European Heart Journal (2005) **26**, 1063–1069
doi:10.1093/eurheartj/ehi139

Clinical research

Impact of combined pharmacologic treatment with clopidogrel and a statin on outcomes of patients with non-ST-segment elevation acute coronary syndromes: perspectives from a large multinational registry

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Received 10 July 2004; revised 15 December 2004; accepted 5 January 2005; online publish-ahead-of-print 16 February 2005

This paper was guest edited by Prof. Bernard J. Gersh, Mayo Clinic, Rochester, USA

KEYWORDS
Acute coronary syndrome;
Clopidogrel;
Statin;
Non-ST-segment elevation

Aims To evaluate clinical outcomes associated with the combined use of clopidogrel and statins vs. clopidogrel alone on a background of aspirin therapy in patients with the spectrum of acute coronary syndromes (ACS).
Methods and results Utilizing data from the Global Registry of Acute Coronary Events, we studied 15 693 patients admitted with non-ST-segment elevation myocardial infarction (MI) or unstable angina, dividing them according to discharge medications: aspirin alone (group I); aspirin + clopidogrel (group II); aspirin + statin (group III); aspirin + clopidogrel + statin (group IV). Among the groups of patients in whom clopidogrel was used (groups II and IV), group II patients were older, more likely to have prior MI, but less likely to have a history of prior revascularization. In-hospital cardiac catheterization and revascularization rates were similar between groups II and IV. Importantly, Kaplan–Meier analysis showed that the 6 month mortality rate was lower in group IV (log-rank test 22.8, $P < 0.0001$). The hazard ratio for the 6 month mortality rate was adjusted using the Cox proportional hazard model for confounding variables and for propensity score, and the 6 month mortality rate for patients in group IV remained lower compared with those in group II [0.59 (0.41–0.86), $P < 0.0001$].
Conclusion Our data suggest that the combination of clopidogrel with a statin has synergistic effects on the clinical outcomes of patients with non-ST-segment elevation ACS.

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Introduction

The care of patients presenting with acute coronary syndromes (ACS) has changed dramatically over the past several years, with the latest treatment guidelines adopting an aggressive approach using early coronary angiography in conjunction with the use of multiple pharmacologic agents.[1,2] Large-scale randomized clinical trials have supported the use of early coronary angiography in high-risk patients with ACS,[3–6] as well as the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as effective treatment in patients with coronary artery disease[7–10] and especially those hospitalized with ACS.[11–13] Furthermore, in addition to aspirin, clopidogrel has now been evaluated in two major clinical trials supporting its longer term use in this patient population.[14,15]

A recent study has suggested that there may be a drug–drug interaction between clopidogrel and atorvastatin, which antagonizes some of the antiplatelet effects produced by clopidogrel.[16] The available clinical data from randomized trials to support this hypothesis remain sparse, as only 25% of patients in the Clopidogrel in Unstable angina to prevent Recurring Events (CURE)[14] and 54% of patients in the Clopidogrel for the Reduction of Events During Observation (CREDO) trials[15] received lipid-lowering or statin therapy. Furthermore, neither of these trials was designed and appropriately powered to evaluate this drug–drug interaction, making it unclear whether this antagonism between clopidogrel and statins has any meaningful implications on clinical outcomes of patients with ACS.

In this analysis, we utilized data from the large, observational Global Registry of Acute Coronary Events (GRACE) to study the benefits or possible antagonistic effects on clinical outcomes seen with the combination of clopidogrel and statin treatment compared with clopidogrel alone.

Methods

Grace

The rationale and methods for the GRACE registry have been published.[17–19] GRACE is designed to reflect an unbiased, geographically varied population of patients with ACS. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, UK, and USA) are participating in this observational study.

Patient recruitment

Patients enrolled in this study had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (i.e. have symptoms consistent with acute ischaemia), and have at least one of the following: electrocardiographic (ECG) changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated by significant non-cardiovascular co-morbidity (e.g. trauma or surgery). At $\sim$6 months after hospital discharge, patients were followed up to ascertain the occurrence of selected long-term study outcomes. Where required, study investigators received approval from their local hospital institutional review board and a signed consent form for follow-up was obtained.

Data collection

To ensure the enrollment of an unbiased population, the first 10–20 consecutive patients (depending on each site's patient throughput) were recruited from each site per month. Data were collected at each site by a trained coordinator using a standardized case report form. Demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used.[17–19] Patients were diagnosed with ST-segment elevation myocardial infarction (STEMI) when they have new or presumed new ST-segment elevation $\geq$1 mm seen in any location, or new left bundle branch block on the index, or qualifying ECG with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of non-ST-segment elevation myocardial infarction (NSTEMI), at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or qualifying ECG had to be present. Unstable angina was diagnosed when serum biochemical markers, indicative of myocardial necrosis in each hospital's laboratory, were within the normal range. Patients originally admitted because of unstable angina, but in whom MI evolved during the hospital stay, were classified as having an MI.

