ORIGINAL RESEARCH

Benefit of Clopidogrel Therapy in Patients With Myocardial Infarction and Chronic Kidney Disease—A Danish Nation-Wide Cohort Study

Thalia Marie Blicher, MD; Kristine Hommel, MD, PhD; Søren Lund Kristensen, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Mette Madsen, MSc; Anne-Lise Kamper, MD, DMSc; Jonas Bjerring Olesen, MD, PhD

***Background*—**The aim of the present study was to evaluate clopidogrel treatment after incident myocardial infarction (MI) in patients with and without chronic kidney disease (CKD).

***Methods and Results*—**By linking nation-wide registries, information about patients admitted with incident MI was found. Primary endpoints were all-cause and cardiovascular (CV) mortality, a composite of all-cause mortality and recurrent MI, and a composite of fatal and nonfatal bleedings. Effect of clopidogrel use versus clopidogrel nonuse was estimated using an adjusted Cox's regression model stratified according to percutaneous coronary intervention (PCI) treatment. A total of 69 082 incident MI patients in the period 2002–2011 were included. Clopidogrel treatment was associated with hazard ratios (HRs) for the combined endpoint of all-cause mortality and recurrent MI in PCI-treated patients of 0.90 (95% confidence interval [CI], 0.47 to 1.72) in renal replacement therapy (RRT) patients, 0.59 (95% CI: 0.40 to 0.88) in non-end-stage CKD patients and 0.69 (95% CI, 0.61 to 0.77) in patients without kidney disease (*P* for interaction=0.60). In patients not treated with PCI, HRs were 0.90 (95% CI, 0.68 to 1.21) in RRT patients, 0.86 (95% CI, 0.75 to 0.99) in non-end-stage CKD patients, and 0.91 (95% CI, 0.87 to 0.95) in patients without kidney disease (*P* for interaction=0.74). An increase in bleeding events (not significant) was noted for clopidogrel-treated patients not undergoing PCI and for non-end-stage CKD patients undergoing PCI, whereas clopidogrel was associated with less bleedings in PCI-treated RRT patients and patients without kidney disease.

***Conclusions*—**During a 1-year follow-up, after MI, clopidogrel was associated with improved outcomes in patients with non-end-stage CKD. Even though no effect difference, compared to patients without CKD, was observed, the benefit associated with the use of clopidogrel after MI in patients requiring RRT is less clear. **(*J Am Heart Assoc*. 2014;3:e001116 doi: 10.1161/JAHA.114.001116)**

Key Words: kidney • myocardial infarction • revascularization

Chronic kidney disease (CKD) is associated with a markedly increased risk of cardiovascular (CV) morbidity and mortality, including poor outcomes after myocardial infarction (MI).[1–4] We have previously demonstrated that the use of standard guideline-based invasive and pharmacological treatment of first-time MI was significantly less in patients with CKD, as compared to patients without kidney disease. The chance of filling a prescription for clopidogrel was reduced in both non-end-stage CKD patients and patients on renal replacement therapy (RRT).[5] Studies evaluating the effect of clopidogrel in MI patients with CKD have provided divergent conclusions,[6,7] and reduced platelet response to clopidogrel has been suggested as a mechanism for observed worse outcomes after percutaneous coronary intervention (PCI) in patients with CKD.[8,9] Thus, the benefit of clopidogrel in MI patients with CKD is uncertain and may be outweighed by the risks.[10]

The aim of the present study was, by use of data from nation-wide Danish registries, to describe the effect of clopidogrel treatment on mortality, recurrent MI, and bleeding outcomes after incident MI in patients with CKD, including RRT patients. To do so, we evaluated the effect of clopidogrel therapy in patients requiring RRT, patients with non-end-stage CKD, and patients without kidney disease, respectively.

From the Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup Denmark (T.M.B., S.L.K., J.B.O.); Department of Nephrology, Copenhagen University Hospital Rigshospitalet, Copenhagen Denmark (K.H., A.-L.K.); Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark (C.T.-P.); Department of Public Health, University of Copenhagen, Copenhagen, Denmark (M.M.).

Correspondence to: Thalia Marie Blicher, MD, Department of Cardiology, Copenhagen University Hospital Gentofte, Niels Andersens vej 65, 2900 Hellerup, Denmark. E-mail: thalia@dadlnet.dk

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Methods

Data Sources

Information on patients admitted to Danish hospitals with an incident MI were found by linking nation-wide registries by means of the personal unique civil registration number. All admissions to Danish hospitals since 1978 are registered in the National Patient Registry[11,12] by the International Classification of Diseases (ICD), version 8 (ICD-8) before 1994 and ICD-10 after 1994. The National Patient Registry holds information about primary and secondary discharge diagnoses, procedures, and operations. We had access to information about filled prescriptions from Danish pharmacies in the Danish Register of Medicinal Product Statistics, which provide data on all prescription drugs claimed from Danish pharmacies since 1995, with information of Anatomic Therapeutic Chemical (ATC) codes, dispensing date, drug type, dose, and quantity.[13,14] Information on PCI procedure was retrieved from the National Patient Registry, where all surgical procedures are coded according to the Nordic Medical Statistics Committees Classification of Surgical Procedures. The coding of surgical procedures is compulsory in order to get reimbursement from the Danish National Health Service.

