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Outcomes with prolonged clopidogrel therapy after coronary stenting in patients with chronic kidney disease

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Abstract

Objectives—Patients with chronic kidney disease (CKD) are at high risk of death or myocardial infarction (MI) after percutaneous coronary interventions (PCI). We assessed whether prolonged dual antiplatelet therapy beyond the recommended 12 months may prevent adverse outcomes in patients with CKD receiving drug-eluting stents (DES) or bare-metal stents (BMS).

Methods—We studied all Veterans receiving PCI with BMS or first-generation DES in the Veterans Affairs (VA) Healthcare System between 2002 and 2006, classified by CKD (estimated glomerular filtration rate <60 mL/min) or normal renal function. We used landmark analyses from 12 months after PCI with Cox proportional hazards multivariable and propensity-adjusted models to assess the effect of prolonged clopidogrel (more than 12 months) versus 12 months or less after PCI on clinical outcomes from 1 year to 4 years after PCI.

Results—Of 23 042 eligible subjects receiving PCI, 4880 (21%) had CKD. Compared with normal renal function, patients with CKD had higher risks of death or MI 1–4 years after DES

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Supplementary Material

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(21% vs 12%, HR=1.75; 95% CI 1.51 to 2.04) or BMS (28% vs 15%, HR=2.10; 95% CI 1.90 to 2.32). In patients with CKD receiving DES, clopidogrel use of more than 12 months after PCI was associated with lower risks of death or MI (18% vs 24%, HR=0.74; 95% CI 0.58 to 0.95), and death (15% vs 23%, HR=0.61; 95% CI 0.47 to 0.80), but had no effect on repeat revascularisation 1–4 years after PCI.

Conclusions—In patients with CKD, prolonging clopidogrel beyond 12 months after PCI may decrease the risk of death or MI only in patients receiving first-generation DES. These results support a patient-tailored approach to prolonging clopidogrel after PCI.

INTRODUCTION

Patients with chronic kidney disease (CKD) have higher mortality and myocardial infarction (MI) in the 1–2 years after percutaneous coronary intervention (PCI) than patients without CKD.^{1–10} Current guidelines recommend dual antiplatelet therapy with aspirin and a P₂Y₁₂ inhibitor for at least 1 year after PCI, regardless of CKD, to reduce stent thrombosis, MI and death. Prolonging clopidogrel beyond the recommended 1 year may reduce the risk of ischaemic events in patients, but could increase the risk of serious bleeding, suggested by some²⁸¹¹¹² but not all studies.¹⁰¹³¹⁴ In prior small randomised studies, CKD was not reported or occurred in only one to seven per cent of subjects.^{15–19} The benefits and risks of prolonging clopidogrel in patients with CKD are unknown.

METHODS

Patient population

We identified all patients who received coronary stents at any Veterans Affairs (VA) facility in the USA between April 2002 and September 2006²⁰ and who were alive 12 months after their index PCI. We used the International Classification of Diseases-9 (ICD-9) procedure codes for coronary artery stent placement (36.06 for bare-metal stent (BMS) and 36.07 for drug-eluting stent (DES)) to identify patients. During this time frame, only first-generation DES were available. The index procedure was defined as the first coronary artery stent procedure between 2002 and 2006. Of 42 254 patients receiving coronary stents, 2930 (7%) died within 12 months of their index PCI (figure 1). We excluded another 16 282 patients as outlined in figure 1. Subjects free of the clinical outcomes at 1 year were followed to 1 September 2007 with a maximum follow-up of 4 years after their index PCI.

Demographic data

Data collected at the index procedure included the subject's age, sex, race and MI at the time of the index PCI. Chronic comorbidities were defined by ICD-9 code present between 5 years before the index PCI and up to 12 months after the index PCI (the 1 year landmark). These included diabetes mellitus (ICD-9: 250), smoking (ICD-9: 305.1), hypertension (ICD-9: 401), congestive heart failure (ICD-9: 428), prior stroke (ICD-9: 433.01, 433.11, 434.91, 436, V1254), peripheral vascular disease (ICD-9: 443), chronic obstructive lung disease (ICD-9: 496) and anaemia (ICD-9: 281–285). Comorbidities for prior coronary revascularisation (PCI: ICD-9: 36.01–2, 36.05–7, 00.66, or coronary bypass surgery (coronary artery bypass grafts, CABG): ICD-9: 36.1), were defined as those present between

1 year and 5 years prior to the index PCI, as we excluded subjects with these events in the 1 year prior to their index PCI.

