Ticagrelor Monotherapy in Patients with Concomitant Diabetes Mellitus and Chronic Kidney Disease: A post Hoc Analysis of The GLOBAL LEADERS Trial

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Abstract

Background: Patients with both diabetes mellitus (DM) and chronic kidney disease (CKD) are a subpopulation characterized by ultrahigh ischemic and bleeding risk after the percutaneous coronary intervention (PCI). There are limited data on the impact of ticagrelor monotherapy among these patients.

Methods: In this *post hoc* analysis of the GLOBAL-LEADERS trial, the treatment effects of the experimental (one-month dual-antiplatelet therapy [DAPT] followed by 23-month ticagrelor monotherapy) versus the reference regimen (12-month DAPT followed by 12-month aspirin alone) were analyzed according to DM/CKD status. The primary endpoint was a composite endpoint of all-cause death or new Q-wave myocardial infarction at two-years. The patient-oriented composite endpoint (POCE) was defined as the composite of all-cause death, any stroke, site-reported MI and any revascularization, whereas net adverse clinical events (NACE) combined POCE with BARC type 3 or 5 bleeding events.

Results: At two years, the DM+/CKD+ patients had significantly higher incidences of the primary endpoint (9.5% versus 3.1%, adjusted HR 2.16; 95%CI [1.66-2.80], p<0.001), BARC type 3 or 5 bleeding events, stroke, site-reported myocardial infraction, all revascularization, POCE, and NACE, compared with the DM-/CKD- patients. Among the DM+/CKD+ patients, after adjustment, there were no significant differences in the primary endpoints between the experimental and reference regimen. The experimental regimen was associated with lower rates of POCE (20.6% versus 25.9%, HR 0.74; 95%CI [0.55-0.99], p=0.043, p_{trend}=0.155) and NACE (22.7% versus 28.3%, HR 0.75; 95%CI [0.56-0.99], p=0.044, p_{trend}=0.310), mainly driven by a lower rate of all revascularization, as compared with the reference regimen. The landmark analysis showed that while the experimental and reference regimen had similar rates of all the clinical endpoints during the first year, the experimental regimen was associated with significantly lower rates of POCE (5.8% versus 11.0%, HR 0.49; 95%CI [0.29-0.82], p=0.007, p_{trend}=0.040) and NACE (5.8% versus 11.2%, HR 0.48; 95%CI [0.29-0.82], p=0.007, p_{trend}=0.013) in the second year.

Conclusion: Among patients with both DM and CKD, ticagrelor monotherapy was not associated with lower rates of all-cause death or new Q-wave, or major bleeding complications; however, it was associated with lower rates of POCE and NACE. These findings should be interpreted as hypothesis-generating.

Clinical Trial Registration: ClinicalTrials.gov (NCT01813435).

Background

Patients with coronary artery disease (CAD) and concomitant diabetes mellitus (DM) or chronic kidney disease (CKD) are more susceptible to major adverse cardiovascular and cerebrovascular events [1]. Moreover, the presence of these risk factors is also associated with an increased risk of bleeding complications [2, 3]. DM and CKD frequently co-exist and given that DM is a well-established risk factor for renal dysfunction [2, 4], it is predictable that nearly 25% of DM patients have CKD [5].

Previously, a subgroup analysis of the PLATO study has demonstrated that in acute coronary syndrome (ACS) population, those who had both DM and CKD were associated with a drastically unfavorable prognosis compared to those having one or neither of these comorbidities [6], and among the patients with both DM and CKD, the combination of ticagrelor with aspirin substantially reduced cardiovascular death, myocardial infarction (MI), or stroke compared with clopidogrel plus aspirin; however, the dual antiplatelet therapy (DAPT) with ticagrelor had a higher rate of TIMI non-CABG-related major bleeding events.

In an attempt to mitigate bleeding risk while preserving the anti-ischemic efficacy75402, aspirin-free antiplatelet regimens have been advocated [7–10]. The first and largest trial to date evaluating this concept -GLOBAL LEADERS, failed to show superiority of ticagrelor monotherapy over standard DAPT in an all comer patient population (in terms of all-cause mortality or new Q-wave MI) [7]. Nevertheless, understanding the impact of ticagrelor monotherapy after PCI in patients with DM and CKD in this large all-comer contemporary trial is still of clinical interest. The ever-growing prevalence of CKD in patients with DM [11, 12] underscores the need to specifically investigate the effects of different antiplatelet strategies in these ultrahigh risk patients.

On this background, here we report the results of a *post hoc* analysis of GLOBAL LEADERS trial, in which we compared the outcomes of patients according to the presence or absence of DM and CKD, and also analyzed the effects of the experimental strategy (1-month DAPT followed by 23-month ticagrelor monotherapy) compared to the reference strategy (12-month DAPT followed by aspirin monotherapy for 12 months) after PCI in such defined subgroups. In addition, a landmark analysis was performed at 1 year of follow-up, which was based on the prespecified landmark point when the patients in the reference strategy stopped ticagrelor.

Methods

The present study is a *posthoc* subgroup analysis of the GLOBAL LEADERS trial. GLOBAL LEADERS trial is a prospective, multi-center, randomized controlled trial (NCT01813435), which enrolled a total of 15,991 patients at 130 hospitals in 18 countries (Europe, Asia, Brazil, Australia and, Canada) between July 2013 and November 2015, and aimed to evaluate two antiplatelet strategies after PCI using bivalirudin and biolimus A9-eluting stents (Biomatrix) in an all-comers population [13]. Details of the study have been previously described. In brief, the experimental treatment strategy comprised aspirin 75-100 mg once daily in combination with ticagrelor 90 mg twice daily for one month, followed by ticagrelor 90 mg twice daily alone for 23 months (irrespective of clinical presentation). The reference treatment strategy included aspirin 75-100 mg daily in combination with either clopidogrel 75 mg once daily in patients with stable CAD or ticagrelor 90 mg twice daily in patients with ACS for 1 year, followed by aspirin 75-100 mg once daily

alone for the following 12 months (from 12 to 24 months after PCI). Patients were followed up at 30 days and 3, 6, 12, 18 and 24 months after the index procedure. An illustration of the antiplatelet strategy used in the trial is shown in Figure 1.

The trial was approved by the institutional review board at each center and followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent prior to participation in the trial.

Patients

The GLOBAL LEADERS trial randomized 15,991 participants -23 patients withdrew consent and requested deletion of their data from the database [7] - DM and CKD status was unavailable in 96 patients, leaving 15,872 patients (99.2%) for the present analyses. Patients with DM or CKD were pre-specified subgroups of the GLOBAL LEADERS study [13]. However, the analyses of current analyses were not pre-specified. CKD was defined at the time of randomization, using an eGFR cut-off of 60 ml/min/1.73 m^2 (stage III to V CKD by KDIGO classification), calculated according to the Modification of Diet in Renal Disease (MDRD) equation [14], as pre-specified in the trial protocol. In addition, a sensitive analysis was performed by using an eGFR cut-off of 90 ml/min/1.73 m^2 (stage II to V CKD by KDIGO classification). The status of DM was site-reported and defined at the time of randomization [13]. The PRECISE-DAPT score were calculated by the online calculator [15].