The Danish National Registry on Regular Dialysis and Transplantation holds information on all Danish RRT patients.[15]

Study Population

Our study population consisted of all patients admitted with incident MI (ICD-10 codes I21-I22 as primary or secondary diagnosis) in the period 2002–2011 (Figure 1). The diagnostic coding of MI in the National Patient Registry was found to be valid,[16] but to strengthen the validity of the MI diagnosis, only patients with more than 1 day in-hospital were included. A period of 7 days from discharge was used to allow patients to claim prescriptions on clopidogrel and concomitant medications from the pharmacy, and therefore patients experiencing an event (ie, death, recurrent MI, or bleeding) in this 7-day period were excluded. PCI treatment within 7 days from date of admission was identified in the National Patient Registry. Patients' comorbidities were defined by any hospitalization in the year preceding the incident MI, with one of the following

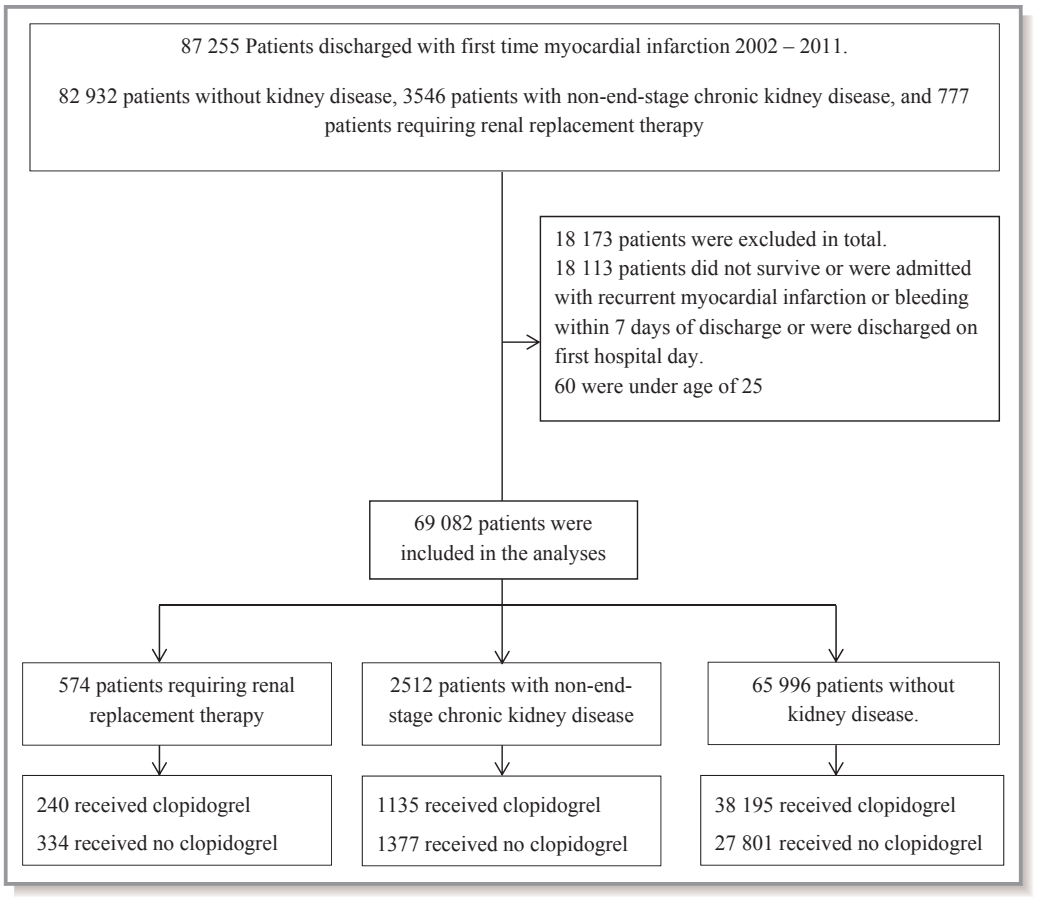

Figure 1. Flow chart of study population.

diagnoses, according to the Ontario MI mortality prediction rules: diabetes with complications, congestive heart failure (CHF), cancer, cerebrovascular disease, pulmonary edema, and shock.[17,18]

Use of clopidogrel and concomitant medications was defined by a dispensed prescription from 180 days preceding the incident MI hospitalization to 7 days postdischarge. Prescription drugs of interest were, besides clopidogrel: aspirin, statins, vitamin K antagonists, and cardioprotective drugs (ie, beta-blockers, alpha-beta blockers, and renin-angiotensin blockers). Our study population was grouped according to kidney disease status and clopidogrel treatment. Patients were followed for up to 1 year from study inclusion (ie, 7 days after discharge for the incident MI). Administrative codes are listed below.

Definition of Patients With CKD

The MI patients requiring RRT were identified in The Danish National Registry on Regular Dialysis and Transplantation, which is valid and complete.[15] Among these patients, 21% had a functioning kidney transplant at the time of MI and these patients were included in the RRT population. Because kidney transplant patients may have a different response to clopidogrel compared with dialysis patients, we performed a sensitivity analysis including kidney transplant patients only.