Renal function and CKD

We defined CKD by estimating the subject's glomerular filtration rate (eGFR) from the serum creatine immediately prior to the index PCI (up to 14 days prior to the index PCI), race and gender using the modification of diet in renal disease equation.²¹ We divided the cohort into subjects with normal renal function (eGFR $\geq$ 60 mL/min) or CKD (eGFR <60 mL/min). CKD was not further divided due to the small number of subjects with eGFR <30 mL/min. If race was unknown, the eGFR was imputed as a weighted average, using the proportion of blacks in the population. Since recent studies suggest that the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation is more precise in estimating renal function,²² we also reclassified CKD based on the CKD-Epi formula in a sensitivity analysis.

Medication use

The VA National Pharmacy Database provided medications used at the index PCI, and use of clopidogrel over the follow-up period. Since VA prescriptions are usually written for 90-day time periods, we defined baseline cardiovascular medications as prescriptions filled within 90 days before the index procedure to up to 7 days after the index procedure. Aspirin use is a VA quality control measure and other studies show very high rates of outpatient aspirin use in VA patients with coronary artery disease.²³ The database tracks the dates of prescription, the amount and delivery of clopidogrel up to 4 years after their index PCI. If a clopidogrel prescription lapsed >30 days from the last day of supply, the patient was considered to be not taking clopidogrel. We defined clopidogrel use as either prolonged (>12 months of use after the index PCI) or $\leq$ 12 months of use after the index PCI.

Outcomes

Clinical outcomes after the index PCI were identified from the VA National Patient Care and VA Death Databases and the Centers for Medicare and Medicaid Services (CMS)/Medicare database using ICD-9 codes through September 2007. The primary outcome was the combined outcome of death or acute MI (ICD-9: 410). Secondary outcomes included death, revascularisation by PCI (ICD-9: 36.01, 36.02, 36.05, 00.66) or by CABG (ICD-9: 36.1), ischaemic stroke (ICD-9: 436, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91) and hospitalisation for disabling or life-threatening bleeding (ICD-9: 569.3, 530.82, 578, 535.01–535.61, 430–432, 379.23, 459).

Statistical analysis

Since prior studies indicated an increased risk of adverse events in subjects with CKD, and different outcomes in patients with DES versus BMS, we prospectively stratified the analyses by CKD and stent type. We used event curves and landmark analyses to analyse outcomes in subjects who were free of the outcome 12 months after index PCI. Patients were followed until they died or had the outcome of interest. Follow-up was censored after September 2007, 12 months after the last recorded VA visit, or 4 years after the index

procedure. We calculated the HRs and 95% CIs for prolonged clopidogrel use versus clopidogrel 12 months for each outcome within each stent and CKD subgroup using Cox proportional hazards regression and robust SEs. Multivariable models were developed from >50 variables and included if they were related to the outcome of interest. The hazards from final multivariable models were adjusted for baseline characteristics related to outcomes including age, diabetes mellitus, hypertension, smoking, prior MI, peripheral vascular disease, congestive heart failure, warfarin use within 7 days of the index procedure and year of stent placement. We also used Cox models to assess stent type by prolonged clopidogrel interactions within each group of CKD or normal renal function. We used a second method of adjustment for confounders by constructing propensity models for prolonged clopidogrel from statistically significant baseline characteristics using multivariable logistic regression²⁰ (see online supplementary appendix). We estimated HRs for each outcome using inverse probability weighting of the propensity score in the Cox proportional hazards models. While there were some covariates that violated the assumption of proportionality of hazards, they did not change the estimates of the main effects or conclusions. We also performed a sensitivity analysis to assess the robustness of our results using the CKD-Epi formula to estimate eGFR. All analyses used SAS v 9.2 statistical software. Since we stratified the analysis by the two stent types, statistical significance for the primary end point of death or MI was $p<0.025$.

RESULTS

After exclusions, 23 042 patients receiving BMS or DES between April 2002 and September 2006 were included for analysis (figure 1). DES were deployed in 11 455 subjects and 11 587 received a BMS. CKD occurred in 2297 (20%) subjects receiving DES and 2583 (22%) subjects receiving BMS. Table 1 lists the baseline characteristics at the index PCI for subjects receiving DES, grouped by CKD and clopidogrel use beyond 12 months. Table 2 lists baseline characteristics for subjects receiving BMS. In both stent types, patients with CKD had higher rates of diabetes mellitus, peripheral vascular disease, anaemia, stroke and heart failure, and lower rates of smoking.

