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ORIGINAL RESEARCH

Efficacy and Safety of Adjunctive Cilostazol to Clopidogrel-Treated Diabetic Patients With Symptomatic Lower Extremity Artery Disease in the Prevention of Ischemic Vascular Events

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BACKGROUND: Type 2 diabetes mellitus is a risk factor for lower extremity arterial disease. Cilostazol expresses antiplatelet, anti-inflammatory, and vasodilator actions and improves the claudication intermittent symptoms. We investigated the efficacy and safety of adjunctive cilostazol to clopidogrel-treated patients with type 2 diabetes mellitus exhibiting symptomatic lower extremity arterial disease, in the prevention of ischemic vascular events and improvement of the claudication intermittent symptoms.

METHODS AND RESULTS: In a prospective 2-arm, multicenter, open-label, phase 4 trial, patients with type 2 diabetes mellitus with intermittent claudication receiving clopidogrel (75 mg/d) for at least 6 months, were randomly assigned in a 1:1 ratio, either to continue to clopidogrel monotherapy, without receiving placebo cilostazol (391 patients), or to additionally receive cilostazol, 100 mg twice/day (403 patients). The median duration of follow-up was 27 months. The primary efficacy end point, the composite of acute ischemic stroke/transient ischemic attack, acute myocardial infarction, and death from vascular causes, was significantly reduced in patients receiving adjunctive cilostazol compared with the clopidogrel monotherapy group (sex-adjusted hazard ratio [HR], 0.468; 95% CI, 0.252–0.870; P=0.016). Adjunctive cilostazol also significantly reduced the stroke/transient ischemic attack events (sex-adjusted HR, 0.38; 95% CI, 0.15–0.98; P=0.046) and improved the ankle-brachial index and pain-free walking distance values (P=0.001 for both comparisons). No significant difference in the bleeding events, as defined by Bleeding Academic Research Consortium criteria, was found between the 2 groups (sex-adjusted HR, 1.080; 95% CI, 0.579–2.015; P=0.809).

CONCLUSIONS: Adjunctive cilostazol to clopidogrel-treated patients with type 2 diabetes mellitus with symptomatic lower extremity arterial disease may lower the risk of ischemic events and improve intermittent claudication symptoms, without increasing the bleeding risk, compared with clopidogrel monotherapy.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02983214.

Key Words: cilostazol ■ clopidogrel ■ coronary artery disease ■ diabetes mellitus ■ intermittent claudication ■ ischemic stroke

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CLINICAL PERSPECTIVE

What Is New?

- This prospective 2-arm, multicenter, open-label, phase 4 trial reveals that in patients with type 2 diabetes mellitus who presented with symptomatic lower extremity arterial disease and had been treated with clopidogrel (75 mg/d) for at least 6 months, the addition of cilostazol (100 mg twice/day) significantly reduced the incidence of ischemic events, defined as acute ischemic stroke/transient ischemic attack, acute myocardial infarction, and death from vascular causes, compared with patients who continued in clopidogrel monotherapy.
- Adjunctive cilostazol to clopidogrel-treated patients with type 2 diabetes mellitus also significantly reduced the acute ischemic stroke/transient ischemic attack events and improved the ankle-brachial index and the pain-free walking distance values compared with clopidogrel monotherapy.
- The risk of overall bleeding, including severe or life-threatening bleeding, with the combination of cilostazol with clopidogrel was similar to that observed in the clopidogrel monotherapy group.

What Are the Clinical Implications?

- The present study suggests that long-term treatment with a combination of cilostazol and clopidogrel of patients with type 2 diabetes mellitus who presented with symptomatic lower extremity arterial disease could be an effective therapeutic regimen in these high thrombotic risk patients.

Nonstandard Abbreviations and Acronyms

DORIC	Diabetic Artery Obstruction: Is It Possible to Reduce Ischemic Events With Cilostazol?
LEAD	lower extremity arterial disease
T2DM	type 2 diabetes mellitus

Lower extremity arterial disease (LEAD) is one of the manifestations of atherosclerotic cardiovascular disease and therefore it has similar risk factors to coronary and cerebrovascular diseases.[1–3] LEAD is associated with a high risk of cardiovascular morbidity and mortality, as well as by decreased quality of life.[1–3]

The most frequent clinical manifestation of LEAD is intermittent claudication, which results from poor oxygenation of muscles of the lower extremities and is experienced typically as an aching pain, cramping, or numbness in the calf, buttocks, hip, thigh, or arch of foot. Intermittent claudication symptoms are induced by walking or exercise and relieved by rest.[4,5]

A potent risk factor for atherosclerotic cardiovascular disease as well as for LEAD is type 2 diabetes mellitus (T2DM).[6–9] Indeed, 20% to 30% of patients with LEAD have T2DM,[10] and the risk of developing LEAD is proportional to the severity and duration of diabetes mellitus.[11,12] LEAD in patients with T2DM is being associated with other vascular events, such as stroke and myocardial infarction, and it is also an important risk factor for lower limb amputation.[11,12]