Patients with non-end-stage CKD were identified in the National Patient Registry by a previous diagnosis of one of the following conditions: diabetic nephropathy; chronic glomerulonephritis; chronic tubulo-interstitial nephropathy; hypertensive nephropathy; autosomal dominant polycystic kidney disease; chronic nephropathy of other origin; or chronic nephropathy of unknown etiology. Estimated glomerular filtration rate (eGFR) is not registered in the National Patient Registry; however, we had access to a representative sample of 357 patients from our non-end-stage CKD study population with an eGFR at the day of MI. Seventy-eight percent of these patients belonged to CKD stage 3 to 5 with an eGFR <60 mL/min at the day of MI.

Main Outcome Parameters

The effect of clopidogrel treatment was studied in relation to the following outcome parameters: (1) all-cause mortality; (2) CV mortality (immediate or contributing cause of death; ICD-10 code I00-I99); (3) a composite of all-cause mortality and recurrent MI (ICD-10 code; I21-I22); and (4) bleeding, that is, a composite of nonfatal and fatal bleeding events (gastrointestinal [GI], cerebral, airway and urinary tract bleedings, and anemia from acute and chronic bleeding). Recurrent MI was defined as an admission to a Danish hospital with an MI diagnosis more than 7 days after discharge for the incident MI. ICD-10 codes that were used to define admissions resulting from bleeding events are shown in Appendix. If one of these ICD-10 codes were registered as cause of death, the event was classified as a fatal bleeding event. Follow-up was 1 year from study start, which was 7 days after discharge.

Statistics

Crude 1-year incidence rates were calculated for the main outcome parameters and Cox's proportional hazard models, adjusted for sex, age, and comorbidity (diabetes with complications, CHF, cancer, cerebrovascular disease, pulmonary edema, cardiac dysrhythmias, and shock), and concomitant drug therapy (aspirin, statins, vitamin K antagonists, and cardioprotective drugs), were used to estimate hazard ratios (HRs) of the main outcome parameters in clopidogrel-using patients, compared to clopidogrel nonusers, for all 3 patient groups in the same model. Patients were censored at outcomes of interest, death, or if none of these occurred, 365 days after study start. For each of the outcomes, time to first occurrence of the event was included in the statistical model. Patients surviving an event were censored at time of event, and subsequent events were not recorded for the specific outcome. There was a significant interaction between kidney disease status (patients requiring RRT, patients with non-end-stage CKD, and patients without kidney disease) and PCI within 7 days from date of admission for incident MI for all 4 main outcome parameters: all-cause mortality; CV mortality; the composite of all-cause mortality and recurrent MI; and the composite of nonfatal and fatal bleedings. Hence, we stratified our analyses for patients according to performed PCI or not. Assumptions on linearity of continuous variables, proportional hazards, and lack of interactions were found valid unless otherwise indicated.

Additionally, propensity score-based analyses were performed using logistic regression of clopidogrel treatment on all baseline characteristics from Table 1 (including PCI performed within 7 days) using the entire MI population. Then, clopidogrel using patients were matched 1:1 with patients not using clopidogrel on the propensity score using the Greedy matching macro (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros). Finally, we performed an analysis, using a 30-day period instead of the 7-day period, to fill a prescription on clopidogrel. A $P<0.05$ was considered statistically significant. Data management and statistical analyses were performed with SAS (version 9.2; SAS Institute Inc., Cary, NC) and R software (version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria) (2013-05-16).

Table 1. Baseline Characteristics

Study Population (No.)	Disease Requring RRT (N=574)		Non-End-Stage CKD Patients (N=2512)		Patients Without Kidney Disease (N=65 996)	
	Clopidogrel	No Clopidogrel	Clopidogrel	No Clopidogrel	Clopidogrel	No Clopidogrel
No. of patients, n (%)	240 (42)	334 (58)	1135 (45)	1377 (55)	38 195 (58)	27 801 (42)
Age at MI, mean y (SD)	65±12	67±12	72±12	75±12	66±13	72±14
Female gender, n (%)	85 (35.4)	108 (32.3)	370 (32.6)	537 (39.0)	12 670 (33.2)	12 082 (43.5)
Comorbidity, n (%)						
Diabetes with complications	72 (30.0)	117 (35.0)	436 (38.4)	544 (39.5)	3292 (8.6)	3016 (10.8)
Congestive heart failure	28 (11.7)	60 (18.0)	245 (21.6)	379 (27.5)	3031 (7.9)	4146 (14.9)
Cancer	13 (5.4)	29 (8.7)	72 (6.3)	107 (7.8)	1025 (2.7)	1419 (5.1)
Cerebrovascular disease	19 (7.9)	31 (9.3)	114 (10.0)	172 (12.5)	1327 (3.5)	1959 (7.0)
Pulmonary edema	14 (5.8)	23 (6.9)	27 (2.4)	40 (2.9)	282 (0.7)	527 (1.9)
Cardiac dysrrhythmias	42 (17.5)	68 (20.4)	178 (15.7)	334 (24.3)	3403 (8.9)	4736 (17.0)
Shock	0 (0.0)	3 (0.9)	3 (0.3)	13 (0.9)	83 (0.2)	143 (0.5)
Drugs						
Aspirin	180 (75.0)	176 (52.7)	974 (85.8)	930 (67.5)	34 794 (91.1)	18 256 (65.7)
Cardioprotective drugs*	207 (86.2)	262 (78.4)	1042 (91.8)	1046 (76.0)	35 134 (92.0)	18 400 (66.2)
Antidiabetics	57 (23.8)	99 (29.6)	463 (40.8)	542 (39.4)	3875 (10.1)	3433 (12.3)
Statins	162 (67.5)	143 (42.8)	914 (80.5)	627 (45.5)	33 624 (88.0)	12 777 (46.0)
Vitamin K antagonists	25 (10.4)	36 (10.8)	91 (8.0)	167 (12.1)	1794 (4.7)	2422 (8.7)