Events in the CKD group and normal renal function between the index procedure and 1 year were respectively 250 (5.9%) and 754 (4.5%) with MI, 590 (14%) and 2190 (13%) with repeat revascularisation by CABG or PCI, 33 (0.7%) and 54 (0.3%) stroke, and 73 (1.7%) and 137 (0.8%) major bleeding. For patients receiving DES, the mean durations of clopidogrel use for patients in the >12 months versus 12 months clopidogrel groups were: 17.9 months vs 6.1 months for CKD and 17.1 months vs 6.2 months for normal renal function. For patients receiving BMS, the mean durations of clopidogrel use for patients in the >12 months versus 12 months clopidogrel groups were: 22.1 months vs 2.5 months for CKD and 21.0 months vs 2.7 months for normal renal function.

Risk of outcomes with CKD versus normal renal function

Among patients alive at 12 months, CKD associated with a higher risk of subsequent death or MI for DES (21% vs 12%, HR=1.75; 95%CI 1.51 to 2.04) and BMS (28% vs 15%, HR=2.10; 95% CI 1.90 to 2.32). CKD associated with a higher risk of death among patients

receiving DES (18% vs 8%, HR=2.33; 95% CI 1.97 to 2.75) and BMS (23% vs 10%, HR=2.47; 95% CI 2.21 to 2.76), and a higher risk of disabling or life-threatening bleeding for DES (4% vs 2%, HR=1.87; 95% CI 1.26 to 2.76) and BMS (4% vs 2%, HR=1.79; 95% CI 1.36 to 2.35).

Univariate risk associated with prolonged clopidogrel use

Figure 2 shows event curves for the outcomes of death, and death or MI for subjects receiving DES and BMS, stratified by CKD and prolonged clopidogrel use. The curves start at the landmark 12 months after the index PCI. Among patients with CKD, prolonged clopidogrel associated with a lower risk of death (15% vs 23%), and death or MI (18% vs 24%) for patients receiving DES (figure 2B, D), but not BMS (death: 23% vs 23%, death or MI: 27% vs 28%, figure 2A, C). In patients without CKD, prolonged clopidogrel >12 months associated with a lower risk of death or MI for both stent types (DES: 11% vs 14%, BMS: 13% vs 15%, figure 2A–D). The absolute difference in risk for prolonged clopidogrel was greater in patients with CKD receiving DES (6% vs 1%).

Table 3 shows the crude HRs for prolonged clopidogrel for each end point stratified by CKD and stent type. Among subjects with CKD, prolonged clopidogrel (>12 months) associated with a relative 25–40% lower risk of death, and death or MI, in subjects who received DES, but not in those receiving BMS. Among patients without CKD, the HRs were similar for each stent type and prolonged clopidogrel associated with a 20% lower risk of death, and death or MI. Prolonged clopidogrel did not relate to the risk of revascularisation or stroke in patients with or without CKD. The numbers of subjects with hospitalisation for disabling or life-threatening bleeding were small, but this analysis indicated no increased risk of serious bleeding with prolonged clopidogrel in subjects with CKD receiving DES.

Adjusted analysis

Table 3 shows the HRs for prolonged clopidogrel use from multivariable models and from propensity adjusted models. The adjusted HRs for prolonged clopidogrel in subjects with CKD were very similar to the univariate analysis, suggesting that these estimates are robust to the known confounders included in these multivariable models.

Models with interaction effects

Among subjects with CKD there was a significant interaction between prolonged clopidogrel and stent type, whereby prolonged clopidogrel had a significantly greater effect on lower risk of death for DES compared with BMS (interaction $p=0.005$). There was a borderline interaction effect for prolonged clopidogrel and stent type for death or MI (interaction $p=0.13$). None of the interaction terms were statistically significant for subjects with normal renal function ($eGFR \geq 60$). There were no significant CKD-by-prolonged clopidogrel interactions (all $p>0.50$).

Sensitivity analysis

In a sensitivity analysis using the CKD-Epi formula to estimate $eGFR$, 440 subjects were reclassified as CKD in the DES group (total 2737 (24%) subjects with CKD), and 456 subjects were reclassified as CKD in the BMS group (total 3039 (26%) subjects with CKD).