Cilostazol is a 2-oxoquinolone derivative that selectively and reversibly inhibits cellular phosphodiesterase-3; thus, it suppresses cAMP degradation, increasing its intracellular levels in various cell types, including endothelial cells, platelets, vascular smooth muscle cells, cardiomyocytes, and adipocytes.[13] Cilostazol also inhibits equilibrative nucleoside transporter-1 and prevents extracellular adenosine uptake.[13,14] Through these mechanisms, cilostazol expresses several actions, including antiplatelet-antithrombotic, anti-inflammatory, vasodilator, and antimitogenic effects.[14,15]

Cilostazol is licensed as a therapeutic agent to improve the maximal and pain-free walking distances in patients with intermittent claudication.[16] Especially in patients with T2DM, cilostazol combined with aspirin and/or clopidogrel is more effective in secondary prevention of stroke than aspirin and clopidogrel alone.[17,18]

The aim of the the DORIC (Diabetic Artery Obstruction: Is It Possible to Reduce Ischemic Events With Cilostazol?) trial (ClinicalTrials.gov Identifier: NCT02983214) was to investigate whether adjunctive cilostazol to clopidogrel-treated patients with T2DM exhibiting symptomatic LEAD reduces the incidence of ischemic events and improves intermittent claudication symptoms, without increasing the bleeding risk, compared with clopidogrel monotherapy.

METHODS

Trial Design and Study Participants

The data that support the findings of this study are available from the corresponding author on reasonable request. The DORIC trial was a prospective 2-arm, multicenter (12 centers), open-label, phase 4 clinical trial. The executive and operations committee designed and oversaw the conduct of the study. The raw database was provided to this committee, which performed the data analyses, prepared this report, and made the decision to submit the article for publication. The members of the executive and operations committee assume responsibility for the accuracy and

completeness of the data and all analyses and for the fidelity of this report to the study protocol.

Eligible patients were White men and women ≥50 years old, with T2DM who presented with symptomatic LEAD, intermittent claudication, or rest pain (stage IIa, IIb, or III, according to the Fontaine classification, or stage 1 to 4, according to the Rutherford classification),[3,17] and were receiving clopidogrel (75 mg/d) for at least 6 months. Presence of T2DM and diabetes mellitus treatment at enrollment was determined using the "Medical History" case report form at screening or baseline visits. The diagnosis of T2DM was documented by the participating physicians, according to American Diabetes Association guidelines.[8] If information on diabetes mellitus history was missing, the patient was not included in this study. Medical records were obtained and physical examination was performed in all patients, accessing cardiovascular risk factors. Ankle-brachial index (ABI) measurements in right and left leg were performed in a supine position after at least 30 minutes of rest at baseline and at 12 months of follow-up, using a Doppler probe (5–10 MHz), on the posterior and the anterior tibial arteries of each leg and on the brachial artery of each arm. The ABI of each leg was calculated by dividing the highest ankle systolic blood pressure by the highest arterial pressure measured in arm.[19–21] The pain-free walking distance, as walking on a treadmill under the supervised examination of the patient's physician, was recorded at baseline and at 12 months of follow-up.[19,22] Each patient was submitted to 3 treadmill examinations, and the best approach was recorded. The pain-free walking distance was also recorded in all patients at home-based exercise. Patients were instructed to walk 3 times per week, up to 45 minutes, at a self-selected pace. The exercise activity was recorded by each patient in a structured form in which the date, duration of walking, and free pain distance were noted. This form was delivered monthly to the physician. Patients who presented with heart failure, history of ventricular tachycardia, ventricular fibrillation, multifocal ventricular contractions, or corrected QT prolongation in resting ECGs were excluded from the study. Patients with atrial fibrillation receiving anticoagulant treatment or patients with a history of cardioembolic ischemic stroke or hemorrhagic stroke were also excluded from the study. The exclusion criteria also included patients with a history (≤12 months) of an acute coronary syndrome receiving dual antiplatelet therapy or patients treated with aspirin. Patients with chronic liver disease (Child-Turcotte-Pugh score ≥5) or chronic kidney disease, stages 4 to 5 (glomerular filtration rate, <30 mL/min), patients with cancer, or patients with a recent peptic ulcer or a history of hypersensitivity to cilostazol were excluded from the study.

Randomization

Patients were randomly assigned in a 1:1 ratio, either to continue to clopidogrel monotherapy (75 mg/d), without receiving placebo cilostazol, or to additionally receive a brand of cilostazol (Claudiasil) (100 mg twice a day). To prevent adverse drug reactions, such as tachycardia, palpitations, or headache, cilostazol treatment was started at a daily dose of 50 mg twice a day for 15 days and then increased to 100 mg twice a day. Antiplatelet treatment was continued for at least 18 months, with a maximum of 36 months. Outpatient visits or telephone contacts were scheduled every month the first year and every 3 months thereafter. Compliance to the antiplatelet drugs as well as adverse events were assessed at each visit. Changes in the antiplatelet treatment were not permitted during the study.

