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Increased Mortality Associated With Low Use of Clopidogrel in Patients With Heart Failure and Acute Myocardial Infarction Not Undergoing Percutaneous Coronary Intervention

A Nationwide Study

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Objectives We studied the association of clopidogrel with mortality in acute myocardial infarction (AMI) patients with heart failure (HF) not receiving percutaneous coronary intervention (PCI).

Background Use of clopidogrel after AMI is low in patients with HF, despite the fact that clopidogrel is associated with absolute mortality reduction in AMI patients.

Methods All patients hospitalized with first-time AMI (2000 through 2005) and not undergoing PCI within 30 days from discharge were identified in national registers. Patients with HF treated with clopidogrel were matched by propensity score with patients not treated with clopidogrel. Similarly, 2 groups without HF were identified. Risks of all-cause death were obtained by the Kaplan-Meier method and Cox regression analyses.

Results We identified 56,944 patients with first-time AMI. In the matched cohort with HF (n = 5,050) and a mean follow-up of 1.50 years (SD = 1.2), 709 (28.1%) and 812 (32.2%) deaths occurred in patients receiving and not receiving clopidogrel treatment, respectively (p = 0.002). The corresponding numbers for patients without HF (n = 6,092), with a mean follow-up of 2.05 years (SD = 1.3), were 285 (9.4%) and 294 (9.7%), respectively (p = 0.83). Patients with HF receiving clopidogrel demonstrated reduced mortality (hazard ratio: 0.86; 95% confidence interval: 0.78 to 0.95) compared with patients with HF not receiving clopidogrel. No difference was observed among patients without HF (hazard ratio: 0.98; 95% confidence interval: 0.83 to 1.16).

Conclusions Clopidogrel was associated with reduced mortality in patients with HF who do not undergo PCI after their first-time AMI, whereas this association was not apparent in patients without HF. Further studies of the benefit of clopidogrel in patients with HF and AMI are warranted. (J Am Coll Cardiol 2010;55:1300–7) © 2010 by the American College of Cardiology Foundation

Heart failure (HF) complicating acute myocardial infarction (AMI) is associated with a poor prognosis (1,2). Current European and American guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel in all patients with AMI in the absence of an increased risk of bleeding (3–5). Three major randomized controlled studies have provided important knowledge regarding the benefit of clopidogrel in patients hospitalized with acute coronary syndrome. One trial investigated the effect of clopidogrel versus aspirin (6), another investigated the effect of clopidogrel versus placebo (7), and another showed an effect of

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clopidogrel versus placebo in addition to aspirin (8). A favorable effect of clopidogrel with respect to the composite end point of death, reinfarction, or stroke was found in all studies, and in the latter study, also a decreased risk of all-cause mortality was found (7–9). Patients with HF comprised a modest part of the study population in all 3 studies, and no subgroup analyses of patients with HF were performed. The clinical benefit of clopidogrel in AMI patients with HF is not clarified, which may cause uncertainty and may lead to differences in clinical practice among physicians treating this high-risk patient population. This notion is supported by studies evaluating the implementation of non–ST-segment elevation myocardial infarction (NSTEMI) guidelines, which have demonstrated low initiation rates of clopidogrel in patients not undergoing percutaneous coronary intervention (PCI) and even lower initiation rates of clopidogrel in patients with HF (10–13).

Patients with HF have an approximately 3% annual risk of atherothrombotic events, which may be because of the significantly increased platelet activity (14). Indeed, it has been demonstrated that the addition of clopidogrel to aspirin in patients with HF significantly inhibits the increased platelet activity (15). Whether clopidogrel provides additional survival benefit for AMI patients with concomitant HF compared with patients without HF is unknown. This uncertainty prompted us to conduct a nationwide study examining the effect of clopidogrel on mortality in a population of patients with and without HF discharged after their first-time AMI and not undergoing PCI.

Methods

In Denmark, all citizens are registered with a personal number in the Central Population Register, which enables linkage of information on each individual across different registers. The Danish National Patient Register holds information on all hospitalizations in Denmark since 1978, and each hospitalization is registered with 1 primary diagnosis and, if appropriate, a secondary diagnosis according to the World Health Organization's International Classification of Diseases. The Danish Register of Medicinal Product Statistics registers all prescriptions dispensed from Danish pharmacies since 1995. Each prescription is coded according to the international classification of pharmaceuticals (Anatomic Therapeutical Chemical [ATC] system) and includes information on dispensing date, strength, formulation, quantity dispensed, and affiliation of the doctor issuing the prescription. As part of partial coverage of drug expenses by the Danish health care system, pharmacies are requested to register all dispensed prescriptions, ensuring complete registration nationwide (16). In Denmark, all cardiovascular pharmaceuticals require a prescription, except for aspirin, which is also dispensed as an over-the-counter drug.