Drugs: filled prescriptions 180 days before and 7 days after incident MI. CKD indicates chronic kidney disease; MI, myocardial infarction; RRT, renal replacement therapy.
*Cardioprotective drugs are a composite of renin-angiotensin blockers, beta-blockers, and alpha/beta blockers.

Ethical Considerations

The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0015, int.ref: GEH-2014-014, I-Suite nr: 02732). Registry-based studies do not require ethical approval in Denmark.

Results

We included 69 082 patients with incident MI in the period 2002–2011: 574 RRT patients; 2512 non-end-stage CKD patients; and 65 996 patients without kidney disease (Figure 1). Approximately one third of patients were female. Non-end-stage CKD patients were oldest, followed by patients without kidney disease and RRT patients (Table 1). Less than half of CKD patients were treated with clopidogrel, compared to 58% of patients without kidney disease (Table 1). PCI within 7 days of incident MI was performed in 20% (n=116) of RRT patients, 21% (n=535) of non-end-stage CKD patients, and in 41% (n=27 126) of patients without kidney disease (Table 2). Median follow-up time for all patients was 365 days. Interquartile range was 106 to 365 days for RRT patients, 128 to 365 days for non-end-stage CKD patients, and 365 to 365 days for patients without kidney disease.

Clopidogrel use was associated with lower crude incidence rates of all-cause mortality, CV mortality, and the combined endpoint of all-cause mortality and recurrent MI, regardless of kidney disease status. Crude incidence bleeding rates were higher in clopidogrel using non-end-stage CKD patients only (Table 2).

Outcomes Associated With Clopidogrel Treatment

Patients requiring RRT

Overall mortality for RRT patients in the study period was 24% (28 of 116) and 34% (157 of 458) for PCI-treated and non-PCI-treated patients, respectively. In general, the lower event rates of the CV outcomes associated with clopidogrel in RRT patients did not translate into significant associations in the adjusted analyses, although the interaction between clopidogrel and kidney disease status was insignificant (Figures 2 and 3). HRs for all-cause mortality was 0.83 (95% confidence interval [CI], 0.39 to 1.77) in PCI-treated and 0.93 (95% CI, 0.66 to 1.30) in non-PCI-treated RRT patients. HRs for CV mortality was 1.02 (95% CI, 0.42 to 2.47) and 1.10 (95% CI, 0.74 to 1.62) for PCI-treated and non-PCI-treated RRT patients, respectively. Corresponding numbers for the

Table 2. Crude Incidence Rates

Study Population (No.)	Disease Requiring RRT (N=574)		Non-End-Stage CKD (N=2512)		Without Kidney Disease (N=65 996)	
	Clopidogrel	No Clopidogrel	Clopidogrel	No Clopidogrel	Clopidogrel	No Clopidogrel
Overall population (n)	240	334	1135	1377	38 195	27 801
All-cause mortality						
Events/total No.	64	121	243	486	2424	5082
Person-years	202	250	980	1040	36 691	24 319
Crude incidence rates	31.7 (24.8 to 40.5)	48.5 (40.6 to 57.9)	24.8 (21.9 to 28.1)	46.7 (42.7 to 51.1)	6.6 (6.3 to 6.9)	20.9 (20.3 to 21.5)
Cardiovascular mortality						
Events/total no.	52	82	194	371	1879	3808
Person-years	202	250	980	1040	36 691	24 319
Crude incidence rates	25.8 (19.6 to 33.8)	32.9 (26.5 to 40.8)	19.8 (17.2 to 22.8)	35.7 (32.2 to 39.5)	5.1 (4.9 to 5.4)	15.7 (15.2 to 16.2)
Combined endpoint (all-cause mortality and recurrent MI)						
Events/total no.	90	159	346	619	5090	7403
Person-years	182	220	906	929	34 581	22 407
Crude incidence rates	49.6 (40.3 to 60.9)	72.3 (61.9 to 84.4)	38.2 (34.4 to 42.5)	66.6 (61.6 to 72.1)	14.7 (14.3 to 15.1)	33.0 (32.3 to 33.8)
All bleedings (including fatal bleedings)						
Events/total no.	18	32	105	106	1422	1371
Person-years	195	236	932	996	35 995	23 740
Crude incidence rates	9.2 (5.8 to 14.7)	13.5 (9.6 to 19.1)	11.3 (9.3 to 13.6)	10.6 (8.8 to 12.9)	4.0 (3.8 to 4.2)	5.8 (5.5 to 6.1)

Crude incidence rates are based on the number of events per 100 person-years. Combined endpoint refers to the first recurrent MI and all-cause mortality. Bleedings were fatal and nonfatal bleedings combined. CKD indicates chronic kidney disease; MI, myocardial infarction; RRT, renal replacement therapy.

combined endpoint of all-cause mortality and recurrent MI was 0.90 (95% CI, 047 to 1.72) and 0.90 (95% CI, 0.68 to 1.21). Clopidogrel was associated with less bleeding events in RRT patients undergoing PCI (HR, 0.15; 95% CI, 0.03 to 0.75) and more bleeding events in patients not undergoing PCI (HR, 1.17; 95% CI, 0.63 to 2.17).