Table 4 lists the HRs for the outcomes, with similar conclusions to the analysis using the modification of diet in renal disease formula for eGFR. Other models assessing bleeding risk after excluding patients on warfarin at baseline showed no substantial differences in bleeding risk with prolonged clopidogrel (all $p>0.05$).

DISCUSSION

Patients with CKD have poorer outcomes inhospital and in the year after PCI.^{1–10} Our study shows a higher risk of death, death or MI, and disabling or life-threatening bleeding compared with patients with normal renal function even after excluding events in the 1st year after PCI. This risk remains high up to 4 years after the index PCI. Although the second generation DES may improve these outcomes,²⁴ there are large numbers of patients with CKD who have received first generation DES and BMS and are beyond the 12-month window recommended for dual-antiplatelet therapy.

The five relatively small randomised trials of clopidogrel duration after coronary stenting did not address patients with CKD who face much higher risks of death and MI.^{15–19} Four studies assessed 12 month versus shorter duration clopidogrel therapy on outcomes predominately up to 1 year after stenting.^{15–17,19} These studies had few cardiovascular end points to conclusively assess the value of prolonged clopidogrel. In the much larger Dual Antiplatelet Study of 9961 patients receiving DES, prolonged clopidogrel therapy (for 30 months vs 12 months) associated with less cardiovascular events over 3 years.²⁵ However, all of the randomised trials enrolled a small proportion of patients with CKD. Our study had over five times the number of patients with CKD receiving DES as the Dual Antiplatelet Study, and included another 2583 patients with CKD receiving BMS.

Our study explored whether prolonging clopidogrel beyond the standard guidelines of 12 months after PCI may help to reduce this long-term increased risk in patients with CKD. We only addressed this question in the clinically relevant situation of patients who were free of events in the first 12 months after their index PCI. Our study shows that, among patients with CKD, continuing clopidogrel more than 12 months after the PCI is associated with lower risks of death, and death or MI only with DES. There was no significant benefit of prolonged therapy in patients with CKD receiving BMS. This effect of stent type in CKD is supported by the significant interaction term and striking difference in absolute risk (figure 2).

In contrast, among patients without CKD, prolonged clopidogrel had similar lower relative risks of death, and death or MI with both stent types. Notably the magnitude of absolute risk difference related to prolonged clopidogrel was less than patients with CKD receiving DES.

These comparisons highlight the importance of considering renal function as well as stent type in the decision to continue clopidogrel in patients who have reached the 12-month landmark without major ischaemic or bleeding events.

Events and very late stent thrombosis and target vessel revascularisation

The mechanisms of benefit from prolonged clopidogrel may differ in patients with CKD compared with those without CKD. Death or MI are related to progression of coronary disease and plaque disruption beyond the stented segment, or to restenosis or thrombosis within a stent. If prolonged clopidogrel predominantly prevented plaque disruption beyond the stented segment, the reduction in ischaemic events should be similar in DES and BMS. However, if the major effect is on very late stent thrombosis, there may be differences in the reduction of ischaemic events between stent types with prolonged clopidogrel. Short-term studies of up to 1 year after PCI suggest stent thrombosis is higher in patients with CKD with DES, in some^{426–28} but not all studies.²⁹³⁰ Our results suggest that the mechanism of less ischaemic events with prolonged clopidogrel differs in patients with CKD (greater effects on very late stent thrombosis) and those without CKD (greater effects on plaque disruption beyond the stent).

Disabling and life-threatening bleeding

CKD itself was associated with a higher risk of disabling and life-threatening bleeding beyond the 12-month landmark. However, prolonged clopidogrel did not increase this risk further in this group of patients or in those with normal renal function. Few studies have systematically evaluated the risk of bleeding with dual-antiplatelet therapy in patients with CKD as these patients are often excluded from randomised trials. Patients with CKD had higher rates of bleeding up to 1 year after PCI with DES in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial of patients with stable angina and a meta-analysis of acute coronary syndromes.¹²¹⁴ However, in the CathPCI registry of 121 446 patients with CKD, major bleeding up to 12 months after PCI was no higher with DES (and longer clopidogrel use) compared with BMS.¹⁰

It is important to recognise that many patients at risk of serious or life-threatening bleeding may have had an event within the 1st year after their stent and been excluded from our analysis. Thus our study reflects patients who have tolerated 12 months of clopidogrel without serious bleeding and are likely to be at lower risk of subsequent bleeding with continued clopidogrel. This may explain why our cohort had a low number of serious and life-threatening bleeds.