Population. Patients discharged between January 1, 2000, and December 31, 2005, after their first-time hospitalization for AMI (World Health Organization's International Classification of Diseases-10th revision, codes I21-I22 as the primary or secondary diagnosis) were identified using the Danish National Patient Register. We included patients aged 30 years or more who survived for at least 30 days after discharge. Patients with PCI (Danish National Board of Health classification code KFNG02-05) treated within the first 30 days after hospitalization were excluded. To ensure a homogenous study population, we excluded patients with a history of AMI within a minimum of 22 years before hospitalization. Each patient's vital status as of December 31, 2005, was obtained from the Central Population Register. Comorbidity was defined according to the modified Ontario AMI mortality prediction rules by diagnoses from the index admission and 1 year before admission (17). The use of glucose-lowering therapy (ATC code A10) was used as a proxy for the diagnosis of pharmacologically treated diabetes. Patients were categorized as patients with HF if they had been discharged with the diagnosis code of HF (World Health Organization's International Classification of Diseases-10th revision, codes I11.0, I42, I50, J81.9) within 1 year of AMI admission or had claimed prescriptions for loop diuretics (ATC code cC03C) 90 days before admission to 90 days after discharge (18,19). Severity of HF was classified into 4 groups according to average daily dosage of loop diuretics during the first 90 days after discharge: group I, 0 to 39 mg; group II, 40 to 80 mg; group III, 81 to 160 mg; and group IV, ≥160 mg (18).

Abbreviations and Acronyms

CI = confidence interval
HF = heart failure
HR = hazard ratio
AMI = acute myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention

Medical treatment. We defined initiation of clopidogrel (ATC code B01AC04) if a prescription was claimed within 30 days after discharge and concomitant pharmacotherapy (beta-blockers, angiotensin-converting enzyme inhibitors, statins, glucose-lowering drugs, and vitamin K antagonist) within 90 days after discharge, respectively.

Statistical analyses. For descriptive statistics, continuous variables are presented as mean values with SD and categorical variables are presented as frequencies (Table 1). Statistical comparisons were performed using the Student *t* test for continuous variables and the chi-square test for categorical data. Significance level was determined as a 2-tailed p value of ≤0.05. We found a positive interaction between HF and clopidogrel in the total population and, therefore, stratified the population into 2 cohorts, with and without HF. All further analyses were performed separately in the 2 groups. Logistic regression models were used in the populations with and without HF to estimate the propensity score for claiming a prescription within 30 days from discharge, that is, each patient's probability of receiving clopidogrel. The models were conditional on baseline covariates, that is, age, gender, calendar year, severity of HF (only for patients with HF), concomitant medical treatment, and comorbidity. To account for potential

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Table 1 Baseline Characteristics: Patients Admitted From 2000 Through 2005 With First-Time Acute Myocardial Infarction Without Percutaneous Coronary Intervention and Surviving the First 30 Days