Outcomes

The events definitions have been reported previously [16]. The primary endpoint was a composite of all-cause mortality or new Q-wave myocardial infarction (MI). The key secondary safety endpoint was investigator-reported Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding [17]. Other secondary endpoints included: individual components of the primary endpoint (all-cause death, new Q-wave MI), individual components of key secondary safety endpoint (BARC defined bleeding type 3 or type 5 bleeding), any stroke, site-reported MI, any revascularization, target vessel revascularization (TVR), definite stent thrombosis (ST) defined according to the Academic Research Consortium criteria [18]. The site-reported MI was defined according to the Third Universal Myocardial Infarction definition, as pre-specific in the study protocol [13]. The patient-oriented composite endpoint (POCE) - advocated by Academic Research Consortium (ARC)-2, and net adverse clinical events (NACE) were explored up to two years [17, 19]. POCE was defined as the composite of all-cause death, any stroke, site-reported MI (including periprocedural or spontaneous with ST elevation MI [STEMI] or non-ST-segment elevation MI [NSTEMI]) and any revascularization (re-PCI or coronary artery bypass graft surgery [CABG] in the target or non-target vessel)[19], whereas NACE combined POCE with BARC type 3 or 5 bleeding events. Composite endpoints were analyzed hierarchically and the individual components of the composite endpoints were reported non-hierarchically.

Statistical analysis

All the analyses were performed by the intention-to-treat principle. Continuous variables with normal distribution are expressed as mean ± standard deviation and those with skewed distribution are expressed as median ± interquartile range. Categorical variables are presented as counts and percentage. Survival was estimated by the Kaplan-Meier method. The effect of CKD and DM on outcomes were assessed in the multivariable Cox proportional hazards model. The covariates in the multivariable model included age, sex, body mass index (BMI), clinical presentation (ACS versus stable CAD), stroke, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), previous PCI, hypercholesterolemia, current smoking status, treatment regimen (experimental versus. reference regimen), and complex PCI. Cox proportionality assumptions were checked by using the Schoenfeld residuals against the transformed time and the assumptions were met in all models. Landmark analyses were performed at 365 days of follow-up, which was based on the prespecified landmark point in the GLOBAL LEADERS design. There was no formal correction for multiple testing for subgroup analyses of the trial, taking into account the *post hoc* nature of the analysis [20]. Analyses were performed using R-project (R Foundation, Vienna, Austria). A two-sided p value less than 0.05 was considered as statistical significance.

Results

Patients and outcomes according to DM and CKD status

A total of 15,872 patients from the GLOBAL LEADERS trial population were classified according to the DM and CKD status as follows: DM-/CKD- (n=10513), DM+/CKD- (n=3189), DM-/CKD+ (n=1332), and DM+/CKD+ (n=838). Baseline characteristics are presented in Table 1. Patients with DM+/CKD+ were older, more often had a prior history of revascularization (PCI or CABG), previous stroke, previous MI, PVD, COPD. In DM+/CKD+ patients, the percentages of patients who had a Paris bleeding risk score ≥8 (23.5%), thrombotic risk score ≥5 (73.4%), and PRECISE-DAPT score ≥25 (71.0%) were higher compared with DM-/CKD- patients.

The DM+/CKD+ patients had a 2.16-fold higher incidence of the primary endpoint at 24 months, compared with the DM-/CKD- individuals (9.5% versus 3.1%, adjusted HR 2.16; 95%CI [1.66-2.80], Table 2). The DM-/CKD+ (6.9%, adjusted HR 1.53; 95%CI [1.20-2.80]) and DM+/CKD- patients (4.6%, adjusted HR 1.40; 95%CI [1.15-1.72]) had intermediate risk profile. With the DM+/CKD+ patients exhibiting the highest risk, the hazard ratio gradually decreased in the order of DM-/CKD+, DM+/CKD- and DM-/CKD- (P_{Trend} <0.001; Figure 2 and Table 2). Similar trends were observed in the key secondary endpoint (Bleeding Academic Research Consortium [BARC] type 3 or 5 bleeding), and other secondary endpoints including all-cause mortality, stroke, MI, revascularization, TVR, POCE, and NACE (Table 2).

The DM+/CKD- and DM-/CKD+ patients exhibited similar thrombotic event rates, including the primary endpoint, MI, any revascularization and TVR (Table 2). However, irrespective of the presence or absence of DM, patients with CKD had a higher incidence of BARC type 3 or 5 bleeding events (Table 2 and Figure 2B).

Outcomes of experimental versus reference regimen according to CKD and DM status

Compared with the reference regimen (DAPT for 12 months and then aspirin for 12 months), the experimental regimen (DAPT for 1 month followed by ticagrelor monotherapy for 23 months) did not show lower rates of the primary or the key safety secondary endpoints in DM+/CKD+ patients, or in any of the other three subgroups (Figure 3A, B, and Table 3). The absolute risk reduction of the primary endpoint gradually increased numerically in the order of DM-/CKD-, DM-/CKD+, DM+/CKD-, DM+/CKD+ (0.3%, 1.0%, 1.1%, and 2.3%) in patients receiving the experimental regimen.

Among the DM+/CKD+ patients, the experimental regimen was associated with lower rates of POCE (20.6% versus 25.9%, HR 0.74; 95%CI [0.55-0.99], p=0.043, p_{trend}=0.155) and NACE (22.7% versus 28.3%, HR 0.75; 95%CI [0.56-0.99], p=0.044, p_{trend}=0.310), mainly driven by lower rates any revascularization (11.5% versus 15.6%; adjusted HR 0.67; 95%CI [0.45-0.99], P=0.042, P_{trend}=0.286) and TVR (6.1% versus 10.0%; adjusted HR 0.56; 95%CI [0.33-0.93], P=0.026, P_{trend}=0.238; Figure 3C-F, and Table 3), as compared with the reference regimen. The numbers needed-to-treat to reduce a POCE, NACE, any revascularization and TVR event were 19, 18, 24 and 25, respectively.

Landmark analysis

The landmark analysis showed that among DM+/CKD+ patients, between 0-365 days after randomization, the experimental and reference regimen had similar rates of all investigated endpoints (Supplemental Table 4 and Supplemental Figure 1), whereas between 365-730 days after randomization, compared with the reference regimen, the experimental regimen was associated with significantly lower rates of POCE (5.8% versus 11.0%, HR 0.49; 95%CI [0.29-0.82], p=0.007, p_{trend}=0.040), NACE (5.8% versus 11.2%, HR 0.48; 95%CI [0.29-0.82], p=0.007, p_{trend}=0.013), any revascularization (2.3% versus 6.6%, adjusted HR 0.29; 95%CI [0.13-0.65], P=0.003, P_{trend}=0.056) and TVR (1.4% versus 2.9%, adjusted HR 0.29; 95%CI [0.09-0.91], P=0.033, P_{trend}=0.112) (Table 4 and Supplemental Figure 1). The rate of BARC type 3 or 5 bleeding events (0.7% versus 1.5%, P=0.331) was similar between the two antiplatelet regimens between 365-730 days after randomization.