Limitations

This study draws data from several administrative databases, and therefore known and unknown confounders could influence the results. However, we did use several methods to adjust our analyses for known confounders including multivariable and propensity score models. Our results were consistent across these models and in an analysis with the newer, more accurate, CKD-Epi method of calculating eGFR. We used a single imputation method for missing race by assuming a race-mix proportional to the majority of subjects with known race. The impact of this method is likely minimal as an assumption that all missing race subjects were black versus all were white reclassified the eGFR category of only 73 (0.3%) and 33 (0.1%) subjects, respectively—an effect much smaller than our sensitivity analysis. Although our study includes one of the largest samples of patients with CKD receiving PCI, we had too few patients with an eGFR <30 mL/min to assess differences between more and

less severe degrees of CKD. Our study did not include later generation DES, and more powerful thienopyridine inhibitors.

CONCLUSION

Our study showed that in patients with CKD who are free of major cardiovascular or bleeding events in the 1st year after coronary stenting, continuing clopidogrel was beneficial only for those receiving DES. There was no benefit in patients with CKD receiving BMS. In patients without CKD, prolonged clopidogrel had a similar, although smaller absolute risk reduction for patients receiving either stent type. These results suggest a patient-tailored approach to prolonging clopidogrel and should be tested in ongoing large randomised trials of clopidogrel duration.²⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

What is already known on this subject?

Continuing dual antiplatelet therapy with clopidogrel and aspirin more than 1 year after percutaneous coronary intervention (PCI) may reduce major adverse events. However, the balance of risk in patients with chronic kidney disease (CKD) who are at higher risk of ischaemic events and bleeding is unknown.

What might this study add?

In patients with CKD, continuing dual antiplatelet therapy more than 12 months associated with a lower risk of death or myocardial infarction (18% vs 24%, HR=0.74; 95% CI 0.58 to 0.95) only in patients receiving drug-eluting stents.

How might this impact on clinical practice?

This suggests a patient tailored approach to continuing dual antiplatelet therapy, whereby dual antiplatelet therapy is only considered in patients with CKD receiving drug-eluting stents.

Figure 1.

Study population with exclusion criteria. DES, Drug-eluting stent; BMS, Bare-metal stent; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; VA, Veterans Affairs; eGFR, estimated glomerular filtration rate; Clopid, clopidogrel.

Figure 2.

Event curves for incidence of death (A and B), and death or myocardial infarction (C and D), from the 12-month landmark after the index PCI. Graphs are by each stent type, with event curves for each CKD and clopidogrel duration group. CKD, chronic kidney disease; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate.

Table 1

Baseline characteristics in subjects receiving drug-eluting stents

Characteristic	eGFR ≥60 Clopidogrel use		eGFR<60 Clopidogrel use	
	12 months	>12 months	12 months	>12 months
Age, mean (SD), years	63.1 (9.9)	63.2 (9.2)	70.7 (9.8)	70.3 (9.6)
Men, n (%)	3928 (98.6)	5099 (98.5)	951 (96.7)	1287 (98.0)
Race, n (%)				
White	3086 (77.5)	4219 (81.5)	826 (84.0)	1160 (88.3)
Black	510 (12.8)	523 (10.1)	98 (10.0)	73 (5.6)
Other	32 (0.8)	25 (0.5)	4 (0.4)	9 (0.7)
Unknown	355 (8.9)	408 (7.9)	55 (5.6)	72 (5.5)
ACS (during index admission), n (%)	2382 (59.8)	3171 (61.3)	599 (60.9)	811 (61.7)
Comorbidities 5 years prior to 1 year after index PCI, n (%)				
Current smoking	1794 (45.0)	2192(42.4)	255 (26.0)	355 (27.0)
Alcohol	498 (12.5)	565 (10.9)	565 (10.9)	76 (5.8)
Prior MI	1029 (25.8)	1543 (29.8)	297 (30.2)	438 (33.3)
Angina	1619 (40.7)	2181 (42.1)	399 (40.6)	582 (44.3)
Hypertension	3622 (90.9)	4805 (92.9)	945 (96.1)	1274 (97.0)
Diabetes mellitus	1586 (39.8)	2218 (42.9)	531 (54.0)	720 (54.8)
COPD	1033 (25.9)	1471 (28.4)	332 (33.7)	428 (32.6)
Peripheral vascular disease	606 (15.2)	840 (16.2)	267 (27.2)	331 (25.2)
Anaemia (haemoglobin <12 mg/dL)	498 (13.6)	573 (11.1)	257 (28.9)	324 (24.7)
Stroke	203 (5.1)	246 (4.8)	81 (8.2)	100 (7.6)
Heart failure	851 (21.4)	1138 (22.0)	443 (45.0)	547 (41.6)
Comorbidities 1–5 years prior to index PCI, n (%)				
Prior CABG	78 (2.0)	70 (1.4)	35 (3.6)	20 (1.5)
Prior PCI	73 (1.8)	67 (1.3)	28 (2.9)	27 (2.1)
Baseline medication, n (%)				
Aspirin	3591 (90.2)	4689 (90.6)	868 (88.3)	1185 (90.2)
Statin or lipid lowering	3759 (94.4)	4928 (95.2)	921 (93.7)	1254 (95.4)
β blocker	3620 (90.1)	4742 (91.6)	897 (91.3)	1220 (92.9)
Calcium channel blocker	870 (21.9)	1334 (25.8)	350 (35.6)	501 (38.1)
ACE inhibitor or ARB	2925 (73.4)	3887 (75.1)	708 (72.0)	1015 (77.3)
Proton pump inhibitors	1927 (48.4)	2759 (53.3)	514 (52.3)	775 (59.0)
Warfarin	323 (8.1)	370 (7.1)	151 (15.4)	156 (11.9)