Simple randomization was based on a computer-generated randomization list using Microsoft Excel software (Microsoft Hellas Co, Athens, Greece). The list was given to the study's investigators, who enrolled the patients and assigned them in 1 of the 2 groups. Medical personnel and patients were not blinded to treatment assignment during the whole study period. Therefore, outcomes were submitted to a 3-member adjudication committee constituted by the Atherothrombosis Research Center of the University of Ioannina.

End Points

The primary efficacy end point was the composite of acute ischemic stroke/transient ischemic attack (TIA), acute myocardial infarction (AMI), and death from vascular causes. Acute ischaemic stroke/TIA was adjudicated by physical examination as well as by performing urgent imaging of the brain and supra-aortic vessels (computed tomography scan angiography and magnetic resonance angiography).[23,24] The diagnosis of AMI, characterized as either AMI with ST-segment elevation or high-risk unstable angina or AMI without ST-segment elevation, was performed according to the Third Universal Definition of Myocardial Infarction.[25] Secondary efficacy end points were acute ischemic stroke/TIA, AMI, coronary stent thrombosis, percutaneous coronary intervention, coronary restenosis (adjudicated by the recurrence of signs and symptoms of cardiac ischemia in a patient with a history of coronary artery disease and prior stent implantation, and confirmed by coronary angiography), death from cardiovascular causes, death from any cause, hospitalization for acute limb ischemia, lower extremity arterial revascularization, as well as the improvement of ABI and pain-free walking distance values.

The primary safety end point was the rate of bleeding events, as defined by Bleeding Academic Research

Consortium criteria. Other adverse events were also recorded, including headache, palpitations, tachycardia, diarrhea, urticaria, neoplasms, transient thrombocytopenia, and leucopenia.

Bioethics

The study protocol was approved by the ethics committee of each hospital that participated in the trial. The study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonised Tripartite Guideline for Good Clinical Practice. Written informed consent was obtained from each eligible patient before being randomly assigned to treatment.

Statistical Analysis

Values of continuous variables were presented as mean and SD, whereas categorical variables were expressed as counts and percentages. Efficacy analyses were done in the intention-to-treat population, focused only on time to first event. Safety analyses were done with patients who had received at least one dose of a trial regimen. Baseline characteristics and medical history comparisons were examined using the Pearson χ^2 test in the case of categorical variables or the independent sample *t* test in the case of continuous ones. The Shapiro-Wilk test was applied to assess normality where necessary. The Pearson χ^2 test was also used to assess independence of bleeding events in the 2 treatment groups. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs for the adjunctive cilostazol group compared with the clopidogrel monotherapy group, for all outcomes except for the improvement of ABI values and of pain walking free distance values, which were only measured at the entry to the study and at the end of the follow-up for each patient. The analysis was adjusted for patients' sex, and the assumption of proportional hazards was confirmed when performing each analysis. Patients who did not develop events were treated as censored at the last observational date. A secondary per-protocol analysis of the primary outcome that included patients who had received at least one dose of a trial regimen, with data censored 1 day after permanent discontinuation of trial medication, was also performed. Statistical significance was set at 0.05 in all cases, and the Bonferroni correction was applied to adjust the type I error for the primary efficacy outcome. All analyses were performed using IBM SPSS software, version 21 (IBM Co, Armonk, NY). Sample size calculations were performed before the initiation of the study on the basis of the assumption of a 30% improvement in efficacy under the adjunctive cilostazol treatment versus the clopidogrel monotherapy, according to the test of proportion comparisons for 2 independent groups. One year after the initiation of the study, the observed incidence of an interim analysis for the primary efficacy end point in the adjunctive cilostazol arm and in the clopidogrel monotherapy arm in this high-risk population was found equal to 4% and 8%, respectively. On the basis of these findings and assuming a total dropout rate of 7%, and a follow-up period of 2 years, the study had a power >80% at 0.05 to reject the null hypothesis of equality in incidence of events in the study arms, according to the test of proportion comparisons for 2 independent groups. Significance (2 tailed) was set at $P<0.05$. The G power 3.1 was used for the power analysis.

RESULTS

The patients' recruitment started in November 2016, and the enrollment duration was initially planned to be 12 months. The steering committee extended the enrollment period for 6 months to increase the number of recruited patients because the power analysis had indicated 795 patients per arm. During the 18-month period, 826 consecutive patients with T2DM who presented with symptomatic LEAD were enrolled (Figure 1). Among them, 26 patients declined to participate once the procedure of participation had been explained, whereas 6 patients did not meet the inclusion criteria. Thus, 794 patients underwent randomization. Among them, 391 patients were assigned to continue to clopidogrel monotherapy and 403 were assigned to receive adjunctive cilostazol on top of clopidogrel (Figure 1). The follow-up was initially planned to be 12 months. However, on the basis of the number of major events recorded within this follow-up period, the steering committee decided to extend this period for 6 months. In this regard, the data were examined once at 12 months of follow-up, looking only at the number of cases with the primary efficacy end point in each arm. This look on the data was not initially planned and was the only one throughout the 12-month follow-up period. It was conducted because of the smaller number of the total accrued patients compared with the initial target. For this comparison only, the Bonferroni adjustment was applied at the end of the trial to adjust for type I error. The result remained significant after the adjustment as well.