		Heart Failure (n = 15,438)			No Heart Failure (n = 15,813)		
		Clopidogrel	No Clopidogrel	p Value	Clopidogrel	No Clopidogrel	p Value
Total	31,251	2,659 (17.2)	12,779 (82.8)		3,453 (21.8)	12,360 (78.2)	
Men	17,956	1,453 (54.6)	6,526 (51.1)	<0.001	2,240 (64.9)	7,737 (62.6)	0.014
Age (yrs)	68.4 (12.7)	75.1 (10.1)	76.1 (10.7)	<0.001	65.5 (12.8)	66.8 (13.3)	<0.001
Year of admittance to hospital							
Year 2000–2001	12,516	136 (5.1)	5,897 (46.1)	<0.001	213 (6.2)	6,270 (50.7)	<0.001
Year 2002–2003	10,772	1,119 (42.1)	4,221 (33.0)	<0.001	1,512 (43.8)	3,920 (31.7)	<0.001
Year 2004–2005	7,963	1,404 (52.8)	2,661 (20.8)	<0.001	1,728 (50.0)	2,170 (17.6)	<0.001
Comorbidity							
Cerebral vascular disease	2,175	207 (7.8)	1,066 (8.3)	0.34	151 (4.4)	751 (6.1)	<0.001
Diabetes with complications	2,069	302 (11.4)	1,162 (9.1)	<0.001	132 (3.8)	473 (3.8)	0.99
Cardiac dysrhythmias	4,294	453 (17.0)	2,445 (19.1)	0.01	233 (6.7)	1,163 (9.4)	<0.001
Acute renal failure	408	46 (1.7)	265 (2.1)	0.25	9 (0.3)	88 (0.7)	0.003
Chronic renal failure	600	90 (3.4)	381 (3.0)	0.27	21 (0.6)	108 (0.9)	0.13
Malignancy	1,315	109 (4.1)	677 (5.3)	0.01	84 (2.4)	445 (3.6)	<0.001
Shock	403	41 (1.5)	243 (1.9)	0.21	10 (0.3)	109 (0.9)	<0.001
Pulmonary edema	684	97 (3.6)	523 (4.1)	0.29	11 (0.3)	53 (0.4)	0.37
Severity of HF*							
Group I	566	113 (4.2)	453 (3.5)	0.08			
Group II	9,818	1,702 (64.0)	8,116 (63.5)	0.63			
Group III	3,572	606 (22.8)	2,966 (23.4)	0.64			
Group IV	845	142 (5.3)	703 (5.5)	0.74			
Concomitant pharmacotherapy							
Beta-blockers	22,221	2,025 (76.2)	8,161 (63.9)	<0.001	2,941 (85.2)	9,094 (73.6)	<0.001
ACE inhibitors	13,441	1,606 (60.4)	6,562 (51.3)	<0.001	1,367 (39.6)	3,906 (31.6)	<0.001
Statins	15,929	1,689 (63.5)	4,709 (36.8)	<0.001	2,915 (84.4)	6,616 (53.5)	<0.001
Glucose-lowering drugs†	4,251	558 (21.0)	2,276 (17.8)	<0.001	339 (9.8)	1,078 (8.7)	0.046
Vitamin K antagonist	2,599	225 (8.5)	1,540 (12.1)	<0.001	123 (3.6)	711 (5.8)	<0.001
Loop diuretics	14,821	2,566 (96.5)	12,255 (95.9)	0.15	0 (0.0)	0 (0.0)	

Values are n (%) and/or mean ± SD. *Loop diuretics are used as a proxy for heart failure. According to average daily dosage of loop diuretic (furosemide) in the first 90 days after discharge (group I, 0 to 39 mg; group II, 40 to 80 mg; group III, 81 to 160 mg; group IV, > 160 mg). †Glucose-lowering drugs used as a proxy of diabetes.
ACE = angiotensin converting enzyme; HF = heart failure.

confounding, we performed a match-pair analysis based on the propensity score for receiving clopidogrel and the period of hospitalization (2000 through 2001, 2002 through 2003, and 2004 through 2005), that is, 2 patients with the same propensity estimate and period were matched; however, 1 patient had claimed a prescription of clopidogrel and the other patient had not. The cohorts were matched by the greedy match algorithm (20). The hazard ratio (HR) for death from all causes was estimated by univariate Cox proportional hazards analysis with individual lifetime starting at 30 days from discharge. Survival estimates on the 2 subgroups of the matched population were calculated separately for each group using the Kaplan-Meier method and were evaluated with the log-rank test.

All analyses were performed with the Statistical Analytical System, version 9.1 (SAS Institute, Cary, North Carolina). No ethical approval is required for retrospective register studies in Denmark.

Results

Study population and patient characteristics. We identified 56,944 patients discharged after their first AMI from January 1, 2000, through December 31, 2005. A total of 40,902 (71.8%) patients did not undergo PCI and of these, 31,295 (76.5%) patients survived at least 30 days after discharge and were eligible for study inclusion. The selection of patients is shown in Figure 1. Of the 31,251 patients included, 6,112 (19.6%) patients were treated with clopidogrel and 15,438 (49.4%) were categorized with HF. After matching according to propensity score for receiving clopidogrel, the HF population included 2,525 matched pairs; each pair including one patient treated with clopidogrel and one treated without. Likewise, we identified 3,046 matched pairs without HF. Because of emigration, 7 patients were lost to follow-up in the matched populations and were censored at the time of disappearance. The mean follow-up in the population with HF was 1.50 years (SD = 1.2) and 2.05 years (SD = 1.3) in the population without HF. The matched population included 91.1% of all patients receiving clopidogrel in the unmatched population. The propensity score analysis had a C-statistics value of 0.77, indicating good discriminatory power of the model.