ACS, acute coronary syndrome; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2

Baseline characteristics in subjects receiving bare-metal stents

Characteristic	eGFR ≥60 Clopidogrel use		eGFR<60 Clopidogrel use	
	12 months	>12 months	12 months	>12 months
Age, mean (SD), years	62.5 (9.9)	63.1 (9.6)	70.0 (9.9)	70.3 (9.6)
Men, n (%)	5988 (98.8)	2906 (98.6)	1628 (97.1)	885 (97.6)
Race, n(%)				
White	4808 (79.4)	2376 (80.7)	1440 (85.9)	806 (88.9)
Black	893 (14.7)	383 (13.0)	180 (10.7)	68 (7.5)
Other	39 (0.6)	16 (0.54)	16 (1.0)	2 (0.2)
Unknown	318 (5.3)	171 (5.8)	40 (2.4)	31 (3.4)
ACS (during index admission), n (%)	3763 (62.1)	1890 (64.1)	1066 (63.6)	610 (67.3)
Comorbidities 5 years prior to 1 year after index PCI, n (%)				
Smoking	2673 (44.1)	1220 (41.4)	477 (28.5)	246 (27.1)
Alcohol	829 (13.7)	320 (10.9)	117 (7.0)	39 (4.3)
Prior MI	1853 (30.6)	1004 (34.1)	580 (34.6)	326 (35.9)
Angina	2886 (47.6)	1403 (47.6)	831 (49.6)	460 (50.7)
Hypertension	5504 (91.0)	2753 (93.5)	1605 (95.8)	878 (96.8)
Diabetes mellitus	2383 (39.3)	1305 (44.3)	837 (49.9)	503 (55.5)
COPD	1659 (27.4)	817 (27.7)	579 (34.6)	314 (34.6)
Peripheral vascular disease	1031 (17.0)	510 (17.3)	488 (29.1)	275 (30.3)
Anaemia (haemoglobin <12 mg/dL)	580 (13.1)	384 (13.0)	341 (28.6)	261 (28.8)
Stroke	344 (5.7)	165 (5.6)	180 (10.7)	93 (10.3)
Heart failure	1371 (22.6)	732 (24.9)	756 (45.1)	400 (44.1)
Comorbidities 1–5 years prior to index PCI, n (%)				
Prior CABG	118 (2.0)	55 (1.9)	47 (2.8)	26 (2.9)
Prior PCI	279 (4.6)	108 (3.7)	110 (6.6)	39 (4.3)
Baseline medications, n (%)				
Aspirin	5628 (92.9)	2717 (92.2)	1553 (92.7)	832 (91.7)
Statin or lipid lowering	5627 (92.3)	2784 (94.5)	1538 (91.8)	856 (94.4)
β blocker	5588 (92.2)	2752 (93.4)	1576 (94.0)	848 (93.5)
Calcium channel blocker	1533 (25.3)	836 (28.4)	689 (41.1)	373 (41.1)
ACE inhibitor or ARB	4686 (77.4)	2310 (78.4)	1310 (78.1)	699 (77.0)
Proton pump inhibitors	2721 (44.9)	1506 (51.1)	862 (51.4)	523 (57.7)
Warfarin	519 (8.6)	195 (6.6)	251 (15.0)	103 (11.4)