Discussion

The main findings of this *post hoc* analysis of the GLOBAL LEADERS trial can be summarized as follows:

1) The concomitant presence of DM and CKD is not uncommon in an “all-comers” trial, representing 21% of the patients with DM and 5% of the overall study population.

2) Up to two years post-PCI, there was a gradient in the thrombotic and bleeding risk among patients stratified according to the presence or absence of DM or CKD, with the highest risk found among subjects having both comorbidities.

3) In patients with both DM and CKD, the primary endpoint (all-cause mortality or new Q-wave MI) or the key safety secondary endpoint (BARC type 3 or 5 bleeding) did not differ significantly between the experimental and the reference regimens. Notwithstanding, the experimental regimen was associated with lower rates of POCE and NACE, mainly driven by repeat revascularization.

Both DM and CKD are independently associated with an increased risk of cardiovascular ischemic events, which can be attributed to patients’ pro-thrombotic and pro-inflammatory status [2, 3]. These two risk factors of coronary heart disease have also been shown to synergistically amplify the hazards when they co-exist. Reports published nearly two decades ago showed that mortality rates one year after successful PCI in DM patients with moderate and severe CKD were respectively, 5- and 12-times higher when compared to patients with normal renal function [21]. A subgroup analysis of the PLATO trial -a trial conducted over a decade ago [22], showed that patients with the combination of DM and CKD had a greater than 3-fold increase in the risk of mortality [6]. In the contemporary GLOBAL LEADERS trial, we found that despite the progressive improvements in stent design and secondary preventive pharmacotherapies, patients with both DM and CKD still had a 2.5-fold higher risk of mortality, 1.6-fold higher risk of repeat revascularization, and 1.8-fold higher risk of BARC 3 or 5 bleeding, compared with patients without these risk factors. Although these results suggest that the hazards of having both comorbidities have somewhat attenuated over the years, patients with both DM and CKD were still at high risk of ischemic and bleeding events. These observations underscore the need to identify novel therapeutic approaches which can reduce the risks in this specific population.

The optimal DAPT strategy for DM+/CKD + patients remains a matter of debate owing to scarce evidence [23]. Generally, DM+/CKD + patients are at high bleeding risk. In the GLOBAL LEADERS population, 71.0% of the DM+/CKD + patients had a PRECISE-DAPT score of 25 or more, with a median score in these patients of 29. As suggested by the 2018 European Society of Cardiology guidelines on Myocardial Revascularization [1], patients with high bleeding risk should discontinue DAPT after 3- (in stable CAD) or 6-months (in ACS) post-PCI to reduce the risk of bleeding; however, DM+/CKD + patients were also at high thrombotic risk (73.4% of these patients had a Paris thrombotic risk score of > 5). Indeed, a short DAPT strategy would reduce bleeding events, but at the same time might plausibly augment the thrombotic risk [24, 25].

Considering the dilemma of DAPT duration, the strategy of ticagrelor monotherapy has been proposed as a means to reduce the risk of bleeding while maintaining a similar risk of thrombotic events after PCI. The TWILIGHT trial [8], in which either DM or CKD represented an enrichment criterion according to the protocol (2620 pts with DM and 1145 pts with CKD in the TWILIGHT trial), compared 3-month DAPT followed by 12-month ticagrelor monotherapy after PCI with standard DAPT strategy. The results showed a significant reduction of BARC type 2, 3 or 5 bleeding events in the ticagrelor monotherapy arm, while demonstrating a similar risk of the composite secondary endpoint of all-cause death, non-fatal MI, or stroke. Compared with the TWILIGHT trial, the present subgroup analysis of the GLOBAL LEADERS study (4027 pts with DM and 2170 pts with CKD), in which ticagrelor monotherapy was sustained up to 23 months, showed that compared with standard DAPT strategy, the ticagrelor monotherapy had similar BARC type 2, 3 or 5 bleeding events, meanwhile, was associated with lower rates of POCE and NACE, which were predominantly confined to reductions in any revascularization or TVR events that occurred during the second year of the trial.

There is no direct evidence showing the underlying mechanism of how ticagrelor can reduce the rate of revascularization. Nevertheless, in bench studies, ticagrelor was found to attenuate vascular dysfunction and atherogenesis through the inhibition of inflammatory activation of endothelial cells in a diabetic and hyperlipidemic mouse model [26]. In clinical observational studies, dysregulated platelet activation was found to be associated with increased wall thickness of the carotid artery, and with progressive carotid vessel wall thickening in patients with DM [27]. Platelets can also undoubtedly trigger the onset of arterial thrombosis in response to atherosclerotic plaque rupture [28]. Moreover, although an *in vitro* study reported that platelet response to aspirin did not differ by diabetes status [29], there are data suggesting a reduction in the cardioprotective benefits of aspirin in patients with diabetes [30], raising concerns about “aspirin resistance”. These observations can be attributed to a number of factors, including increased platelet turnover rates in DM patients, suggesting that alternative aspirin dosing regimens (i.e., twice daily, the ANDAMAN trial, NCT02520921) or formulations be used [31–33]. The use of ticagrelor, which is administered twice daily and also provides more effective antiplatelet effects, thus becomes a reasonable treatment option in DM patients. The recently reported THEMIS/THEMIS-PCI trial [34, 35] have demonstrated that in DM patients with stable CAD and a history of PCI, compared to aspirin, ticagrelor reduced the composite ischemic endpoint of cardiovascular death, MI, and stroke. Such benefit was enhanced among patients with a history of PCI. In summary, the reduction in repeat revascularization in DM+/CKD + patients receiving ticagrelor versus aspirin monotherapy, can be explained in part by the need for greater platelet inhibition to reduce atherogenesis, and the potential thrombotic complications in DM+/CKD + patients who are known to have high platelet reactivity [36]. Nevertheless, the findings of the current analysis should merely be interpreted as hypothesis-generating. Future dedicated trials with specific stratification and adequate sample sizes are needed to support this hypothesis.

Limitations

The following limitations have to be considered in the present analysis. 1) Given that the two antiplatelet strategies did not differ significantly with regard to rates of the primary endpoint in the overall trial [7], and the *post hoc* nature of the study, all reported analyses have to be considered strictly exploratory. 2) The randomization in the GLOBAL LEADERS trial was not stratified according to the presence of DM or CKD, therefore some imbalances between the randomized groups may exist among the four sub-categories. Although multivariable adjusted Cox proportional hazard models were performed to try to estimate the true treatment effects of the different regimens, the usual deficiency for observational studies exists, such as the inability to include all relevant confounders especially those unmeasured, causing bias which cannot be adjusted.

Conclusions

The present analysis showed that in a contemporary PCI cohort, patients with DM and CKD are at markedly increased risk of long-term thrombotic and bleeding events, compared with patients one or neither of these risk factors. In patients with both comorbidities, ticagrelor monotherapy was not associated with a lower rate of the primary endpoint (all-cause mortality or new Q-wave MI) or bleeding (BARC type 3 or 5 bleeding), but was associated with a lower rate of POCE and NACE.

