be considered more severe than other outcomes. Although the presented on-treatment results accounted for discontinuation of randomized study treatment during follow-up, changes in other treatments that may modify risk were not accounted for in the analyses. Finally, other aspects of disease burden were not a part of the analysis, including increased risk of bleeding associated with antiplatelet therapy.

CONCLUSIONS

The observation that patients with PAD are at high risk for cardiovascular and limb events is largely based on a focus on first events, whereas considering total events (ie, first and potentially subsequent) may better quantify total disease burden. Over a median of 2.7 years of follow-up in the EUCLID trial, total event risk among patients with symptomatic PAD was considerable, with >60 total cardiovascular and limb events occurring per 100 patients through 3 years of follow-up. There were no statistically significant differences between the ticagrelor and clopidogrel groups in this risk, overall or by selected subgroups, although the analyses revealed patient subgroups, including those with disease in 3 vascular territories, who were at exceptionally high risk for events and may benefit from more potent antithrombotic therapy. These findings reinforce the clinical importance of quantifying total disease burden and the need for long-term preventive strategies in high-risk patient populations.

Affiliations

CPC Clinical Research, Aurora, CO (M.S., C.H., J.H., M.P.B.); Department of Medicine, University of Colorado, Aurora, CO (M.S., C.H., J.H., M.P.B.); SUNY Downstate Health Sciences University, Brooklyn, NY (M.S.); Duke Clinical Research Institute, Durham, NC (M.R.P., W.S.J., F.W.R.); Division of Cardiology, Duke University Medical Center, Durham, NC (M.R.P., W.S.J.); New York University School of Medicine, New York, NY (J.S.B.); Swiss Cardiovascular Center, Inselspital, Bern University Hospital, University of Bern, Switzerland (I.B.); AstraZeneca Gaithersburg, Gaithersburg, MD (B.K.); Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA (K.W.M.); Faculty of Medicine and Health, Örebro University, Örebro, Sweden (L.N.); Turku University Hospital, Turku, Finland (J.B.); and Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK (F.G.F.).

Disclosures

Supplemental Material

Tables S1–S4
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Selected Baseline Characteristics.

Characteristic	Ticagrelor (n = 6930)	Clopidogrel (n = 6955)
Median age (Q1-Q3), years	66 (60, 72)	66 (60, 73)
Female sex, n (%)	1908 (27.5)	1980 (28.5)
Geographic region, n (%)		
Asia	806 (11.6)	796 (11.4)
Central/South America	871 (12.6)	869 (12.5)
Europe	3739 (54.0)	3759 (54.0)
North America	1514 (21.8)	1531 (22.0)
PAD inclusion criterion, n (%)		
Revascularization >30 days prior to randomization	3923 (56.6)	3952 (56.8)
Abnormal ankle-brachial index and no prior revascularization	3007 (43.4)	3003 (43.2)
Median ankle-brachial index (Q1-Q3)	0.70 (0.58, 0.82)	0.70 (0.58, 0.82)
Medical history, n (%)		
Coronary or carotid revascularization	1914 (27.6)	1901 (27.3)
Coronary stent implantation	1004 (14.5)	964 (13.9)
Coronary artery disease[*]	2019 (29.1)	2013 (28.9)
Number of vascular territories affected[†]		
1	3874 (55.9)	3930 (56.5)
2	2333 (33.7)	2355 (33.9)
3	723 (10.4)	670 (9.6)
Medications before randomization, n (%)		

Aspirin	4667 (67.3)	4604 (66.2)
Clopidogrel	2193 (31.6)	2280 (32.8)
Statin	5058 (73.0)	5123 (73.7)
Angiotensin-converting-enzyme inhibitor	2826 (40.8)	2809 (40.4)
Angiotensin-receptor blocker	1741 (25.1)	1747 (25.1)

[*]Coronary artery disease is defined as myocardial infarction, percutaneous coronary intervention (PCI), or coronary-artery bypass grafting (CABG).

[†]An affected vascular territory was defined by the presence of peripheral artery disease, coronary artery disease, or cerebrovascular disease (including previous stroke, transient ischemic attack, carotid-artery stenosis, or carotid revascularization).

Table S2. On-treatment Analyses of Total Cardiovascular and Limb Events and Procedures by Event Type.