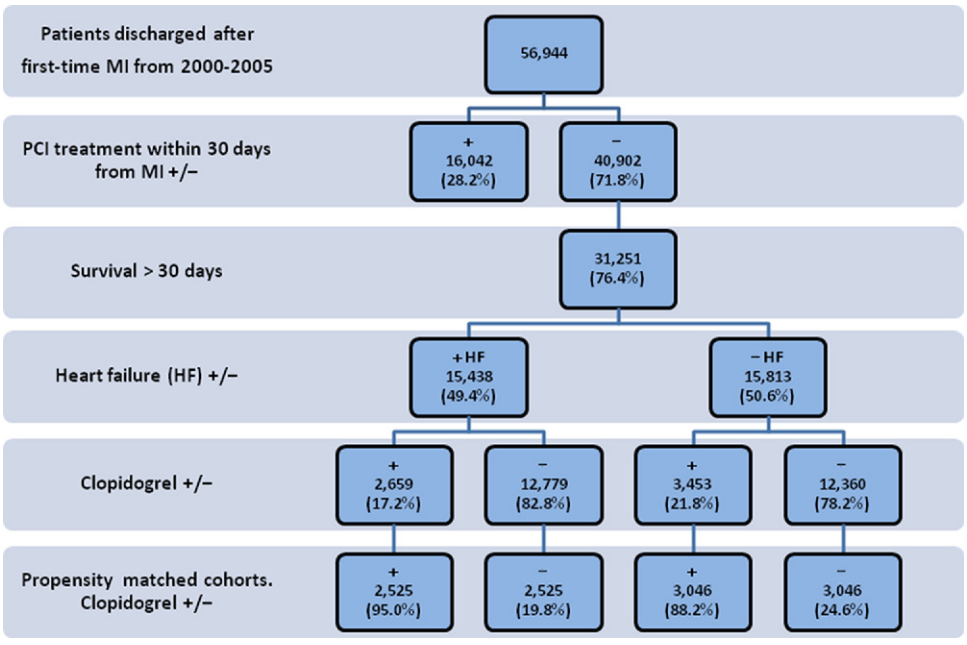

Figure 1 **Population Selection Process**

Identification of 4 propensity score-matched cohorts: 2 cohorts with heart failure (HF), and 2 cohorts without HF. MI = myocardial infarction; PCI = percutaneous coronary intervention; +/÷ clopidogrel = patients treated with or without clopidogrel; +/÷ HF = patients with or without HF; +/÷ PCI = patients treated with or without PCI.

In the unmatched population, patients with HF were less likely to receive clopidogrel compared with patients without HF. The 2 subgroups were unbalanced in selected variables, for example, year of hospital admittance and concomitant pharmacotherapy. There was an increase in the initiation rate of clopidogrel during the study period from 1.1% to 17.6% in patients with HF and from 1.7% to 21.7% in patients without HF, respectively (Table 1). Baseline characteristics of the two matched populations are shown in Table 2.

All-cause mortality. We found interaction between clopidogrel and HF on the effect of clopidogrel on mortality (HR: 1.17; 95% confidence interval [CI]: 1.00 to 1.33; p = 0.048) in the unmatched population. In the matched population and among patients with HF, a total of 812 (32.2%) died while not being treated with clopidogrel compared with 709 (28.1%) deaths in the group receiving clopidogrel (p = 0.002). In patients without HF, 294 (9.7%) died without clopidogrel treatment and 285 (9.4%) died in the group that received clopidogrel (p = 0.83) (Fig. 2). Results of the Cox proportional hazards analysis for death are illustrated in Figure 3. We found a decreased risk of death associated with clopidogrel in the HF cohort (HR: 0.86; 95% CI: 0.78 to 0.95; p = 0.002). The effect of clopidogrel was not significant in the cohort without HF (HR: 0.98; 95% CI: 0.83 to 1.16; p = 0.83).