List Of Abbreviations

Abbreviations	Definition
ACS	Acute coronary syndrome
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
BMI	Body mass index
CABG	Coronary artery bypass graft surgery
CAD	coronary artery disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
DAPT	Dual-antiplatelet therapy
DES	Drug Eluting Stent
DM	Diabetes Mellitus
ECG	Electrocardiogram/electrocardiography
eGFR	Estimated glomerular filtration rate
MDRD	Modification of Diet in Renal Disease
NACE	Net adverse clinical events
NSTEMI	Non-ST-segment elevation MI
PCI	Percutaneous Coronary Intervention
POCE	Patient-oriented Composite Endpoint
ST	Stent thrombosis
STEMI	ST elevation MI
TIMI	Thrombolysis In Myocardial Infarction
TLF	Target Lesion Failure
TV MI	Target vessel Myocardial Infarction
TVR	Target vessel revascularization

Declarations

Ethics approval and consent to participate

The trial was approved by the institutional review board at each center and followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent prior to participation in the trial.

Consent for publication

All authors have participated in the work and have reviewed and agree with the content of the article. None of the article contents are under consideration for publication in any other journal or have been published in any journal. No portion of the text has been copied from other material in the literature (unless in quotation marks, with citation). We are aware that it is the authors responsibility to obtain permission for any figures or tables reproduced from any prior publications, and to cover fully any costs involved. Such permission must be obtained prior to final acceptance.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

Dr. Steg received grants and personal fees from Bayer/Janssen, grants and personal fees from Merck, grants and personal fees from Sanofi, grants and personal fees from Amarin, personal fees from Amgen, personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Regeneron, personal fees from Lilly, personal fees from AstraZeneca, grants, personal fees and non-financial support from Servier, outside the submitted work. Dr. Hamm received advisory Board fees from AstraZeneca. Dr. van Geuns received

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Authors' contributions

CG, MT, KT, HK, RT, HH, MO, and DA analyzed and interpreted data, wrote the first draft of the article and contributed to all revisions. GM, SG, MH, TS, PV, RG gathered and cleaned the data. MV, SW, CH, PS, YO, PWS gathered and interpreted data and contributed to critical revision of the manuscript. All authors read and approved the final manuscript

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Tables

Table 1
Baseline Characteristics according to DM/CKD status

Characteristic	DM (-) CKD (-)	DM (+) CKD (-)	DM (-) CKD (+)	DM (+) CKD (+)
	n = 10513	n = 3189	n = 1332	n = 838
Age, years	63.0 (10.2)	65.0 (9.2)	71.5 (9.5)	71.3 (8.8)
Male	8387/10513 (79.8%)	2445/3189 (76.7%)	830/1332 (62.3%)	518/838 (61.8%)
Mean body-mass index, kg/m2	27.65 (4.3)	29.59 (5.0)	28.01 (4.5)	29.91 (5.0)
Medical history				
Insulin-dependent diabetes mellitus	0/10513 (0.0%)	869/3155 (27.3%)	0/1332 (0.0%)	352/836 (42.0%)
Hypertension	7047/10471 (67.3%)	2721/3185 (85.4%)	1118/1329 (84.1%)	770/838 (91.9%)
Hypercholesterolemia	6771/10196 (64.4%)	2421/3085 (75.9%)	879/1286 (66.0%)	634/813 (75.7%)
Current smoker	3135/10513 (29.8%)	686/3189 (21.5%)	207/1332 (15.5%)	110/838 (13.1%)
Previous stroke	209/10501 (2.0%)	120/3182 (3.8%)	48/1330 (3.6%)	44/838 (5.3%)
Previous Peripheral vascular disease	480/10433 (4.6%)	273/3158 (8.6%)	121/1317 (9.1%)	126/826 (15.0%)
Chronic obstructive pulmonary disease	485/10474 (4.6%)	179/3174 (5.6%)	86/1327 (6.5%)	69/828 (8.2%)
Previous myocardial infarction	2265/10487 (21.5%)	815/3176 (25.6%)	344/1330 (25.8%)	269/835 (32.1%)
Previous PCI	3107/10504 (29.6%)	1249/3186 (39.2%)	471/1331 (35.4%)	372/838 (44.4%)
Previous CABG	477/10506 (4.5%)	266/3185 (8.4%)	91/1331 (6.8%)	107/838 (12.8%)
Previous bleeding	59/10504 (0.6%)	18/3181 (0.6%)	15/1331 (1.1%)	6/838 (0.7%)
Clinical presentation				
Stable coronary artery disease	5298/10513 (50.4%)	1913/3189 (60.0%)	690/1332 (51.8%)	514/838 (61.3%)
Acute coronary syndrome	5215/10513 (49.6%)	1276/3189 (40.0%)	642/1332 (48.2%)	324/838 (38.7%)
Complex PCI	2976/10513 (28.3%)	934/3189 (29.3%)	377/1332 (28.3%)	263/838 (31.4%)
Multivessel PCI	2216/10513 (21.1%)	671/3189 (21.0%)	282/1332 (21.2%)	189/838 (22.6%)
Lesion treated ≥ 3	851/10513 (8.1%)	266/3189 (8.3%)	113/1332 (8.5%)	68/838 (8.1%)
Stent implanted ≥ 3	1793/10513 (17.1%)	568/3189 (17.8%)	235/1332 (17.6%)	162/838 (19.3%)
Bifurcation PCI with ≥ 2 stents	323/10513 (3.1%)	88/3189 (2.8%)	31/1332 (2.3%)	28/838 (3.3%)
Total stent length≥60 mm	1346/10513 (12.8%)	437/3189 (13.7%)	180/1332 (13.5%)	106/838 (12.7%)
Total Stent Length	35.2 (25.1)	36.0 (25.2)	35.7 (25.8)	36.3 (26.2)
Medications on discharge				
ACE-inhibition and/or ARB	6346/10450 (60.4%)	1986/3162 (62.3%)	730/1320 (54.8%)	457/826 (54.5%)
Beta-blockade	8194/10452 (77.9%)	2577/3163 (80.8%)	1069/1321 (80.3%)	669/826 (79.8%)
Statin	9718/10459 (92.4%)	2916/3168 (91.4%)	1212/1322 (91.0%)	764/827 (91.2%)
Paris bleeding risk score[37]	3 (2,4)	3 (2,4)	6 (5,7)	6 (5,7)
Paris thrombotic risk score	2 (0,4)	3 (2,4)	4 (2,7)	5 (4,7)
Paris bleeding risk score ≥ 8	100/10039 (1.0%)	41/3060 (1.3%)	269/1288 (20.9%)	189/803 (23.5%)
Paris thrombotic risk score ≥ 5	140/10506 (1.3%)	655/3185 (20.8%)	243/1331 (18.3%)	615/838 (73.4%)
PRECISE DAPT score[15]	14 (9,19)	15 (10,20)	27 (23,32)	29 (24,34)
PRECISE DAPT score ≥ 25	731/9849 (7.4%)	323/3007 (10.7%)	846/1266 (66.8%)	567/799 (71.0%)
Antiplatelet therapy				
Reference Treatment Strategy	5297/10513 (50.4%)	1575/3189 (49.4%)	662/1332 (49.7%)	410/838 (48.9%)
Experimental Treatment Strategy	5216/10513 (49.6%)	1614/3189 (50.6%)	670/1332 (50.3%)	428/838 (51.1%)