The last date of patient contact was October 31, 2019, and the trial database was locked in November 2019. The trial medication was continued for 18 months, up to 36 months, and the median duration of follow-up was 27 months. Discontinuation of follow-up for reasons other than development of major events occurred in 22 patients in the adjunctive cilostazol group and in 15 patients in the clopidogrel monotherapy group (Figure 1). Among patients in the adjunctive cilostazol

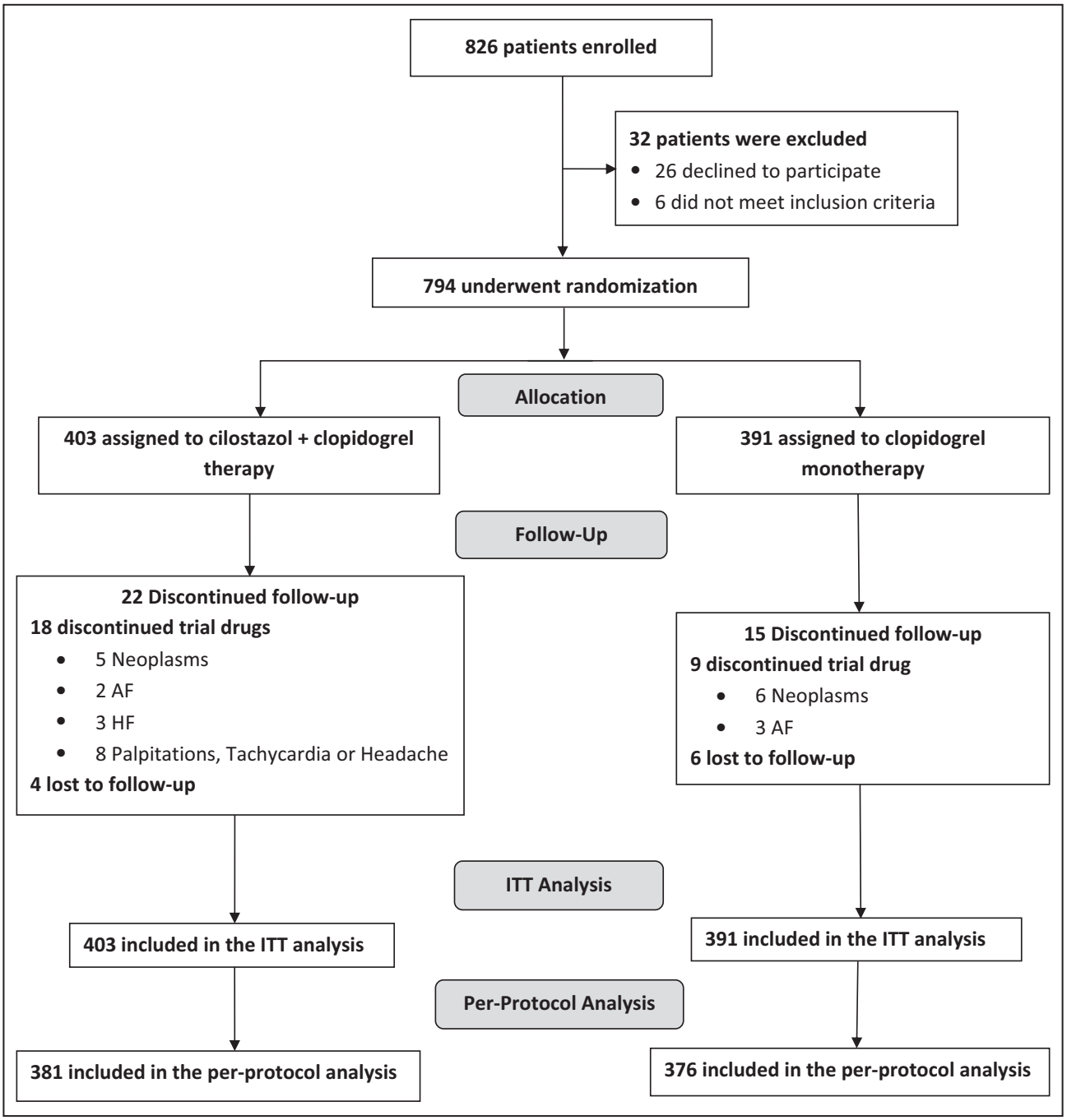

Figure 1. Consolidated Standards of Reporting Trials flow diagram showing the study design of the DORIC (Diabetic Artery Obstruction: Is It Possible to Reduce Ischemic Events With Cilostazol?) trial.
AF indicates atrial fibrillation; HF, heart failure; and ITT, intent to treat.