Additional analyses. We performed Cox proportional hazards analysis for death in the unmatched population adjusting for all baseline variables. In the group with HF, we found a decreased risk of death associated with clopidogrel in HF patients (HR; 0.88; 95% CI: 0.81 to 0.96; p = 0.004) compared with no use of clopidogrel. Clopidogrel use in the group without HF showed no level of significance (HR: 0.96; 95% CI: 0.84 to 1.09; p = 0.50). In the matched population, we divided patients with HF into 2 subgroups, one group including patients identified by the discharge diagnosis codes of HF and another with patients identified by prescriptions of loop diuretics. The effect of clopidogrel on these 2 HF groups showed equal results (data not shown).

Discussion

This nationwide study evaluated the effect of clopidogrel on mortality in patients admitted with first-time AMI who did not undergo PCI within 30 days. The principal finding was a 14% relative risk reduction in mortality associated with clopidogrel in patients with HF compared with patients without clopidogrel. No mortality benefit with clopidogrel among patients without HF was observed. The importance of this finding is underlined by the previously described low initiation rate of clopidogrel in AMI patients not receiving PCI and the fact that a substantial part of the patients not receiving clopidogrel had HF (12).

A favorable survival effect of clopidogrel in patients with AMI and HF may in part be explained by reduction of the

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Table 2 Baseline Characteristics of Propensity-Matched Population: Patients Admitted From 2000 through 2005 With First-Time Acute Mycardial Infarction Without Percutaneous Coronary Intervention and Surviving the First 30 Days

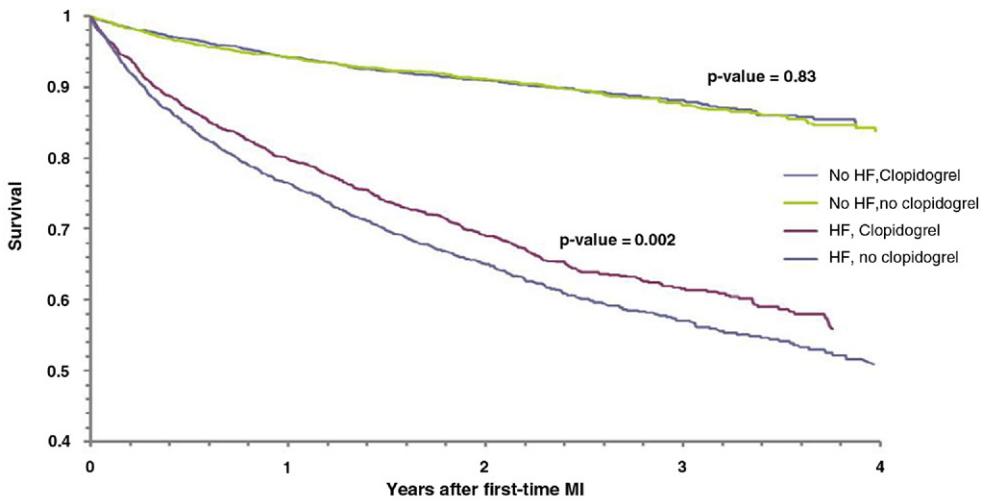
		Heart Failure (n = 5,050)			No Heart Failure (n = 6,092)		
		Clopidogrel	No Clopidogrel	p Value	Clopidogrel	No Clopidogrel	p Value
Total	11,142	2,525 (50.0)	2,525 (50.0)	1.00	3,046 (50.0)	3,046 (50.0)	1.00
Men	6,676	1,377 (54.5)	1,352 (49.6)	0.48	1,958 (64.3)	1,989 (65.3)	0.41
Age (yrs)	70.1 (12.6)	75.1 (10.0)	75.3 (10.6)	0.46	65.7 (12.9)	66.1 (12.6)	0.28
Year of admittance to hospital							
Year 2000–2001	690	132 (5.2)	132 (5.2)	1.00	213 (7.0)	213 (7.0)	1.00
Year 2002–2003	5,172	1,075 (42.6)	1,075 (42.6)	1.00	1,511 (49.6)	1,511 (49.6)	1.00
Year 2004–2005	5,280	1,318 (52.2)	1,318 (52.2)	1.00	1,322 (43.4)	1,322 (43.4)	1.00
Comorbidity							
Cerebral vascular disease	868	194 (7.7)	196 (7.8)	0.92	148 (4.9)	148 (4.9)	1.00
Diabetes with complications	783	290 (11.5)	259 (10.3)	0.16	118 (3.9)	116 (3.8)	0.89
Cardiac dysrhythmias	1,333	425 (16.8)	442 (17.5)	0.53	227 (7.5)	239 (7.8)	0.56
Acute renal failure	108	42 (1.7)	47 (1.9)	0.59	9 (0.3)	10 (0.3)	0.82
Chronic renal failure	210	86 (3.4)	83 (3.3)	0.81	21 (0.7)	20 (0.7)	0.88
Malignancy	350	104 (4.1)	90 (3.6)	0.31	82 (2.7)	74 (2.4)	0.52
Shock	102	41 (1.6)	43 (1.7)	0.83	10 (0.3)	8 (0.3)	0.64
Pulmonary edema	189	92 (3.6)	79 (3.1)	0.32	9 (0.3)	9 (0.3)	1.00
Severity of HF*							
Group I	210	106 (4.2)	104 (4.1)	0.89			
Group II	3,362	1,676 (66.4)	1,686 (66.8)	0.77			
Group III	1,197	601 (23.8)	596 (23.6)	0.87			
Group IV	281	142 (5.6)	139 (5.5)	0.85			
Concomitant pharmacotherapy							
Beta-blockers	8,888	1,912 (75.7)	1,884 (74.6)	0.36	2,548 (83.7)	2,544 (83.5)	0.89
ACE inhibitors	5,395	1,497 (59.3)	1,509 (59.8)	0.73	1,184 (38.9)	1,205 (39.6)	0.58
Statins	8,115	1,583 (62.7)	1,534 (60.8)	0.16	2,508 (82.3)	2,490 (81.8)	0.55
Glucose lowering drugs†	1,614	538 (21.3)	499 (19.8)	0.17	304 (10.0)	273 (9.0)	0.18
Vitamin K antagonist	674	223 (8.8)	200 (7.9)	0.34	119 (3.9)	132 (4.3)	0.40
Loop diuretic	5,050	2,525 (100)	2,525 (100)	1.00	0 (0.0)	0 (0.0)	