Table 2
Clinical outcomes according to DM/CKD subgroup

	DM (-) CKD (-)		DM (+) CKD (-)		DM (-) CKD (+)		DM (+) CKD (+)		P_{trend}
	n = 10513	HR 95%CI	n = 3189	HR 95%CI	n = 1332	HR 95%CI	n = 838	HR 95%CI	
All-cause mortality or New Q-wave MI	330 (3.1%)	1.00 (Ref)	148 (4.6%)	1.40 (1.15–1.72)	92 (6.9%)	1.53 (1.20–2.80)	80 (9.5%)	2.16 (1.66–2.80)	< 0.001
All-cause mortality	226 (2.1%)	1.00 (Ref)	107 (3.4%)	1.51 (1.19–1.91)	74 (5.6%)	1.67 (1.27–3.33)	67 (8%)	2.48 (1.85–3.33)	< 0.001
New Q-wave MI	108 (1%)	1.00 (Ref)	46 (1.4%)	1.30 (0.91–1.86)	19 (1.4%)	1.18 (0.71–2.29)	13 (1.6%)	1.25 (0.69–2.29)	0.259
Stroke	78 (0.7%)	1.00 (Ref)	47 (1.5%)	1.91 (1.32–2.77)	18 (1.4%)	1.18 (0.70–3.65)	19 (2.3%)	2.14 (1.26–3.65)	0.007
MI	273 (2.6%)	1.00 (Ref)	119 (3.7%)	1.44 (1.15–1.80)	52 (3.9%)	1.57 (1.15–3.42)	53 (6.3%)	2.50 (1.82–3.42)	0.001
Any Revascularization	917 (8.7%)	1.00 (Ref)	360 (11.3%)	1.26 (1.11–1.43)	129 (9.7%)	1.17 (0.96–1.92)	113 (13.5%)	1.57 (1.28–1.92)	< 0.001
TVR	466 (4.4%)	1.00 (Ref)	220 (6.9%)	1.50 (1.27–1.77)	71 (5.3%)	1.26 (0.97–2.37)	67 (8.0%)	1.81 (1.38–2.37)	< 0.001
Definite stent thrombosis	82 (0.8%)	1.00 (Ref)	27 (0.8%)	1.07 (0.68–1.67)	13 (1.0%)	1.37 (0.74–2.22)	6 (0.7%)	0.94 (0.40–2.22)	0.623
MACE	394 (3.7%)	1.00 (Ref)	187 (5.9%)	1.50 (1.25–1.80)	101 (7.6%)	1.41 (1.12–2.72)	93 (11.1%)	2.14 (1.68–2.72)	< 0.001
POCE	1242 (11.8%)	1.00 (Ref)	511 (16%)	1.32 (1.19–1.47)	219 (16.4%)	1.30 (1.12–2.14)	194 (23.2%)	1.82 (1.55–2.14)	< 0.001
NACE	1360 (12.9%)	1.00 (Ref)	548 (17.2%)	1.29 (1.17–1.43)	245 (18.4%)	1.30 (1.13–2.09)	213 (25.4%)	1.80 (1.54–2.09)	< 0.001
BARC 3 or 5 bleeding	188 (1.8%)	1.00 (Ref)	62 (1.9%)	1.07 (0.80–1.43)	44 (3.3%)	1.21 (0.86–2.53)	37 (4.4%)	1.74 (1.20–2.53)	0.008
BARC 5 bleeding	27 (0.3%)	1.00 (Ref)	6 (0.2%)	0.65 (0.26–1.60)	8 (0.6%)	1.13 (0.49–3.16)	5 (0.6%)	1.15 (0.42–3.16)	0.802
BARC 3 bleeding	173 (1.6%)	1.00 (Ref)	59 (1.9%)	1.12 (0.83–1.52)	41 (3.1%)	1.26 (0.88–2.74)	35 (4.2%)	1.86 (1.27–2.74)	0.003
BARC 3a bleeding	77 (0.7%)	1.00 (Ref)	31 (1%)	1.30 (0.85–1.99)	25 (1.9%)	1.64 (1.02–2.64)	13 (1.6%)	1.42 (0.77–2.64)	0.051
BARC 3b bleeding	74 (0.7%)	1.00 (Ref)	22 (0.7%)	1.04 (0.64–1.69)	17 (1.3%)	1.41 (0.81–3.86)	14 (1.7%)	2.11 (1.15–3.86)	0.021
BARC 3c bleeding	38 (0.4%)	1.00 (Ref)	9 (0.3%)	0.74 (0.35–1.55)	3 (0.2%)	0.36 (0.11–4.44)	10 (1.2%)	2.08 (0.98–4.44)	0.580
BARC 2 bleeding	489 (4.7%)	1.00 (Ref)	155 (4.9%)	0.97 (0.81–1.17)	82 (6.2%)	1.08 (0.84–1.49)	54 (6.4%)	1.11 (0.83–1.49)	0.478
BARC 2, 3 or 5 bleeding	647 (6.2%)	1.00 (Ref)	206 (6.5%)	0.99 (0.84–1.16)	118 (8.9%)	1.11 (0.90–1.62)	84 (10%)	1.28 (1.00-1.62)	0.064

TVR: Target vessel revascularization

MACE: all-cause death, any stroke, or non-fatal new Q-wave MI

POCE: all-cause death, any stroke, any myocardial infarction or any revascularization

NACE: POCE and BARC 3 or 5 bleeding

Table 3 Forest plot of the endpoints according to treatment regimen and DM/CKD status