group, 4 were lost to follow-up and 18 discontinued trial drugs (2 patients diagnosed as having atrial fibrillation and switched to anticoagulants, 5 patients diagnosed as having neoplasms, and 3 patients developed heart failure, whereas 8 patients had palpitations, tachycardia, or headache). Among the patients in the monotherapy group, 6 were lost to follow-up and 9 discontinued trial drugs (3 patients diagnosed as having atrial fibrillation and switched to anticoagulants and 6 patients diagnosed as having neoplasms [Figure 1]). Thus, 403 patients assigned to receive cilostazol in addition to clopidogrel and 391 patients assigned to the clopidogrel monotherapy group were included in the intention-to-treat analysis, whereas 381 patients in the adjunctive cilostazol group and 376 patients in the monotherapy group were included in the per-protocol analysis. The patients' baseline characteristics are shown in Table 1. Patients in the adjunctive cilostazol

group exhibited higher male/female ratio, which was taken into account in the analysis followed on. No difference between groups was observed in patients' medical history, their distribution among the stages of Fontaine classification, ABI values, and pain-free walking distance values, as well as in major medications administered at baseline (Table 1).

Efficacy End Points

The primary efficacy end point of acute ischemic stroke/TIA, AMI, and death from vascular causes occurred in 15 (3.7%) of 403 patients of the adjunctive cilostazol group and in 31 (7.9%) of the 391 patients in the clopidogrel monotherapy group (sex-adjusted HR, 0.468; 95% CI, 0.252–0.870; *P*=0.016) (Table 2 and Figure 2). Among the secondary efficacy outcomes, acute ischemic stroke/TIA was significantly lower in the adjunctive cilostazol group than in the clopidogrel monotherapy group (sex-adjusted HR, 0.38; 95% CI, 0.15–0.98; *P*=0.046) (Table 2). The ABI values in both legs as well as the pain-free walking distance values were improved in both patient groups (*P*=0.02 for all comparisons in the clopidogrel monotherapy group and *P*=0.001 for all comparisons in the adjunctive cilostazol group). The improvement in both parameters was significantly higher in the adjunctive cilostazol group compared with the clopidogrel monotherapy group (Table 2). There was a trend for reduction in coronary restenosis and lower extremity revascularization in the adjunctive cilostazol group versus the clopidogrel monotherapy group; however, it did not reach statistical significance (Table 2). No significant reduction was found in AMI, coronary stent thrombosis,

Table 1. Baseline Characteristics, Medical History, and Main Medications of the Participants in the Study

Characteristics	Cilostazol+Clopidogrel (n=403)	Clopidogrel (n=391)	*P* Value
Age, y	67.5±8.5	68.2±8.2	0.24
Sex (men/women), n	281/122	227/164	0.001
BMI, kg/m^2	30.1±5.8	29.8±5.1	0.54
HbA1c, %	7.1±1.2	7.2±1.3	0.31
Fontaine classification, n			
Stage IIa	285	280	0.30
Stage IIb	87	81	0.40
Stage III	31	30	0.62
ABI values			
Right leg	0.73±0.14	0.75±0.10	0.69
Left leg	0.72±0.12	0.77±0.09	0.23
Pain-free walking distance, m	237.9±48.3	252.1±63.9	0.13
Medical history, n (%)			
Current smoking	89 (22.1)	77 (19.7)	0.76
Hypertension	354 (87.8)	340 (86.9)	0.74
Hyperlipidemia	356 (88.3)	347 (88.7)	0.91
Family history of CAD	13 (3.2)	16 (4.1)	0.51
History of CAD	91 (22.6)	82 (20.9)	0.63
History of noncardioembolic ischemic stroke/TIA	39 (9.6)	35 (8.9)	0.12
History of carotid artery disease	64 (15.9)	54 (13.8)	0.46
History of valvular disease	8 (2.0)	9 (2.3)	0.60
CKD stage 1–3	36 (8.9)	40 (10.2)	0.12
Thyroid gland disease	45 (11.2)	43 (10.9)	0.10
COPD	6 (1.4)	4 (1.0)	0.31
Main medications, n (%)			
Antidiabetics	403 (100)	391 (100)	0.89
Lipid-lowering agents	356 (88.3)	347 (88.7)	0.10
Antihypertensive agents	354 (87.8)	340 (86.9)	0.52
PPIs	32 (7.9)	27 (6.9)	0.54

Data are given as mean±SD, unless otherwise indicated. ABI indicates ankle-branchial index; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin; PPI, proton pump inhibitor; and TIA, transient ischemic attack.