Non-end-stage CKD patients

Ten percent (56 of 535) and 34% (673 of 1977) of non-end-stage CKD patients (PCI treated and not PCI treated, respectively), died during the 1-year follow-up. Use of clopidogrel was associated with lower event rates for the CV outcomes in non-end-stage CKD patients. The adjusted analysis (Figures 2 and 3) showed that clopidogrel treatment in non-end-stage CKD patients was associated with a reduction in the all-cause mortality with HRs of 0.49 (95% CI, 0.29 to 0.84) and 0.91 (95% CI, 0.77 to 1.07) in PCI-treated and non-PCI-treated patients, respectively. HRs for CV mortality was 0.59 (95% CI, 0.31 to 1.10) and 0.94 (95% CI, 0.78 to 1.13) for PCI versus non-PCI and HRs for the combined endpoint of all-cause mortality and recurrent MI was 0.59 (95% CI, 0.40 to 0.88) and 0.86 (95% CI, 0.75 to 0.99) for PCI and non-PCI, respectively. For all 3 CV outcomes, the interaction between kidney disease status and clopidogrel was insignificant, suggesting comparable clopidogrel effect across kidney disease status. There was a tendency of an increased bleeding risk associated with clopidogrel in non-end-stage CKD patients with an HR of 1.65 (95% CI, 0.77 to 3.54) in PCI-treated patients and 1.16 (95% CI, 0.85 to 1.59) in not PCI-treated patients (Figures 2 and 3).

Patients without kidney disease

For the MI patients without kidney disease, the 1-year mortality was 3% (840 of 27 126) and 17% (6666 of 38 870) for the PCI treated and non-PCI treated, respectively. The adjusted analysis showed that in patients without CKD, clopidogrel was associated with a significant benefit on all-cause mortality with HRs of 0.57 (95% CI, 0.48 to 0.68) and 0.82 (95% CI, 0.77 to 0.87) for PCI versus non-PCI treatment. For CV mortality the HRs were 0.49 (95% CI, 0.41 to 0.59) for the PCI treated and 0.83 (95% CI, 0.78 to 0.89) for those non-PCI treated. HRs for the combined endpoint of all-cause mortality and recurrent MI were 0.69 (95% CI, 0.61 to 0.77) and 0.91 (95% CI, 0.87 to 0.95) for PCI versus non-PCI (Figures 2 and 3). No significant effect of clopidogrel on bleeding events was observed, with HRs for bleeding in PCI-treated patients of 0.83 (95% CI, 0.69 to 1.01) and 1.08 (95% CI, 0.98 to 1.20) for patients not treated with PCI.

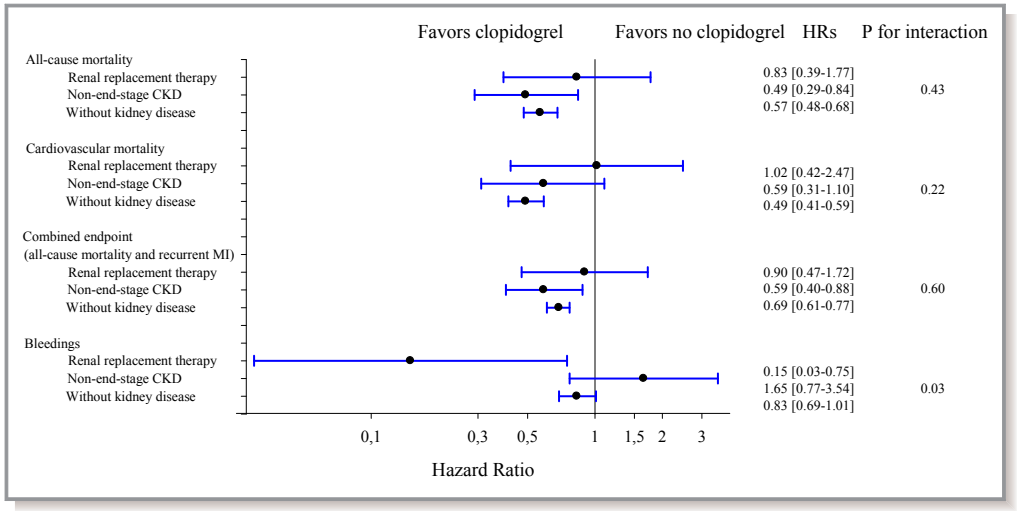

Figure 2. Risk of all-cause mortality, cardiovascular mortality, recurrent myocardial infarction, and bleedings within 1 year according to clopidogrel use in patients treated with PCI after incident MI, adjusted for sex, age, comorbidity (diabetes with complications, congestive heart failure, cancer, cerebrovascular disease, pulmonary edema, cardiac dysrhythmias, and shock), and concomitant drug therapy (aspirin, statins, vitamin K antagonists, and cardioprotective drugs). *P* for interaction denotes the interaction between renal function status and use of clopidogrel. CKD indicates chronic kidney disease; HRs, hazard ratios; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Sensitivity Analyses