	DM/CKD group	Experimental Treatment	Reference Treatment	Hazard ratio (95% CI)	P value	P_{Trend}
All-cause mortality or New Q-wave MI	DM(-) CKD (-)	158/5216 (3.0%)	172/5297 (3.3%)	0.95 (0.76-1.18)	0.645	0.337
	DM(+) CKD(-)	66/1614 (4.1%)	82/1575 (5.2%)	0.78 (0.56-1.1)	0.155	
	DM(-) CKD (+)	43/670 (6.4%)	49/662 (7.4%)	0.85 (0.56-1.28)	0.431	
	DM(+) CKD (+)	36/428 (8.4%)	44/410 (10.7%)	0.75 (0.47-1.18)	0.206	
All-cause mortality	DM(-) CKD (-)	112/5216 (2.1%)	114/5297 (2.2%)	1.05 (0.81-1.38)	0.700	0.097
	DM(+) CKD(-)	49/1614 (3.0%)	58/1575 (3.7%)	0.84 (0.57-1.24)	0.387	
	DM(-) CKD (+)	32/670 (4.8%)	42/662 (6.3%)	0.74 (0.46-1.19)	0.219	
	DM(+) CKD (+)	30/428 (7.0%)	37/410 (9.0%)	0.72 (0.44-1.19)	0.199	
Myocardial infarction	DM(-) CKD (-)	130/5216 (2.49%)	143/5297 (2.7%)	0.93 (0.73-1.19)	0.561	0.496
	DM(+) CKD(-)	64/1614 (3.97%)	55/1575 (3.49%)	1.19 (0.82-1.73)	0.367	
	DM(-) CKD (+)	28/670 (4.18%)	24/662 (3.63%)	1.11 (0.62-1.96)	0.73	
	DM(+) CKD (+)	26/428 (6.07%)	27/410 (6.59%)	1.05 (0.6-1.84)	0.861	
All Revascularization	DM(-) CKD (-)	439/5216 (8.4%)	478/5297 (9.0%)	0.97 (0.85-1.11)	0.689	0.286
	DM(+) CKD(-)	176/1614 (10.9%)	184/1575 (11.7%)	0.96 (0.77-1.19)	0.694	
	DM(-) CKD (+)	66/670 (9.9%)	63/662 (9.5%)	1.04 (0.73-1.49)	0.831	
	DM(+) CKD (+)	49/428 (11.5%)	64/410 (15.6%)	0.67 (0.45-0.99)	0.042	
Target vessel Revascularization	DM(-) CKD (-)	215/5216 (4.1%)	251/5297 (4.7%)	0.9 (0.75-1.09)	0.27	0.238
	DM(+) CKD(-)	110/1614 (6.8%)	110/1575 (7%)	1.03 (0.78-1.35)	0.839	
	DM(-) CKD (+)	33/670 (4.9%)	38/662 (5.7%)	0.86 (0.53-1.39)	0.527	
	DM(+) CKD (+)	26/428 (6.1%)	41/410 (10%)	0.56 (0.33-0.93)	0.026	
BARC type 3 or 5 bleeding	DM(-) CKD (-)	86/5216 (1.7%)	102/5297 (1.9%)	0.91 (0.68-1.22)	0.536	0.562
	DM(+) CKD(-)	34/1614 (2.1%)	28/1575 (1.8%)	1.15 (0.69-1.91)	0.592	
	DM(-) CKD (+)	25/670 (3.7%)	19/662 (2.9%)	1.45 (0.79-2.68)	0.230	
	DM(+) CKD (+)	18/428 (4.2%)	19/410 (4.6%)	0.86 (0.45-1.64)	0.641	
BARC type 2 bleeding	DM(-) CKD (-)	236/5216 (4.5%)	253/5297 (4.8%)	0.95 (0.8-1.14)	0.605	0.258
	DM(+) CKD(-)	83/1614 (5.1%)	72/1575 (4.6%)	1.18 (0.85-1.62)	0.319	
	DM(-) CKD (+)	42/670 (6.3%)	40/662 (6.0%)	1.08 (0.69-1.7)	0.724	
	DM(+) CKD (+)	31/428 (7.2%)	23/410 (5.6%)	1.21 (0.69-2.12)	0.503	
BARC type 2, 3 or 5 bleeding	DM(-) CKD (-)	310/5216 (5.9%)	337/5297 (6.4%)	0.95 (0.82-1.12)	0.558	0.386
	DM(+) CKD(-)	112/1614 (6.9%)	94/1575 (6.0%)	1.19 (0.9-1.58)	0.214	
	DM(-) CKD (+)	62/670 (9.3%)	56/662 (8.5%)	1.16 (0.8-1.68)	0.421	
	DM(+) CKD (+)	44/428 (10.3%)	40/410 (9.8%)	0.98 (0.63-1.51)	0.917	
POCE - all-cause death, any stroke, any myocardial infarction or any revascularization	DM(-) CKD (-)	598/5216 (11.5%)	644/5297 (12.2%)	0.98 (0.88-1.1)	0.749	0.155
	DM(+) CKD(-)	248/1614 (15.4%)	263/1575 (16.7%)	0.94 (0.78-1.12)	0.475	
	DM(-) CKD (+)	106/670 (15.8%)	113/662 (17.1%)	0.94 (0.71-1.23)	0.651	
	DM(+) CKD (+)	88/428 (20.6%)	106/410 (25.9%)	0.74 (0.55-0.99)	0.043	
NACE- POCE and BARC 3 or 5 bleeding	DM(-) CKD (-)	649/5216 (12.4%)	711/5297 (13.4%)	0.96 (0.86-1.07)	0.498	0.310
	DM(+) CKD(-)	267/1614 (16.5%)	281/1575 (17.8%)	0.94 (0.79-1.12)	0.474	
	DM(-) CKD (+)	122/670 (18.2%)	123/662 (18.6%)	1.02 (0.79-1.32)	0.900	
	DM(+) CKD (+)	97/428 (22.7%)	116/410 (28.3%)	0.75 (0.56-0.99)	0.044	

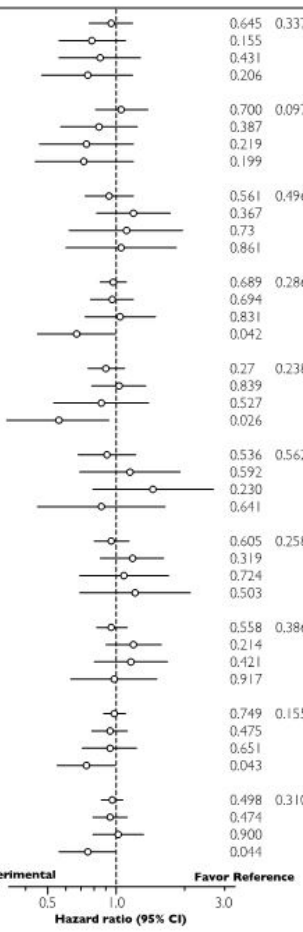
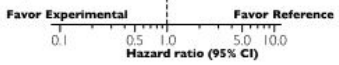


Table 4 Forest plot of the endpoints by landmark analyses (365-730 days)