Values are n (%) and/or mean ± SD. *Loop diuretics are used as a proxy for heart failure. According to average daily dosage of loop diuretic (furosemide) in the first 90 days after discharge (group I, 0 to 39 mg; group II, 40 to 80 mg; group III, 81 to 160 mg; group IV, >160 mg). †Glucose-lowering drugs used as a proxy of diabetes.
Abbreviations as in Table 1.

increased risk of atherothrombotic events (14). In the Effects of CURE (Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation) study, clopidogrel prevented a composite end point of cardiovascular death, AMI, or stroke in patients with NSTEMI or unstable angina regardless of coronary revascularization procedures. The effect of clopidogrel was driven primarily by a reduction in recurrent AMI (7,21). The findings of the current study are compatible with the results of CURE, and the observed beneficial effect of clopidogrel on the mortality of patients with AMI and HF may be related to a reduction of recurrent AMI. In contrast, no statistically significant benefit of clopidogrel on mortality was shown in the CURE trial, although it should be mentioned that CURE was not powered to demonstrate a reduction of mortality. We did not observe a similar reduction of mortality in the cohort without HF. This could be explained by a much lower possibility to detect a difference because these patients have a much better prognosis in general (7).

As mentioned in the previous text only a minor part of patients in the CURE study had HF, and our study's results therefore add important knowledge regarding the use of clopidogrel in post-AMI patients with HF. The randomized trial of COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) evaluated the effect of adding clopidogrel to aspirin in patients with AMI (8). In the COMMIT study, severe HF was not an exclusion criterion and patients with HF therefore comprised a substantial part of the study population (25% with Killip class II or III HF). In this population, there was a 7% relative reduction in all-cause mortality up to 28 days after admission, which seems to be in agreement with the benefits of clopidogrel in patients with HF found in the present study (8).

HF is associated with increased risk of death after AMI, and therefore the recently documented low use of clopidogrel in AMI patients treated without PCI is of concern (10–12). Part of the low use of clopidogrel is related first to the study period (inclusion from 2000 through 2005) and second to exclusion of all patients undergoing primary PCI, which was nationally implemented in 2002. Lack of updated knowledge of NSTEMI treatment guidelines among physicians may explain in part the low initiation rates of clopidogrel after noninvasively treated AMI. In addition,



Number of patients under observation (number of deaths each year).