The propensity score matching identified 358 patients requiring renal replacement therapy, of whom 179 were treated with clopidogrel and 179 not, 1490 non-end-stage CKD patients, of whom 745 were treated with clopidogrel and 745 not, and 31 462 patients without kidney disease, of whom 15 731 were treated with clopidogrel and 15 731 not. The adjusted Cox's proportional hazard analysis for the propensity score-matched population is presented in Table 3. Clopidogrel was associated with improved outcomes for the combined endpoint of all-cause mortality and recurrent MI;

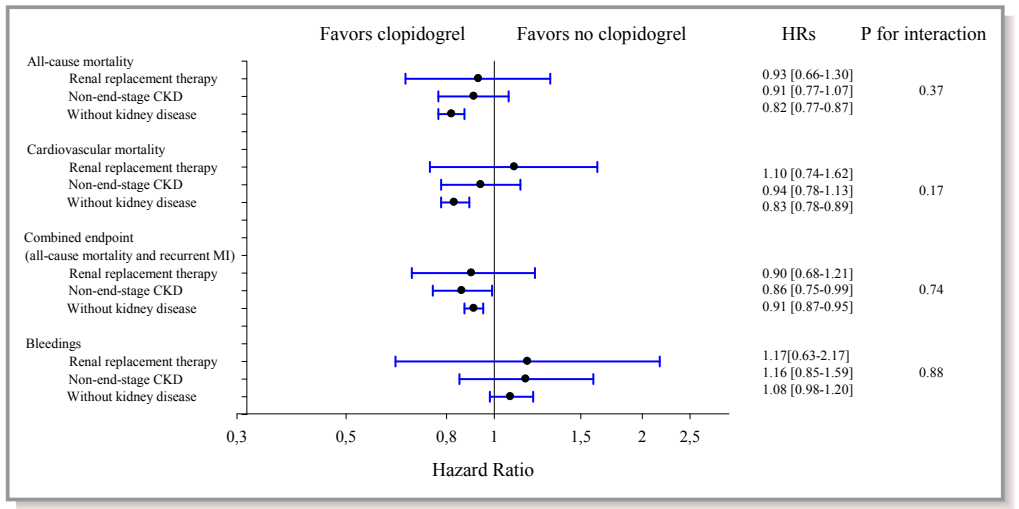

Figure 3. Risk of all-cause mortality, cardiovascular mortality, recurrent myocardial infarction, and bleedings within 1 year according to clopidogrel use in patients not treated with PCI after incident MI, adjusted for sex, age, comorbidity (diabetes with complications, congestive heart failure, cancer, cerebrovascular disease, pulmonary edema, cardiac dysrhythmias, and shock), and concomitant drug therapy (aspirin, statins, vitamin K antagonists, and cardioprotective drugs). *P* for interaction denotes the interaction between renal function status and use of clopidogrel. CKD indicates chronic kidney disease; HRs, hazard ratios; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3. Cox Proportional Hazard Analysis for the Propensity Score Matched Population, Adjusted for Sex, Age, Comorbidity (Diabetes With Complications, Congestive Heart Failure, Cancer, Cerebrovascular Disease, Pulmonary Edema, and Cardiac Dysrhythmias), Concomitant Drug Therapy (Aspirin, Statins, Vitamin K Antagonists, and CardioProtective Drugs), and PCI Within 7 Days

Overall Population (No.)	Disease Requiring RRT (N=358) Hazard Ratio (95% CI)	Non-End-Stage CKD (N=1490) Hazard Ratio (95% CI)	Without Kidney Disease (N=31 462) Hazard Ratio (95% CI)
All-cause mortality	0.80 (0.55 to 1.16)	0.85 (0.70 to 1.04)	0.79 (0.74 to 0.84)
Cardiovascular mortality	0.96 (0.62 to 1.48)	0.91 (0.73 to 1.13)	0.79 (0.73 to 0.85)
Combined end point (all-cause mortality and recurrent MI)	0.82 (0.59 to 1.12)	0.83 (0.70 to 0.98)	0.87 (0.83 to 0.91)
All bleedings (including fatal bleedings)	0.93 (0.46 to 1.88)	1.14 (0.80 to 1.61)	1.02 (0.93 to 1.13)

CI indicates confidence interval; CKD, chronic kidney disease; MI, myocardial infarction; RRT, renal replacement therapy.

however, only significant in non-end-stage CKD patients and patients without kidney disease. The analysis of bleeding events in the propensity score-matched population showed that, for RRT patients, there was a tendency of less bleeding events in the clopidogrel-treated patients, although insignificant (Table 3). For both patients with non-end-stage CKD and no kidney disease, a tendency of insignificant increased bleeding events was observed (Table 3).

Renal transplant patients amounted to 21% of the RRT patients with MI. A Cox's proportional hazard analysis on renal transplant patients only showed a similar effect of clopidogrel in these patients, compared to dialysis patients. The results should be interpreted with caution because of lack of power. We performed a sensitivity analysis where patients had 30 days, instead of 7 days, after discharge for incident MI to claim their prescription on clopidogrel and concomitant medications. For both PCI-treated and non-PCI-treated patients, the 30-day analysis yielded comparable results, compared with the 7-day period, although the results were less significant because of the exclusion of more events in the 30-day period.