Patient population

The population for this study included those patients in the GRACE registry with a hospital discharge diagnosis of unstable angina or NSTEMI. Patients presenting or discharged with a diagnosis of STEMI were excluded. Patients were divided into four groups on the basis of medications prescribed at discharge: group I (aspirin alone); group II (aspirin + clopidogrel); group III (aspirin + statin); group IV (aspirin + clopidogrel + statin). Treatment in GRACE was not mandated by a protocol but was left at the discretion of the treating physician.

Statistical analysis

All categorical measures were reported as counts with percentages. All continuous measures were reported as medians for measures of centrality and 25th and 75th percentiles as measures of variation. The main study comparisons were restricted to the two groups in whom clopidogrel was used (i.e. groups II and IV). Univariable comparisons between these two comparison groups of interest were made using the Pearson's χ^2 test or Fisher's exact test for categorical/binary variables. For continuous variables, the normality test was performed within each group, and if the normality condition was not satisfied, then a non-parametric *P*-value was calculated based on the Wilcoxon rank-sum test. Otherwise, the *P*-values were given based on the Type III SS from a general linear model procedure. Kaplan–Meier curves were constructed to compare the two comparison groups in terms of mortality up to 6 months after hospital discharge.

A multivariable Cox proportional hazard model was used to examine the association between the two therapeutic regimens

(aspirin + clopidogrel vs. aspirin + clopidogrel + statin) and the 6 month mortality rate, with adjustment for baseline characteristics, in-hospital medications, in-hospital procedures, rehospitalization, and revascularization as performed before using the GRACE-risk-score.[20] The assumption of proportional hazards was assessed graphically by comparing estimated $-\ln(-\ln)$ survivor curves over different categories of variables. All variables in the final model met assumptions for proportional hazards.[20] To adjust for the bias inherent in the decision about the choice of therapy, subsequent models were adjusted for the propensity for treatment with the combination of aspirin + clopidogrel + statin vs. aspirin + clopidogrel in addition to the GRACE risk score. The propensity score was estimated by stepwise multivariate logistic regression (backward elimination) using baseline characteristics. The final propensity score model included only those independent variables associated with the probability of being assigned to group IV vs. group II. All statistical analyses were performed using SAS software (version 8.1, SAS Institute, Cary, NC, USA).

Results

A total of 15 693 patients with a diagnosis of unstable angina or NSTEMI were included in this analysis. *Table 1* depicts the baseline demographics, presenting signs and symptoms, and the concomitant medications that were prescribed at discharge according to the four study groups. Among the two groups in whom clopidogrel was used (groups II and IV), group II patients were older with higher rates of ST-segment deviations, but were less likely to have a history of prior MI, smoking, or prior revascularization. The frequency of NSTEMI did not differ between the two groups. However, patients in group II were less likely to receive angiotensin-converting enzyme (ACE) inhibitors and beta-blockers at the time of discharge. In contrast, the use of invasive procedures did not differ between groups II and IV (Figure 1). Stents were implanted in the majority of patients who underwent percutaneous revascularization (95% for group II and 95.6% for group IV; $P = 0.5728$).

As seen in *Table 2*, the incidence of rehospitalization and stroke from hospital discharge to 6 month follow-up was similar among the patients in groups II and IV. In contrast, coronary revascularization rates beyond hospital discharge were lower in group II compared with group IV. The 6 month mortality was more than two-fold higher in group II compared with group IV. A Kaplan–Meier analysis showing overall unadjusted mortality in the two comparison groups over 6 months is shown in *Figure 2* with group II showing higher mortality (log-rank test 22.8, $P < 0.0001$).

Results of propensity analysis are shown in *Table 3*. The 6 month mortality remained higher in group II compared with group IV, even after adjustment for confounders using the GRACE risk score and propensity score (hazard ratio 0.59, 95% CI 0.41–0.86). *Table 4* shows adjusted hazard ratios for diabetics, non-diabetics, those already on clopidogrel at the time of their admission, and those not on clopidogrel before admission with the point estimate consistently favouring those in group IV.