Year	0	1	2	3	4
HF, clopidogrel	2525 (457)	1481 (163)	789 (65)	322 (17)	64
HF, no clopidogrel	2525 (533)	1419 (180)	770 (73)	322 (22)	69
No HF, clopidogrel	3046 (163)	2312 (67)	1510 (34)	688 (16)	172
No HF, no clopidogrel	3046 (165)	2259 (62)	1515 (45)	740 (20)	166

Figure 2 **Kaplan-Meier Survival Curve for Propensity-Matched Population With and Without HF**

Survival of matched populations with and without clopidogrel. HF = heart failure; MI = acute myocardial infarction.

high cost could contribute, because clopidogrel is only partly reimbursed. However, this seems to be a minor problem in Denmark, because reimbursement is equal to all patients independent of social status, participation in the labor market, or availability of private health insurance programs (12).

Previously, Sørensen et al. (12) studied the pattern of clopidogrel use in AMI patients not treated with PCI. The number of AMI patients treated without PCI (72%) stated in the current study (Fig. 1) seems high; however, the division of the observational period into 3 periods of hospitalization (2000 through 2001, 2002 through 2003,

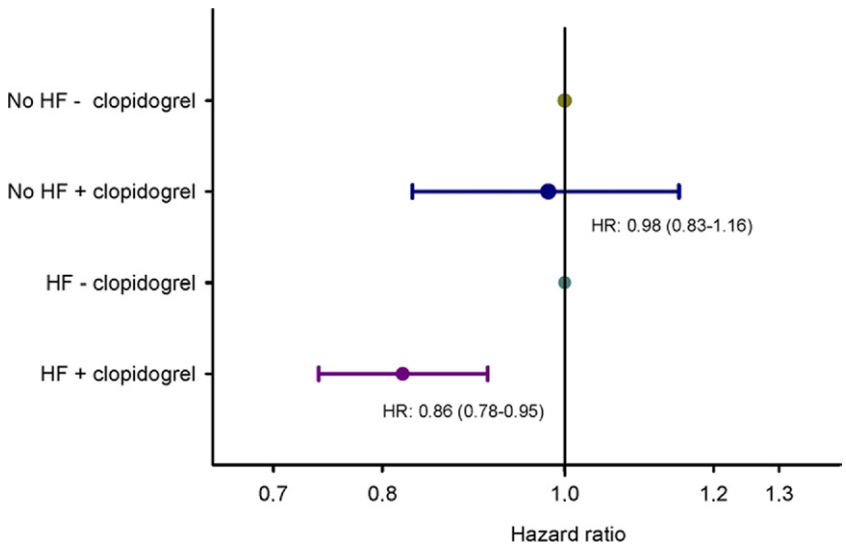


Figure 3 **HRs for Death According to Clopidogrel (No Treatment Reference)**

Two populations of patients with acute myocardial infarction with and without heart failure (HF) matched on propensity score for receiving clopidogrel conditional of baseline covariates. 95% confidence intervals are illustrated. HR = hazard ratio.

and 2004 through 2005) show increasing practice of PCI: 18.1%, 34.3%, and 45.2%, respectively. Concerning the pattern of clopidogrel use, an average of 19.6% initiated clopidogrel during the study period, and again, an increase in practice is shown from 2.8%, to 24.4%, to 39.3%. However, during all periods, patients with HF were less likely to receive clopidogrel compared with patients without HF (12). Absence of evidence-based recommendations regarding optimal antiplatelet therapy in post-AMI patients with HF may have discouraged physicians from prescribing the drug. Similar considerations may apply to concerns about increased bleeding risk of dual antiplatelet therapy in AMI patients with HF, because these patients usually are older, take more concomitant medications, and may have significant fluctuations in liver function, food intake, and drug absorption (22). Thus, a future trial evaluating the effect of clopidogrel in patients with HF may provide an important cornerstone in securing optimal treatment for this patient group. In addition to the low initiation rates of clopidogrel in AMI patients not undergoing PCI, these patients also display a poor short-term adherence to clopidogrel therapy. We previously demonstrated that from 2004 through 2005, only 71.6% of patients initially administered clopidogrel actually completed 90 days of treatment, with numbers further declining to 53.9% of patients completing 9 months of treatment (12). In our present Kaplan-Meier analysis (Fig. 2), the survival benefit of clopidogrel was evident within the first year of follow-up, which underlines the importance of encouraging patients to persist with clopidogrel.