Table 2. Primary and Secondary Efficacy End Points

End Points	Cilostazol+Clopidogrel (n=403)	Clopidogrel (n=391)	HR (95% CI)	*P* Value
Primary efficacy, n (%)				
Acute ischemic stroke/TIA, AMI, and death from vascular causes	15 (3.7)	31 (7.9)	0.468 (0.252–0.870)	0.016
Secondary efficacy				
Acute ischemic stroke/TIA, n (%)	6 (1.5)	15 (3.8)	0.38 (0.15–0.98)	0.046
AMI, n (%)	6 (1.5)	11 (2.8)	0.56 (0.21–1.52)	0.25
Death from vascular causes, n (%)	3 (0.7)	5 (1.3)	0.66 (0.16–2.78)	0.57
Coronary stent thrombosis, n (%)	2 (0.5)	2 (0.5)	0.92 (0.13–6.54)	0.93
PCI, n (%)	4 (1.0)	6 (1.5)	0.63 (0.18–2.24)	0.48
Coronary restenosis, n (%)	1 (0.2)	5 (1.3)	0.2 (0.02–1.75)	0.15
Death from any cause, n (%)	5 (1.2)	6 (1.5)	0.87 (0.26–2.84)	0.81
Improvement of ABI values				
Right leg	0.18±0.05	0.07±0.02		0.001
Left leg	0.17±0.04	0.06±0.01		0.001
Improvement of pain-free walking distance values, m	107.7±27.4	47.7±15.3		0.001
Hospitalization for acute limb ischemia, n (%)	8 (2.0)	14 (3.6)	0.54 (0.23–1.29)	0.17
Lower extremity arterial revascularization, n (%)	13 (3.2)	22 (5.6)	0.53 (0.27–1.06)	0.07

Data are given as mean±SD, unless otherwise indicated. ABI indicates ankle-branchial index; AMI, acute myocardial infarction; HR, hazard ratio; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

percutaneous coronary intervention, and hospitalization for acute limb ischemia as well as in death from vascular causes or from any cause (Table 2). Similar results in the primary and secondary efficacy outcomes were obtained when per-protocol analysis was applied (data not shown).

Safety End Points

The primary safety end point of bleeding events, according to Bleeding Academic Research Consortium criteria, occurred in 21 patients (5.2%) in the adjunctive cilostazol group, compared with 19 patients (4.8%) in the clopidogrel monotherapy group (sex-adjusted HR, 1.080; 95% CI, 0.579–2.015; *P*=0.809) (Table 3 and Figure 3). As shown in Table 3, the HRs of Bleeding Academic Research Consortium 1, 2, 3, and 5 bleeding were similar between the 2 study groups, whereas no bleeding events according to Bleeding Academic Research Consortium 4 were observed in either group. Intracranial hemorrhage occurred in 4 and 3 patients in adjunctive cilostazol group and in clopidogrel monotherapy group, respectively, 1 of which was fatal in each group. Gastrointestinal bleeding occurred in 7 and 5 patients in adjunctive cilostazol group and in clopidogrel monotherapy group, respectively. Similar results in the primary safety end points were obtained when per-protocol analysis was applied (data not shown). Nonthrombotic and nonbleeding adverse events related to the drugs investigated in the present study were also recorded. These events were nonserious, although most of them occurred only in the adjunctive cilostazol group (Table 4).

DISCUSSION

The DORIC trial shows that in patients with T2DM with symptomatic LEAD receiving antiplatelet therapy with clopidogrel, the addition of cilostazol significantly reduces the incidence of ischemic events, defined as acute ischemic stroke/TIA, AMI, and death from vascular causes, compared with patients who continued in clopidogrel monotherapy. The combination of cilostazol with clopidogrel also significantly reduced the secondary efficacy outcome of acute ischemic stroke/TIA. Furthermore, addition of cilostazol to clopidogrel significantly improved the pain-free walking distance and ABI values in both legs compared with clopidogrel monotherapy. The other secondary efficacy outcomes, AMI, death from vascular causes, coronary stent thrombosis, percutaneous coronary intervention, coronary restenosis, hospitalization for acute limb ischemia, and lower extremity arterial revascularization events, were not reduced significantly.

All patients with T2DM of the DORIC trial exhibited symptomatic LEAD, most of them being presented with intermittent claudication, stages IIa and IIb, according to the Fontaine classification. Following the 2016 American College of Cardiology/American Heart Association guidelines[26] as well as more recent guidelines on the management of patients with symptomatic LEAD,[3,19] patients should be given antiplatelet therapy with aspirin alone (75–325 mg/d) or clopidogrel alone (75 mg/d) to improve the LEAD symptoms. In this regard, a systematic review and network meta-analysis of 49 available randomized controlled trials comparing different antiplatelet regimens in 34 518 patients suggests that clopidogrel may be the preferred antiplatelet