ACS, acute coronary syndrome; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafts; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3

Landmark analysis of the risk of clinical end points with clopidogrel use beyond, versus less than or equal to, 12 months

				Clopidogrel use 12 months <u>>12 months</u>			
eGFR		Stent type	n	n	Crude HR (95% CI), p value	Multivariable HR (95% CI), p value	Inverse probability weighting HR (95% CI), p value
<60	Death	DES	123	95	0.61 (0.47 to 0.8), <0.0001	0.63 (0.48 to 0.83), <0.0001	0.64 (0.49 to 0.84), <0.0001
		BMS	343	169	0.99 (0.82 to 1.19), 0.88	0.99 (0.82 to 1.2), 0.91	1.07 (0.89 to 1.3), 0.47
	MI or death	DES	128	117	0.74 (0.58 to 0.95), 0.02	0.79 (0.61 to 1.02), 0.07	0.77 (0.6 to 0.99), 0.04
		BMS	400	185	0.95 (0.79 to 1.13), 0.53	0.93 (0.78 to 1.11), 0.43	1.0 (0.84 to 1.2), 0.99
	PCI or CABG	DES	57	56	0.81 (0.56 to 1.18), 0.28	0.81 (0.56 to 1.18), 0.27	0.85 (0.58 to 1.23), 0.39
		BMS	159	85	1.14 (0.88 to 1.49), 0.32	1.27 (0.96 to 1.67), 0.09	1.12 (0.85 to 1.48), 0.4
	Stroke	DES	8	6	0.59 (0.20 to 1.70), 0.33	0.71 (0.24 to 2.07), 0.53	0.71 (0.24 to 2.1), 2 0.54
		BMS	33	11	0.66 (0.33 to 1.31), 0.23	0.71 (0.35 to 1.44), 0.34	0.69 (0.34 to 1.41), 0.31
	Life-threatening bleed	DES	24	13	0.42 (0.21 to 0.83), 0.01	0.48 (0.24 to 0.95), 0.04	0.63 (0.32 to 1.25), 0.19
		BMS	45	31	1.35 (0.85 to 2.13), 0.20	1.41 (0.87 to 2.28), 0.16	1.57 (0.98 to 2.53), 0.06
60+	Death	DES	191	182	0.82 (0.67 to 1.0), 0.05	0.79 (0.64 to 0.97), 0.02	0.85 (0.69 to 1.04), 0.11
		BMS	572	200	0.81 (0.69 to 1.0), 0.01	0.75 (0.63 to 0.88), <0.0001	0.8 (0.67 to 0.95), 0.01
	MI or death	DES	290	268	0.79 (0.67 to 0.93), 0.01	0.77 (0.65 to 0.91), <0.0001	0.81 (0.69 to 0.96), 0.02
		BMS	771	291	0.87(0.76 to 1.0), 0.05	0.81 (0.71 to 0.94), <0.0001	0.84 (0.73 to 0.96), 0.01
	PCI or CABG	DES	212	240	1.01 (0.84 to 1.22), 0.92	1.02 (0.84 to 1.22), 0.86	1.03 (0.86 to 1.25), 0.73
		BMS	577	261	1.05 (0.91 to 1.22), 0.49	1.06 (0.91 to 1.23), 0.47	0.99 (0.85 to 1.15), 0.85
	Stroke	DES	20	18	0.78 (0.41 to 1.49), 0.46	0.79 (0.41 to 1.49), 0.46	0.89 (0.47 to 1.69), 0.72
		BMS	63	21	0.78 (0.48 to 1.28), 0.32	0.79 (0.47 to 1.31), 0.36	0.82 (0.49 to 1.38), 0.46
	Life-threatening bleed	DES	42	38	0.77 (0.50 to 1.20), 0.25	0.73 (0.47 to 1.13), 0.16	1.05 (0.67 to 1.64), 0.83
		BMS	119	41	0.78 (0.55 to 1.12), 0.18	0.73 (0.54 to 1.13), 0.2	0.84 (0.58 to 1.22), 0.36

eGFR category calculated from the MDRD equation. HRs with p<0.025 are in bold.