Discussion

The main result of the present study was that clopidogrel treatment was associated with improved outcome in CKD patients with incident MI, and no effect difference, compared to patients without kidney disease, was observed. Among patients treated with PCI, the combined endpoint of all-cause mortality and recurrent MI was reached by 34% clopidogrel-treated versus 60% non-clopidogrel-treated RRT patients and 17% clopidogrel-treated versus 39% non-clopidogrel-treated non-end-stage CKD patients. This relative endpoint reduction by clopidogrel was at the same level as in patients without kidney disease, where 7% clopidogrel treated versus 15% nontreated died or had recurrent MI. Although risk reductions in RRT patients were insignificant, the interaction between clopidogrel use and CKD status was insignificant, and thus a difference between event rates associated with clopidogrel treatment could not be demonstrated between patients with and without kidney disease. The relative risk reductions for the 3 CV endpoints were less pronounced in patients who did not undergo PCI. In patients not treated with PCI, clopidogrel use was associated with an increase in bleeding events. However, the relative increases were insignificant and independent of kidney disease status, suggesting an equal effect of clopidogrel on bleeding outcomes in non-PCI-treated patients, in contrast to the PCI-treated patients, where a difference in bleeding events was observed in the 3 patient groups (P for interaction 0.03). The data did not indicate an increase in the risk of bleeding in RRT patients treated with both clopidogrel and PCI; however, because of the small number of patients and events in the RRT group, interpretation of the results is difficult, and the lower rates of bleeding could be explained, in part, by a certain degree of confounding by indication because patients with previous bleeding may not receive clopidogrel.

The propensity score-matched analysis showed that clopidogrel was associated with improved outcomes for the combined endpoint of all-cause mortality and recurrent MI, although insignificant in RRT patients. Insignificant increases in bleeding events were observed for both non-end-stage CKD patients and patients without kidney disease. Less bleeding events occurred in clopidogrel treated RRT patients, but very few bleeding events preclude firm conclusions on the effect of clopidogrel on bleeding in this patient population.

No randomized trial has primarily evaluated the effect of clopidogrel in patients with CKD. Rather, 2 subgroup analyses from the CREDO[6] trial (clopidogrel for the reduction of events during observation) and the CURE[7] trial (clopidogrel in unstable angina to prevent recurrent events) have addressed

the issue. The CREDO[6] trial included 2002 patients and randomly assigned them to receive clopidogrel or placebo for 1 year after PCI. As opposed to our results, clopidogrel was associated with an increase in the primary outcome of death, MI, and stroke, in the 331 patients with moderate CKD (eGFR, <60 mL/min) with an HR of 1.41 (95% CI, 0.81 to 2.45; *P* for interaction=0.007), whereas in the 672 patients with mild CKD (eGFR, 60 to 89 mL/min), and in the 999 patients with normal plasma creatinine, clopidogrel was associated with reductions in the primary outcome with HRs of 0.80 (95% CI, 0.51 to 1.25) for mild CKD and 0.42 (95% CI, 0.26 to 0.69) for patients with normal plasma creatinine. The CURE[7] trial included 12 253 non-ST elevation MI (NSTEMI) patients, who were divided in tertiles of eGFR: 4087 with an eGFR <64 mL/min (lower tertile), 4075 patients with an eGFR 64 to 81.2 mL/min (medium tertile), and 4091 patients with eGFR >81.2 mL/min (upper tertile) and assigned them to either clopidogrel or placebo for a mean of 9 months. HRs for the primary outcome of CV death, MI, and stroke were 0.89 (95% CI, 0.76 to 1.05), 0.68 (95% CI, 0.56 to 0.84), and 0.74 (95% CI, 0.60 to 0.93) for the lower, medium, and upper eGFR tertiles, respectively. There was no evidence of statistical heterogeneity (*P*=0.11), suggesting a similar beneficial effect of clopidogrel in all 3 eGFR tertiles. These CURE[7] substudy observations are in accord with the findings of the present study. Both the CREDO[6] and CURE[7] substudies found increased risk of bleeding events in clopidogrel-treated CKD patients, but in both studies, the risk of bleeding was not increased to a greater degree than in patients with normal renal function, which is in agreement with our results for patients not undergoing PCI as well as for PCI-treated non-end-stage CKD patients.

Among CKD stage 3 to 4 patients (GFR, 15 to 59 mL/min) undergoing PCI, clopidogrel low responders had higher rates of all-cause mortality, cardiac death, and possible stent thrombosis, compared to clopidogrel responders.[9] There was no such relationship between responders and low responders in patients with CKD stage 1 to 2 (GFR, ≥60 mL/min).[9] This corresponds well with the overall increased rates of the outcome parameters observed in RRT patients, compared to non-end-stage CKD patients and patients without kidney disease in the present study.

European guidelines[19] recommend that MI patients with CKD are treated as MI patients without CKD, even though the evidence in the field is sparse. The chances that we will ever have randomized, controlled trials evaluating clopidogrel in patients with CKD are small, which means that treatment strategies have to rely on observational data as with the present study. Although our findings for the population of RRT patients were insignificant, the results suggest that clopidogrel could be beneficial in RRT patients and thus are in line with guideline recommendations.