To our knowledge, this study is the first to evaluate the effect of clopidogrel on all-cause mortality in patients with HF and AMI who do not undergo PCI. Whether these results can be extrapolated to other patients with HF is unknown. Two major randomized studies have been launched to examine the optimal antithrombotic therapy in patients with HF, but the WATCH (Warfarin and Antiplatelet Therapy in Heart Failure) trial was terminated prematurely because of poor enrollment, and an interim analysis showed no difference between warfarin, aspirin, and clopidogrel for a combined end point of all-cause mortality, nonfatal AMI, and nonfatal stroke (23), whereas results from the WARCEF (Warfarin versus Aspirin in Patients with Reduced Cardiac Ejection Fraction) study are pending (24). However, results from the literature support a beneficial effect of clopidogrel in patients with HF. For example, Serebruany et al. (15) showed a significant inhibition of the increased platelet activity in patients with HF after adding clopidogrel to aspirin. Furthermore, Meune et al. (25) observed that in patients with HF receiving angiotensin converting enzyme inhibitors, aspirin had an adverse effect on plasma concentrations of brain natriuretic peptides that was not found with clopidogrel.

Study strengths and limitations. The main strength of the current study is the completeness of the data sample covering the entire population of Denmark. We hereby avoid selection bias related to, for example, age, sex, willingness to participate in the study, demographic factors, and socioeconomic differences. The Danish National Patient Register diagnosis codes of AMI have been validated previously with a sensitivity of 91% and a positive predictive value of 93% (26). However, we were not able to distinguish precisely between patients with ST-segment elevation myocardial infarction and NSTEMI, because the register has not been validated with respect to these diagnosis codes. The diagnosis code of HF has a sensitivity of 29% and a positive predictive value of 91% (27). To avoid underreporting of cases with HF, we decided to include patients receiving treatment with loop diuretics in addition to those with an HF diagnosis (18). We performed subgroup mortality analyses of these 2 HF groups independently and found equal results (data not shown). Potential underreporting of HF, however, is likely to dilute any observed effect of clopidogrel, and without under-reporting, the effect may have been even stronger. Likewise, 12.3% of the patients in the matched population claimed a prescription beyond 30 days from discharge and therefore constituted part of the group treated without clopidogrel. This may also weaken the found effect of clopidogrel and therefore may strengthen the validity of our results. Patients with diabetes were identified by use of glucose-lowering therapy, that is, diabetes patients not requiring pharmacological treatment were not included in this group.

The Danish National Patient Register does not include clinical variables, for example, blood pressure, left ventricular ejection fraction, brain natriuretic peptide levels, and other risk factors that could influence the patients' prognosis. Nor do we know whether the patients started clopidogrel during the admission but stopped again because of side effects or drug intolerance. Also, we do not have information about potential risks of bleeding or knowledge of other risk or benefit considerations related to clopidogrel. However, the results include all-cause mortality, and fatal bleedings thus are included in the results. There is a risk of confounding by indication, for example, sicker patients are not prescribed clopidogrel and die shortly thereafter, regardless of the drug. To ensure a more homogenous population, we therefore included only patients who survived at least 30 days after hospital discharge. Channeling bias also may be of concern, that is, healthier patients are more prone to receive treatment than sicker patients. To diminish this potential bias, we matched our populations according to propensity score with a good discriminative power (C statistics = 0.77), but we cannot rule out unknown risk factors or confounders in the propensity match, and the current study cannot take the place of a randomized trial (28). Finally, the use of claimed prescriptions as a proxy of medical treatment in the study population may imply bias, that is, the claimed prescriptions may not correspond to the consumed medication. In Denmark, however, the medications of interest are dispensed only with a valid prescription and all pharmacies must report every claimed prescription because of a national

reimbursement scheme, which ensures complete registration of dispensed drugs and diminishes the patient's incentive to obtain medication through other sources. Moreover, the Danish Prescription Register has been shown to be highly accurate, and concordance between drug dispensing and consumption is likely to be high (16).

Conclusions

The current study demonstrated an association between clopidogrel and decreased mortality in patients with AMI and HF who do not undergo PCI. These patients have low initiation rates of clopidogrel and the data suggest that increased awareness of the benefit of clopidogrel in such high-risk patients can have considerable clinical impact. A randomized study of the effect of clopidogrel in patients with HF therefore is crucial to improve treatment of this growing patient population.

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