Lankmark analysis from 365-730 days	DM/CKD group	Experimental Treatment	Reference Treatment	Hazard ratio (95% CI)	P value	P_{trend}
All-cause mortality or New Q-wave MI	DM (-) CKD (-)	70/5216 (1.3%)	72/5297 (1.4%)	1.00 (0.72-1.40)	0.985	0.726
	DM (+) CKD (-)	36/1614 (2.2%)	41/1575 (2.6%)	0.84 (0.52-1.33)	0.450	
	DM (-) CKD (+)	24/670 (3.6%)	19/662 (2.9%)	1.19 (0.63-2.21)	0.594	
	DM (+) CKD (+)	17/428 (4.0%)	20/410 (4.9%)	0.77 (0.39-1.50)	0.438	
All-cause mortality	DM (-) CKD (-)	54/5216 (1.0%)	54/5297 (1.0%)	1.02 (0.69-1.49)	0.933	0.373
	DM (+) CKD (-)	31/1614 (1.9%)	33/1575 (2.1%)	0.98 (0.59-1.62)	0.926	
	DM (-) CKD (+)	15/670 (2.2%)	18/662 (2.7%)	0.77 (0.38-1.58)	0.478	
	DM (+) CKD (+)	15/428 (3.5%)	17/410 (4.1%)	0.75 (0.37-1.55)	0.441	
Myocardial Infarction	DM (-) CKD (-)	34/5216 (0.7%)	51/5297 (1.0%)	0.70 (0.44-1.10)	0.124	0.812
	DM (+) CKD (-)	20/1614 (1.2%)	17/1575 (1.1%)	1.30 (0.66-2.55)	0.444	
	DM (-) CKD (+)	11/670 (1.6%)	12/662 (1.8%)	0.80 (0.34-1.90)	0.614	
	DM (+) CKD (+)	4/428 (0.9%)	12/410 (2.9%)	0.34 (0.10-1.11)	0.074	
All revascularization	DM (-) CKD (-)	133/5216 (2.5%)	140/5297 (2.6%)	1.01 (0.79-1.29)	0.949	0.056
	DM (+) CKD (-)	56/1614 (3.5%)	59/1575 (3.7%)	0.95 (0.66-1.39)	0.807	
	DM (-) CKD (+)	21/670 (3.1%)	16/662 (2.4%)	1.41 (0.71-2.79)	0.323	
	DM (+) CKD (+)	10/428 (2.3%)	27/410 (6.6%)	0.29 (0.13-0.65)	0.003	
Target vessel Revascularization	DM (-) CKD (-)	71/5216 (1.4%)	79/5297 (1.5%)	0.93 (0.67-1.29)	0.658	0.122
	DM (+) CKD (-)	37/1614 (2.3%)	33/1575 (2.1%)	1.20 (0.74-1.95)	0.452	
	DM (-) CKD (+)	6/670 (0.9%)	12/662 (1.8%)	0.49 (0.17-1.36)	0.171	
	DM (+) CKD (+)	6/428 (1.4%)	12/410 (2.9%)	0.29 (0.09-0.91)	0.033	
BARC 3 or 5	DM (-) CKD (-)	27/5216 (0.5%)	16/5297 (0.3%)	1.89 (1.01-3.57)	0.048	0.150
	DM (+) CKD (-)	10/1614 (0.6%)	6/1575 (0.4%)	1.74 (0.62-4.86)	0.291	
	DM (-) CKD (+)	8/670 (1.2%)	5/662 (0.8%)	1.77 (0.56-5.54)	0.328	
	DM (+) CKD (+)	3/428 (0.7%)	6/410 (1.5%)	0.48 (0.12-1.97)	0.311	
BARC 2	DM (-) CKD (-)	59/5216 (1.1%)	41/5297 (0.8%)	1.44 (0.96-2.15)	0.075	0.568
	DM (+) CKD (-)	21/1614 (1.3%)	18/1575 (1.1%)	1.33 (0.69-2.55)	0.394	
	DM (-) CKD (+)	7/670 (1.0%)	6/662 (0.9%)	1.10 (0.37-3.30)	0.864	
	DM (+) CKD (+)	9/428 (2.1%)	3/410 (0.7%)	2.62 (0.70-9.89)	0.154	
BARC 2, 3, or 5	DM (-) CKD (-)	310/5216 (5.9%)	337/5297 (6.4%)	0.95 (0.82-1.12)	0.558	0.386
	DM (+) CKD (-)	112/1614 (6.9%)	94/1575 (6.0%)	1.19 (0.90-1.58)	0.214	
	DM (-) CKD (+)	62/670 (9.3%)	56/662 (8.5%)	1.16 (0.80-1.68)	0.421	
	DM (+) CKD (+)	44/428 (10.3%)	40/410 (9.8%)	0.98 (0.63-1.51)	0.917	
POCE - all-cause death, any stroke, any myocardial infarction or any revascularization	DM (-) CKD (-)	201/5216 (3.9%)	210/5297 (4.0%)	1.00 (0.82-1.22)	0.969	0.040
	DM (+) CKD (-)	90/1614 (5.6%)	92/1575 (5.8%)	0.98 (0.73-1.32)	0.904	
	DM (-) CKD (+)	34/670 (5.1%)	37/662 (5.6%)	0.92 (0.57-1.49)	0.744	
	DM (+) CKD (+)	25/428 (5.8%)	45/410 (11.0%)	0.49 (0.29-0.82)	0.007	
NACE- POCE and BARC 3 or 5 bleeding	DM (-) CKD (-)	215/5216 (4.1%)	211/5297 (4.0%)	1.07 (0.88-1.30)	0.526	0.013
	DM (+) CKD (-)	92/1614 (5.7%)	94/1575 (6.0%)	1.00 (0.74-1.34)	0.981	
	DM (-) CKD (+)	35/670 (5.2%)	39/662 (5.9%)	0.91 (0.57-1.45)	0.680	
	DM (+) CKD (+)	25/428 (5.8%)	46/410 (11.2%)	0.48 (0.29-0.82)	0.007	