	Total Events per 100 Patient-Years		HR (95% CI)	p-value
Event	Ticagrelor	Clopidogrel		
Cardiovascular and limb events	16.4	17.6	0.93 (0.86-1.01)	0.09
Acute cardiovascular and limb events	6.6	6.6	0.99 (0.89-1.10)	0.79
Cardiovascular death	1.2	1.2	1.05 (0.85-1.29)	0.66
Non-fatal myocardial infarction	1.8	1.8	0.96 (0.80-1.16)	0.20
Non-fatal ischemic stroke	0.7	0.9	0.87 (0.67-1.13)	0.30
Acute limb ischemia	0.7	0.7	1.08 (0.79-1.47)	0.65
Unstable angina	1.8	1.9	0.97 (0.79-1.18)	0.74
Transient ischemic attack	0.3	0.2	1.11 (0.68-1.83)	0.67
Procedures	9.8	10.9	0.90 (0.81-0.99)	0.0260
Coronary revascularization	1.9	2.1	0.91 (0.76-1.09)	0.29
Carotid revascularization	0.5	0.5	0.93 (0.66-1.31)	0.67
Peripheral revascularization	6.3	7.2	0.87 (0.78-0.98)	0.0192
Amputation for symptomatic PAD	1.1	1.0	1.03 (0.79-1.35)	0.81

Table S3. Subgroup Analyses for Total MACE.

Subgroup	Total Events per 100 Patient-Years		HR (95% CI)	Interaction p-value
	Ticagrelor	Clopidogrel		
PAD inclusion criterion				0.84
ABI/TBI	4.9	4.8	1.01 (0.86-1.20)	
Prior revascularization	5.7	5.8	0.99 (0.87-1.14)	
Ankle-brachial index				0.78
Quartile 1 (<0.58)	6.8	6.6	1.04 (0.86-1.26)	
Quartile 2 (0.58 to <0.70)	5.1	5.0	1.03 (0.83-1.28)	
Quartile 3 (0.70 to <0.82)	5.4	5.3	1.01 (0.81-1.25)	
Quartile 4 (≥0.82)	4.2	4.7	0.90 (0.72-1.13)	
History of coronary stent implantation				0.14
Yes	7.5	8.7	0.85 (0.67-1.08)	
No	5.0	4.8	1.04 (0.92-1.17)	
History of coronary artery disease				0.68
Yes	7.9	8.1	0.97 (0.83-1.15)	
No	4.3	4.2	1.02 (0.89-1.17)	
Number of vascular territories affected				0.67
1	3.9	3.8	1.05 (0.90-1.23)	
2	6.2	6.5	0.95 (0.80-1.12)	
3	10.3	10.5	0.98 (0.76-1.26)	

Table S4. Subgroup Analyses for Total MALE.

Subgroup	Total Events per 100 Patient-Years		HR (95% CI)	Interaction p-value
	Ticagrelor	**Clopidogrel**		
PAD inclusion criterion				0.28
ABI/TBI	1.3	1.5	0.86 (0.62-1.20)	
Prior revascularization	2.9	2.6	1.08 (0.86-1.35)	
Ankle-brachial index				0.0472
Quartile 1 (<0.58)	2.8	3.7	0.77 (0.57-1.06)	
Quartile 2 (0.58 to <0.70)	1.7	1.9	0.86 (0.58-1.27)	
Quartile 3 (0.70 to <0.82)	1.7	1.3	1.37 (0.90-2.08)	
Quartile 4 (≥0.82)	2.5	1.8	1.39 (0.93-2.08)	
History of coronary stent implantation				0.98
Yes	1.6	1.5	1.01 (0.60-1.70)	
No	2.3	2.2	1.01 (0.83-1.24)	
History of coronary artery disease				0.60
Yes	1.9	2.0	0.93 (0.65-1.34)	
No	2.3	2.2	1.04 (0.84-1.30)	
Number of vascular territories affected				0.57
1	2.4	2.2	1.10 (0.86-1.40)	
2	1.9	2.1	0.89 (0.64-1.25)	
3	2.0	2.2	0.91 (0.49-1.69)	