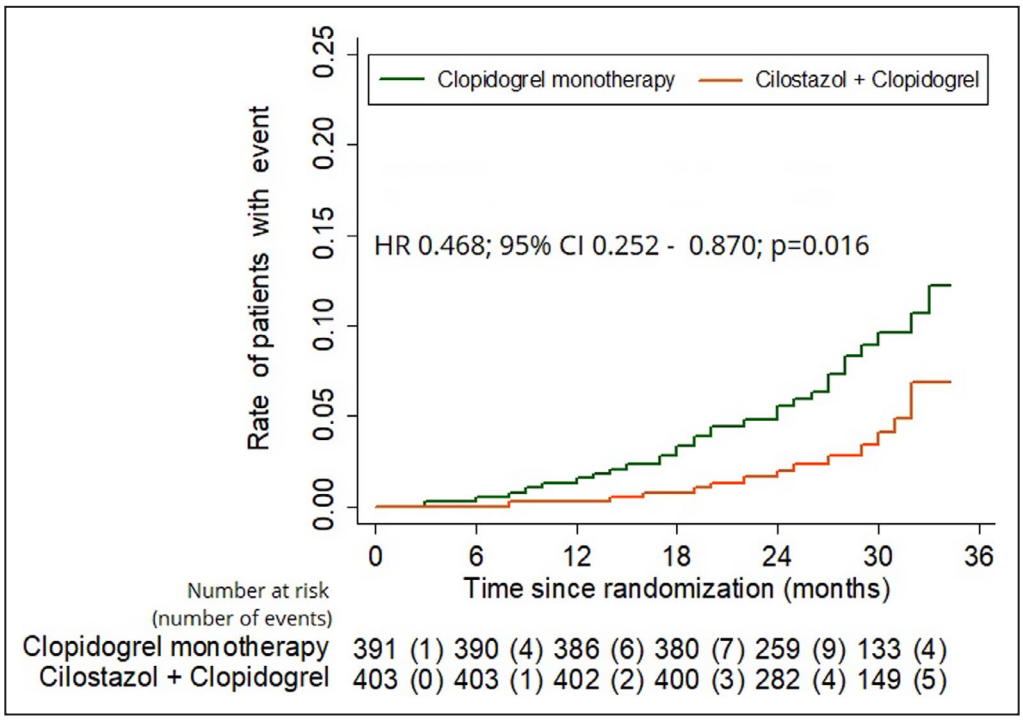

Figure 2. Kaplan-Meier plot of the primary efficacy end point.
The primary efficacy end point was defined as acute ischemic stroke/transient ischemic attack, acute myocardial infarction, and death from cardiovascular causes. HR indicates hazard ratio.

agent to treat patients with LEAD.[27] This therapeutic regimen may also reduce the incidence of ischemic events, such as myocardial infarction, ischemic stroke, and vascular death.[4] Therefore, the present study included patients with T2DM receiving clopidogrel monotherapy.

According to the DORIC trial protocol, the patients with T2DM included in the study should be treated with clopidogrel for at least 6 months before enrollment to exclude, as possible, the existence of high on-treatment platelet reactivity to this drug, because according to previous studies, the platelet response to clopidogrel is improved after drug administration for at least 1 month.[28–31] According to our results, the ABI values and the pain-free walking distance were improved at 12 months of follow-up in the clopidogrel monotherapy group, suggesting that our patients adequately responded to clopidogrel.

Adjunctive cilostazol to the clopidogrel-treated patients with T2DM further improved the ABI and the pain-free walking distance values and consequently the claudication intermittent symptoms, and it also significantly reduced the primary efficacy end point, the composite of acute ischemic stroke/TIA, AMI, and death from vascular causes. This suggests that the use of cilostazol in addition to clopidogrel is an effective therapeutic regimen in patients with T2DM with symptomatic LEAD. This finding is in accordance with previously published results demonstrating that adjunctive cilostazol to clopidogrel significantly improves the clinical outcomes in various patient groups, including patients with coronary artery disease, patients

Table 3. Bleeding Events as Defined by BARC Criteria

End Points	Cilostazol+Clopidogrel (n=403)	Clopidogrel (n=391)	HR (95% CI)	*P* Value
Primary safety, n (%)	21 (5.2)	19 (4.9)	1.080 (0.579–2.015)	0.809
BARC 1	12 (3.0)	11 (2.8)	1.002 (0.44–2.28)	0.99
BARC 2	6 (1.5)	4 (1.0)	1.51 (0.42–5.39)	0.53
BARC 3	2 (0.5)	3 (0.8)	0.69 (0.12–4.18)	0.69
BARC 4	0 (0)	0 (0)	…	…
BARC 5	1 (0.2)	1 (0.3)	1.06 (0.06–17.30)	0.97

BARC indicates Bleeding Academic Research Consortium; and HR, hazard ratio.