Figures

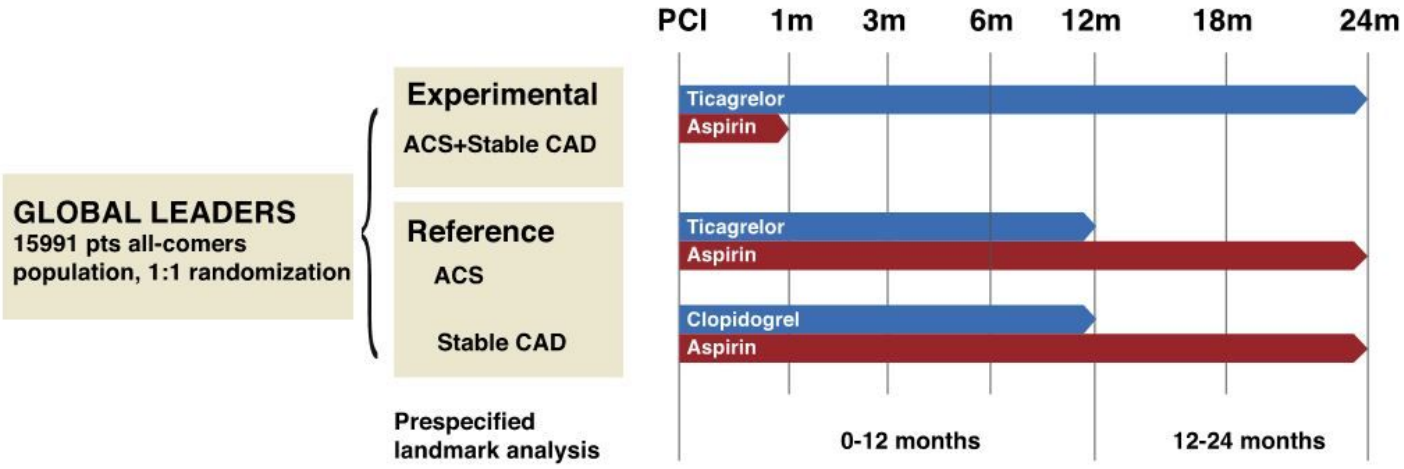


Figure 1

Illustration of the antiplatelet strategy in the GLOBAL LEADERS trial

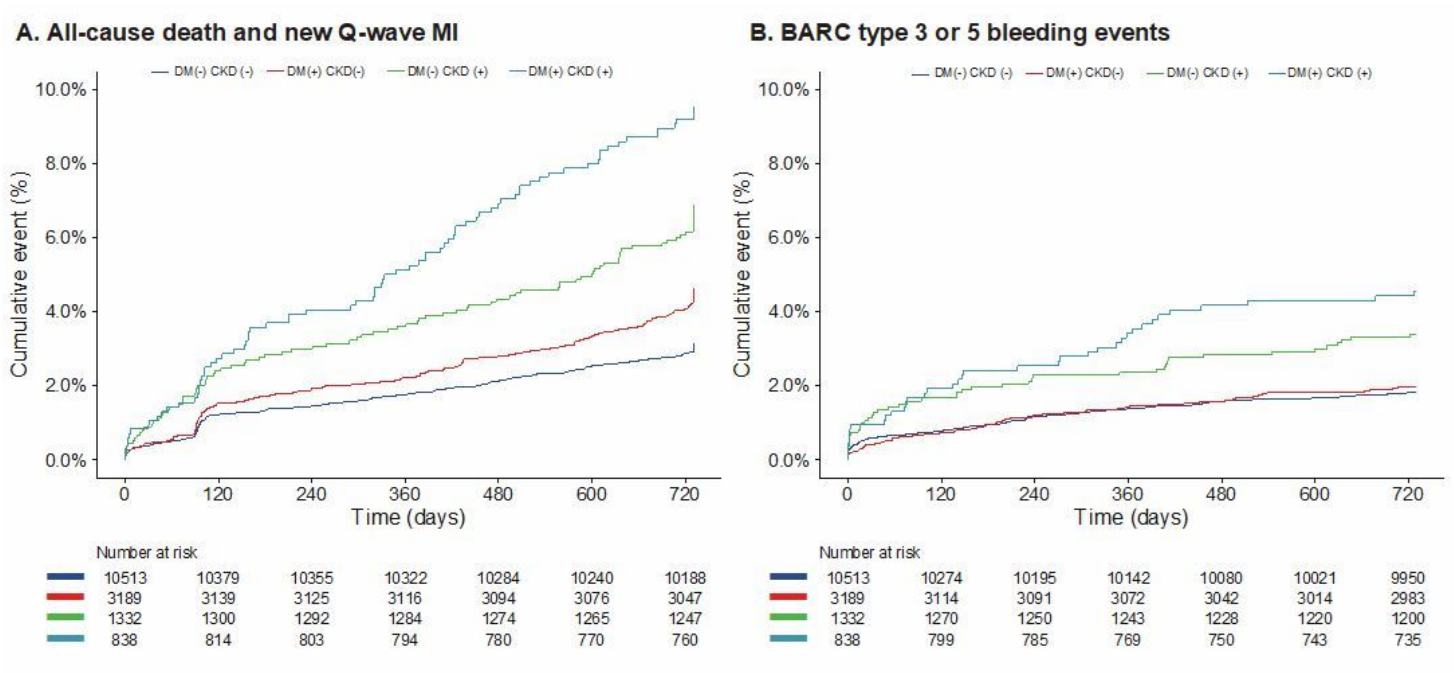


Figure 2

Clinical events shown by Kaplan-Meier curves A. All-cause mortality and new Q-wave MI; B. Bleeding Academic Research Consortium (BARC)–defined type 3 or 5 bleeding events;

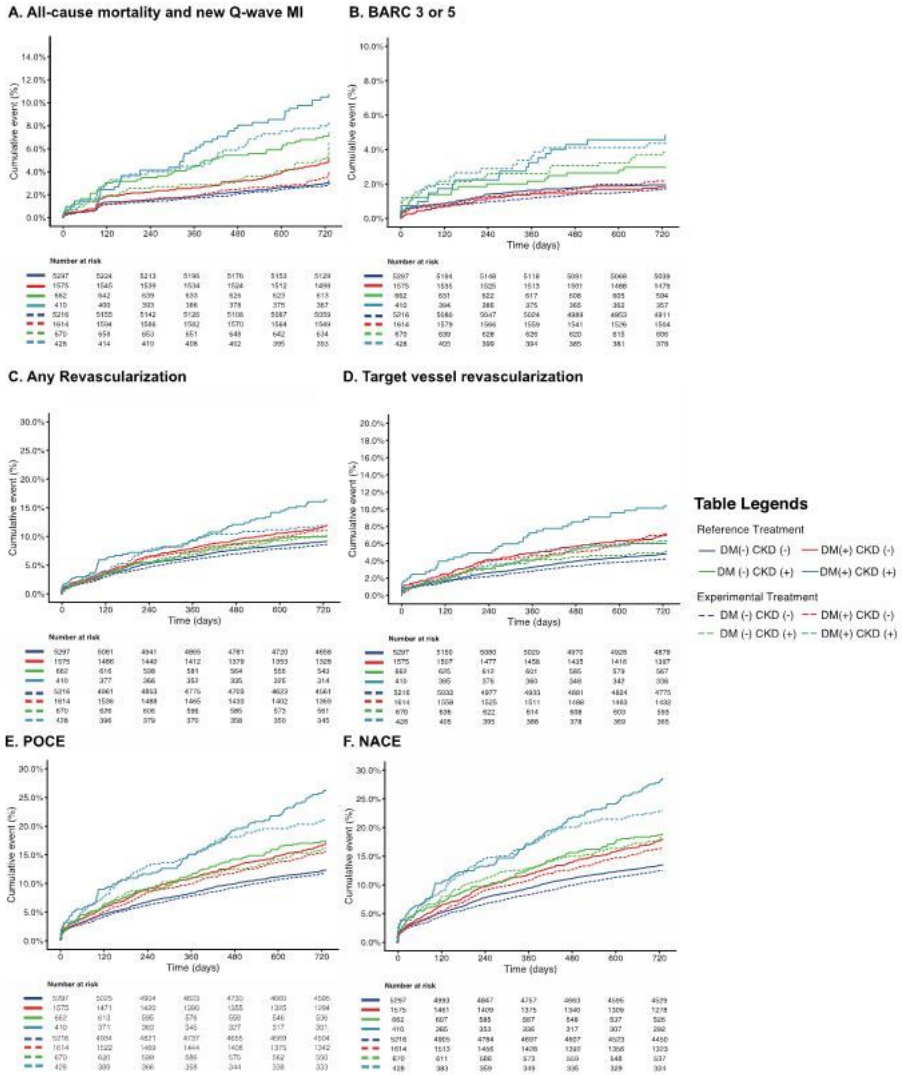


Figure 3

Kaplan-Meier curves showing the clinical events according to treatment regimen and DM/CKD status A. All-cause mortality and new Q-wave MI; B. Bleeding Academic Research Consortium (BARC)–defined type 3 or 5 bleeding events; C. Any revascularization; D. Target vessel revascularization; E. POCE; F. NACE;

Supplementary Files

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- SUPPLEMENTALMATERIAL.docx