Figure S1. Rates of Second MACE or MALE Events by Type of First Nonfatal MACE or MALE Event.
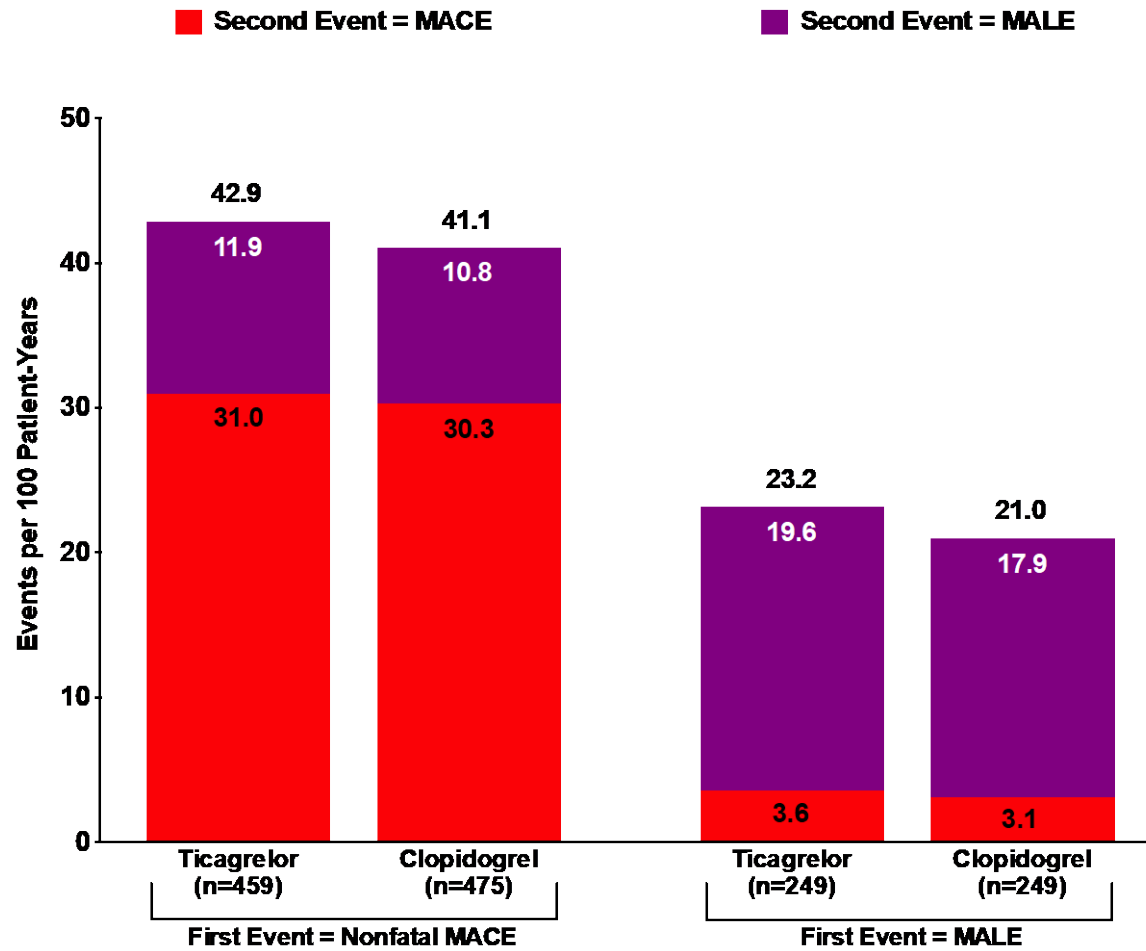
Values above bars are the sum of the rates of cardiovascular events and procedures as a second event. Values within bars are the rates

of MACE or the rates of MALE as a second event. MACE, major adverse cardiovascular event; MALE, major adverse limb events.