Strengths and Limitations

The strength of our study is the nation-wide registries that provide us high-quality data on the entire Danish population. Information on RRT patients in The Danish National Registry on Regular Dialysis and Transplantation is valid and complete.[15] The group of patients with non-end-stage CKD was restricted to patients diagnosed in the National Patient Registry (ie, patients who have been treated in the hospital setting). A subanalysis of our population showed that 78% of the non-end-stage CKD patients had eGFR <60 mL/min (ie, CKD stage 3 to 5). Still, these patients with non-end-stage CKD were analyzed as 1 group because we did not have access to levels of GFR for all patients and hence were unable to stratify non-end-stage CKD patients according to CKD stages. We have previously studied non-end-stage CKD in the same way.[5,20] Other studies have typically used the eGFR at the day of admission for MI to categorize the study population in CKD stages. Our sensitivity analysis of 9434 MI patients with an eGFR at the day of MI admission showed that up to 30% of patients without kidney disease in our study had an eGFR <60 mL/min. This might explain why our sample of non-end-stage CKD patients is smaller, compared to other studies. Unfortunately, we did not have valid information on whether the MI was a STEMI or NSTEMI, but because we evaluated PCI within 7 days from admission, we would include both STEMI and NSTEMI patients. Our bleeding outcome included hospitalization and deaths related to GI, cerebral, airway, and urinary tract bleedings as well as anemia from acute and chronic bleeding, and the results are applicable to these kinds of bleedings only. Another limitation is that we cannot retrieve information on lifestyle habits, such as smoking, alcohol, physical activity, and weight, which may potentially bias our results. Still, we tried to capture at least some of these unmeasured effects by including diabetes and lipid-lowering drugs in our fully adjusted analyses. Patients not hospitalized may still have a coexisting diagnosis not registered in the National Patient Registry; however, the patients' comedication is also a mirror of their comorbidities, and because we have adjusted for comedication in our analyses, at least some of the unregistered comorbidities will be accounted for in this way. Regarding the compliance of drug treatment, we have the information that the patient was actually filling the prescription drug at the pharmacy, but we have no information on whether the patients took the drug or not. Even though the CREDO[6] and CURE[7] study populations differed from our study population because the renal function estimate was determined in the acute hospital setting (in contrast to our definition of CKD, which was based on previous diagnoses of kidney disease conditions), an increased rate of death and recurrent MI with decreased kidney function was observed in both our study and the

CREDO[6] and CURE[7] substudies. In our study, the increased risk of bleeding was less pronounced in patients treated with PCI, compared to those not undergoing PCI. This difference could be caused by different patient profiles in regard to comorbidities.

Conclusion

During a 1-year follow-up, after MI, clopidogrel was associated with improved outcomes in patients with non-end-stage CKD. Even though no effect difference, compared to patients without CKD, was observed, the benefit associated with the use of clopidogrel after MI in patients requiring RRT is less clear.

Appendix

Administrative Codes Used in the Study

Procedural codes according to the Danish health care classification system (SKS), which are registered in the National Patient Registry:

percutaneous coronary intervention, PCI (SKS-code: KFNG).

ATC codes for filled prescriptions from the national prescription register:

statins (C10), clopidogrel (B01AC04), aspirin (B01AC06 and N02BA01), cardioprotective drugs (composite of beta-blockers (C07AB), alpha-beta blockers (C07AG), and angiotensin-renin blockers (C09AA and C09CA).

Comorbidity was defined as primary and secondary discharge diagnoses up to 1 year before the index admission, including:

diabetes with complications: E10-E14; congestive heart failure: I43, I50, I099, I110, I130, I132, I255, I425-I429, and P290; cancer: C, cerebrovascular disease: G45-G46, I6, and H340; pulmonary edema: J182 and J81; cardiac dysrhythmias: I441-I443, I459, R000, R001, R008, T821, Z450, Z950, and I46-I48; shock: R57.

Patients with chronic kidney disease, not on RRT, were selected if they were diagnosed with one of the following ICD-8 or ICD-10 codes in the National Patient Registry any time before occurrence of myocardial infarction:

nephropathia diabetica: 25002, N08.3, E102, E112, E132, and E142; chronic glomerulonephritis: 582, 583, N02, N03, N05, N06, and N07; chronic tubulo-interstitial nephropathy: 59009, 59320, N11, N12, N14, N158, N159, N160, N162, N163, N164, and N168; hypertensive nephropathy: 40039, 404, and I120; autosomal dominant polycystic kidney disease: 75310, Q612, Q613, and Q619; chronic nephropathy of other origin: 75311, N08.0, N08.4, N08.5, N08.8, M32.1B, M30.0, M31.3, M31.9, and Q615; chronic nephropathy of unknown etiology: 581, 584, N04, N18, N19, and N26.

The following ICD-10 codes were used to define admissions resulting from bleeding events:

cerebral bleeding: I60-62 and S06.4-06.6; bleeding from the respiratory tract: J94.2 and R04; gastrointestinal bleeding: K25.0, K25.2, K25.4, K26.0, K26.2, K26.4, K27.0, K27.2, K28.0, K28.2, and K92.0-92.2; bleeding from the urinary tract: R31; and anemia from acute or chronic bleeding: D62 and D50. If one of the above ICD-10 codes were registered as a cause of death, the event was classified as a fatal bleeding event.

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