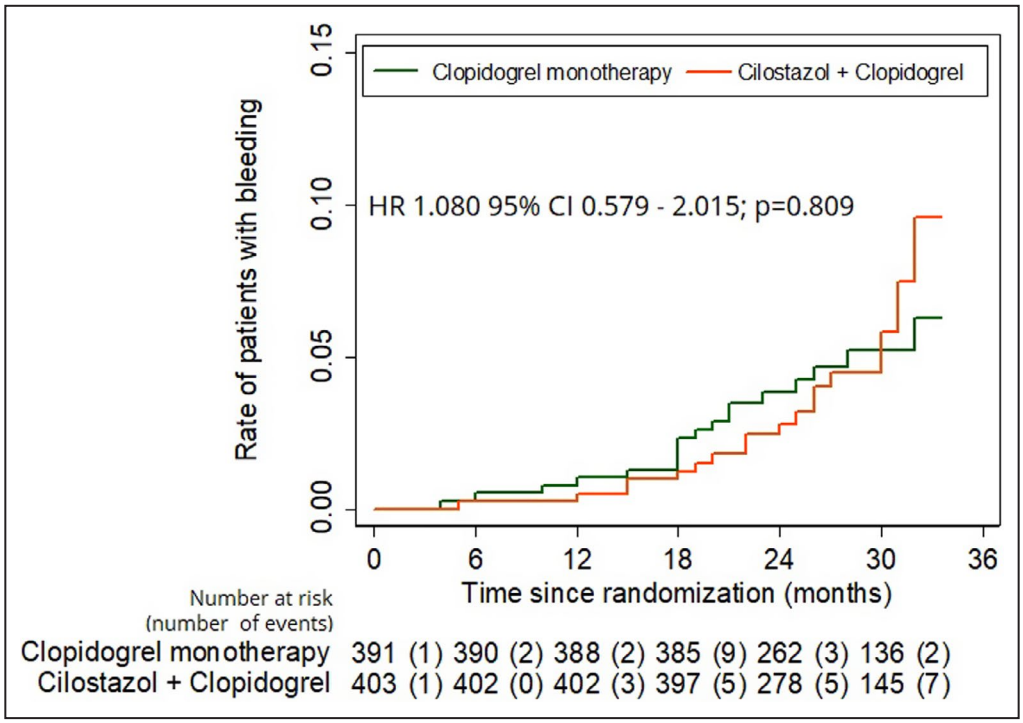

Figure 3. Kaplan-Meier plot of the primary safety end point.
The primary safety end point was defined by Bleeding Academic Research Consortium criteria. HR indicates hazard ratio.

undergoing percutaneous coronary intervention or carotid artery stenting, patients with a prior noncardioembolic ischemic stroke or TIA, and patients with LEAD.[32–36] The DORIC trial further showed that the combination of cilostazol with clopidogrel significantly reduced the secondary efficacy outcome of acute ischemic stroke/TIA compared with clopidogrel monotherapy. This finding is in line with recently published data in patients at high risk for recurrent ischemic stroke, demonstrating that the combination of cilostazol with aspirin or clopidogrel reduces the incidence of ischemic stroke recurrence compared with treatment with aspirin or clopidogrel alone.[37]

Table 4. Nonthrombotic and Nonbleeding Adverse Events in the Study Population

Adverse Events*	Cilostazol+Clopidogrel (n=403)	Clopidogrel (n=391)
Headache	11 (2.7)	0
Palpitations	11 (2.7)	0
Tachycardia	9 (2.2)	0
Diarrhea	6 (1.5)	0
Urticaria	6 (1.5)	4 (1.0)
Neoplasms	5 (1.2)	6 (1.5)

Data are given as number (percentage).
*Only adverse events with >1.0% incidence are presented.

The reduction of ischemic events induced by the addition of cilostazol to clopidogrel could be attributed to several actions expressed by cilostazol in addition to its antiplatelet-antithrombotic effects. These include anti-inflammatory, vasodilator, and antimitogenic effects as well as the inhibition of neointimal hyperplasia and smooth muscle proliferation after endothelial injury.[13–15]

More important, the risk of overall bleeding, including severe or life-threatening bleeding, with the combination of cilostazol with clopidogrel was similar to that observed in the clopidogrel monotherapy group. This finding is in accordance with previously published results of several studies, showing that cilostazol administration as monotherapy or as dual or even triple antiplatelet therapy does not increase bleeding compared with corresponding therapies that do not include cilostazol.[33,34,36]

A limitation of the present study is the relatively small number of enrolled patients; however, the study has adequate power to avoid type II statistical errors. A consequence of this limitation is that the lower numbers in the secondary efficacy outcomes of coronary restenosis and lower extremity arterial revascularization observed in the adjunctive cilostazol group, compared with the clopidogrel monotherapy group, did not reach statistical significance. Previous studies have demonstrated that adjunctive cilostazol to

aspirin, clopidogrel, or both significantly reduces the above end points.[13–15,38,39] Therefore, it remains to be established whether in patients with T2DM, being at high risk for thrombotic events, treatment with cilostazol and clopidogrel would reduce the above clinical end points. The DORIC trial did not include a placebo group, and the patients' treatment was not blind; consequently, the trial investigators were aware of the study drug allocation. These are also limitations of the present study. We should point out that most of clinical studies of cilostazol involved population from East Asia, and this is mentioned as a limitation of these studies, even though there are no reports for differences in the pharmacokinetics of cilostazol among races.[40] The DORIC trial involved White patients, and this provides information on the potential effects of this drug in a non-Asian population. The known early cilostazol adverse effects, such as tachycardia, palpitations, or headache,[41] which lead to drug discontinuation, were lower in our study compared with those reported in previous studies.[42] This could be caused by the fact that cilostazol treatment in our patients was started at a daily dose of 2×50 mg for 15 days and then increased at 2×100 mg/d. This observation accords with recently published results.[37]

In conclusion, in White patients with T2DM with symptomatic LEAD, long-term treatment with a combination of cilostazol with clopidogrel may lower the risk of ischemic events and improve intermittent claudication symptoms, without increasing the bleeding risk, compared with clopidogrel monotherapy. Therefore, the present study suggests that addition of cilostazol to clopidogrel in patients with T2DM with high thrombotic risk, who are eligible to receive this drug, could be recommended as an effective therapeutic regimen in these patients.

ARTICLE INFORMATION

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Disclosures

None.

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