Figure S2. Mean Cumulative Functions.
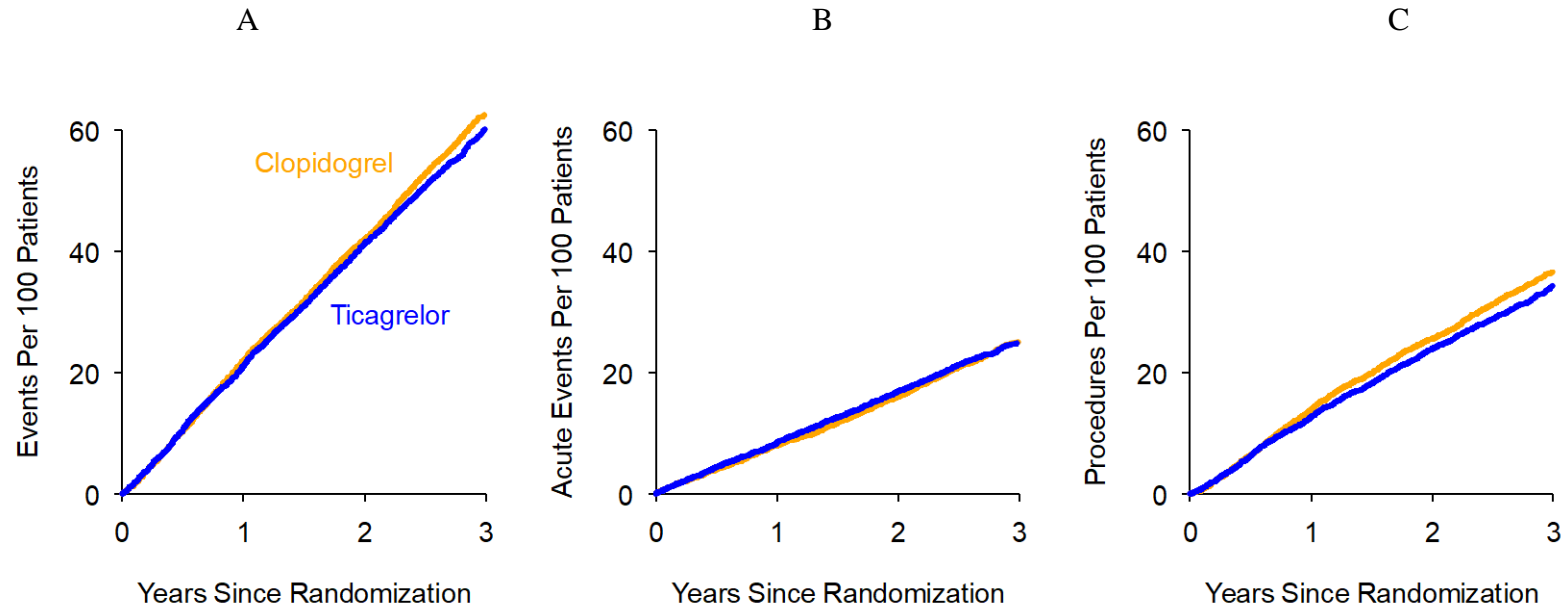
Panel A: total cardiovascular and limb events and procedures. Panel B: total acute cardiovascular and limb events. Panel C: total procedures. The estimated numbers of events per 100 patients in the ticagrelor and clopidogrel groups at 3 years were 60.0 and 62.5 for cardiovascular and limb events, 24.8 and 25.0 for acute cardiovascular and limb events, and 34.2 and 36.6 for procedures, respectively.

Figure S3. Subgroup Analyses for Total Cardiovascular and Limb Events and Procedures.

	Total Events per 100 Patient-Years		HR (95% CI)	Interaction p-value
	Ticagrelor	Clopidogrel		
PAD inclusion criterion				0.64
ABI/TBI	13.8	14.0	0.99 (0.87-1.12)	
Prior revascularization	25.5	26.8	0.95 (0.87-1.04)	
Ankle-brachial index				0.68
Quartile 1 (<0.58)	23.3	25.3	0.93 (0.81-1.06)	
Quartile 2 (0.58 to <0.70)	17.7	18.4	0.96 (0.83-1.12)	
Quartile 3 (0.70 to <0.82)	17.6	16.7	1.05 (0.90-1.22)	
Quartile 4 (>=0.82)	23.3	24.9	0.94 (0.82-1.08)	
History of coronary stent implantation				0.21
Yes	30.2	34.5	0.87 (0.75-1.02)	
No	18.8	19.2	0.98 (0.90-1.06)	
History of coronary artery disease				0.25
Yes	28.8	31.4	0.91 (0.81-1.02)	
No	17.1	17.2	0.99 (0.91-1.09)	
Number of vascular territories affected				0.59
1	15.9	16.0	1.00 (0.90-1.11)	
2	23.7	25.4	0.93 (0.83-1.05)	
3	34.9	38.2	0.91 (0.76-1.09)	

0.60 0.75   1.00   1.33 1.67

Ticagrelor Better   Clopidogrel Better

Marginal proportional hazard regression models with terms for the interaction between treatment and subgroups were constructed to estimate subgroup treatment effects and heterogeneity with respect to total cardiovascular and limb events and procedures. CI, confidence interval; HR, hazard ratio.