BMS, bare-metal stent; CABG, coronary artery bypass grafts; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 4

Sensitivity analysis with eGFR category calculated from the CKD-Epi equation.

eGFR		Stent type	Clopidogrel use 12 months 12 months		Crude HR (95% CI), p value	Multivariable HR (95% CI), p value	Inverse probability weighting HR (95% CI), p value
<60	Death	DES	138	116	0.58 (0.45 to 0.74), <0.0001	0.58 (0.45 to 0.74), <0.0001	0.60 (0.47 to 0.77), <0.0001
		BMS	382	210	0.96 (0.81 to 1.14), 0.66	0.97 (0.82 to 1.16), 0.76	1.05 (0.88 to 1.25), 0.57
	MI or death	DES	145	147	0.71 (0.56 to 0.89), <0.0001	0.74 (0.59 to 0.94), 0.01	0.73 (0.58 to 0.92), 0.01
		BMS	438	241	0.99 (0.85 to 1.16), 0.9	0.99 (0.84 to 1.17), 0.93	1.04 (0.89 to 1.23), 0.6
	PCI or CABG	DES	67	67	0.71 (0.51 to 1), 0.05	0.71 (0.5 to 1.99), 0.05	0.73 (0.52 to 1.03), 0.08
		BMS	170	112	1.21 (0.95 to 1.54), 0.11	1.32 (1.03 to 1.69), 0.03	1.19 (0.93 to 1.52), 0.17
	Stroke	DES	8	7	0.60 (0.22 to 1.64), 0.32	0.68 (0.25 to 1.9), 0.47	0.73 (0.26 to 2.05), 0.55
		BMS	36	12	0.58 (0.3 to 1.11), 0.1	0.61 (0.31 to 1.2), 0.15	0.59 (0.3 to 1.18), 0.14
	Life-threatening bleed	DES	26	17	0.44 (0.24 to 0.80), 0.01	0.48 (0.26 to 0.9), 0.02	0.58 (0.31 to 1.07), 0.08
		BMS	53	38	1.23 (0.81 to 1.86), 0.34	1.37 (0.88 to 2.12), 0.16	1.44 (0.93 to 2.22), 0.1
60+	Death	DES	155	182	0.85 (0.69 to 1.06), 0.15	0.82 (0.66 to 1.01), 0.07	0.88 (0.71 to 1.09), 0.24
		BMS	487	205	0.85 (0.72 to 1), 0.05	0.79 (0.67 to 0.94), 0.01	0.82 (0.69 to 0.97), 0.02
	MI or death	DES	237	274	0.84 (0.71 to 1.01), 0.06	0.82 (0.69 to 0.98), 0.03	0.86 (0.72 to 1.03), 0.10
		BMS	672	296	0.89 (0.78 to 1.02), 0.09	0.83 (0.72 to 0.96), 0.01	0.85 (0.73 to 0.98), 0.02
	PCI or CABG	DES	181	250	1.05 (0.87 to 1.27), 0.62	1.05 (0.87 to 1.27), 0.62	1.05 (0.87 to 1.28), 0.59
		BMS	532	268	1.04 (0.89 to 1.2), 0.64	1.04 (0.89 to 1.21), 0.61	0.99 (0.85 to 1.15), 0.86
	Stroke	DES	17	20	0.88 (0.46 to 1.68), 0.69	0.87 (0.45 to 1.67), 0.67	0.98 (0.51 to 1.88), 0.95
		BMS	58	22	0.78 (0.48 to 1.27), 0.32	0.78 (0.47 to 1.29), 0.33	0.81 (0.49 to 1.36), 0.43
	Life-threatening bleed	DES	32	42	0.96 (0.61 to 1.52), 0.86	0.89 (0.56 to 1.42), 0.64	1.20 (0.75 to 1.91), 0.45
		BMS	104	41	0.79 (0.55 to 1.13), 0.19	0.78 (0.54 to 1.14), 0.20	0.87 (0.59 to 1.26), 0.45

Landmark analysis of the risk of clinical end points with clopidogrel use beyond, versus less than or equal to, 12 months. HRs with $p < 0.025$ are in bold.

CABG, coronary artery bypass grafts; CKD-Epi, Chronic Kidney Disease-Epidemiology Collaboration; DES, drug-eluting stent; BMS, bare-metal stent; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.