Discussion

Our study shows a significantly lower mortality rate among patients who were discharged on aspirin,

Table 1 Patient baseline characteristics

Characteristics	Group I ($n = 4625$)	Group III ($n = 5156$)	Group II ($n = 1614$)	Group IV ($n = 4298$)	*P*-value (group II vs. group IV)
Demographics					
Age, mean (SD)	68 ± 13	65 ± 12	67 ± 12	63 ± 12	<0.0001
Men (%)	60	63	69	72	0.0526
Hypertension (%)	65	66	63	64	0.7405
Diabetes (%)	25	28	27	27	0.8375
Prior MI (%)	35	42	29	36	<0.0001
PVD (%)	11	11	12	11	0.3328
Smoking history (%)	51	58	56	63	<0.0001
Prior CABG (%)	13	20	16	21	<0.0001
Prior PCI (%)	13	21	23	30	<0.0001
Presentation					
ST-segment deviation (%)	36	34	37	33	0.0016
Initial biomarker elevation (%)	30	29	36	36	0.6394
Killip class >II (%)	4.5	3.1	3.6	2.3	0.0636
Unstable angina (%)	58	58	46	46	0.8283
NSTEMI (%)	42	42.2	54	54	0.8283
Discharge medications					
Calcium-channel blockers (%)	25	29	24	24	0.8151
Beta-blockers (%)	68	78	75	83	<0.0001
ACE inhibitors (%)	51	55	52	59	<0.0001
Nitrates (%)	55	54	43	42	0.4915

CABG, coronary artery bypass grafting; PVD, peripheral vascular disease; SD, standard deviation.

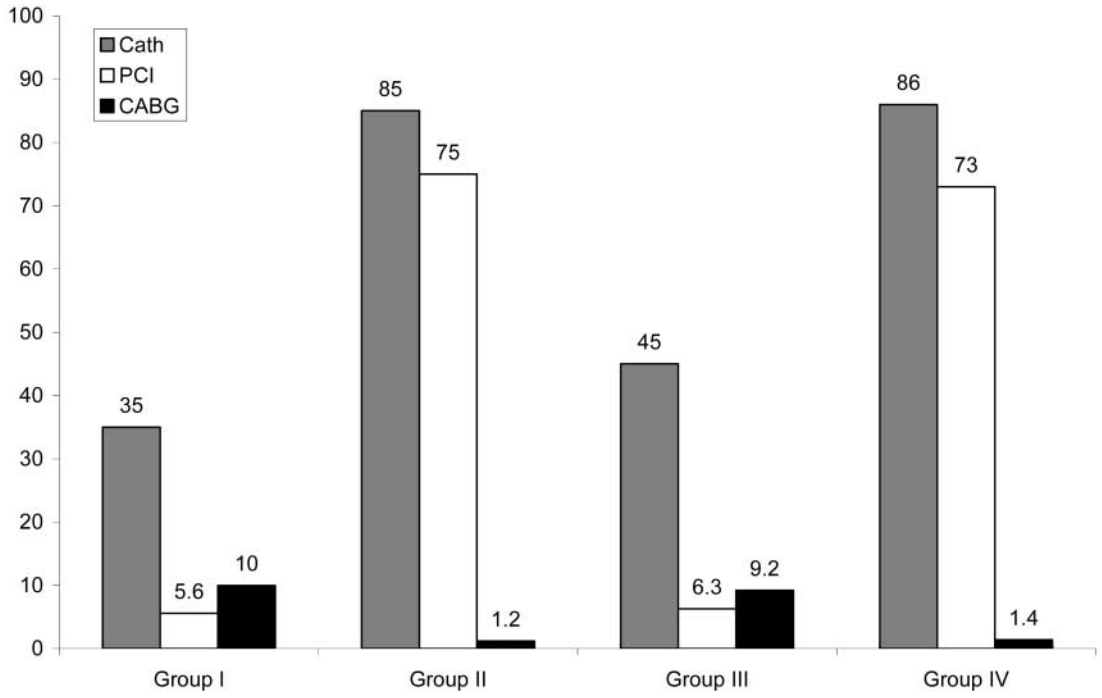

Figure 1 Proportion of patients undergoing procedures in the four study groups. *P*-values (group II vs. group IV): 1, Cath: 0.3522; 2, PCI: 0.3646; 3, CABG: 0.5557.

Table 2 Post discharge to 6 month outcomes

Outcome	Group I ($n = 3342$)	Group III ($n = 3071$)	Group II ($n = 866$)	Group IV ($n = 1728$)	*P*-value (group II vs. group IV)
Rehospitalization (%)	17	19	21	22	0.2229
Stroke (%)	1.3	1.0	1.0	0.7	0.1995
Revascularization (%)	9.5	13	13	15	0.0136
Death (%)	5.8	3.6	4.4	2.1	<0.0001

clopidogrel, and a statin when compared with those receiving aspirin and clopidogrel even when the differences in baseline variables and the bias in treatment allocation were accounted for. In fact, the use of triple therapy (aspirin, clopidogrel, and statins) was associated with the lowest mortality among the four groups of patients. Not surprisingly, we demonstrated that the prescription of clopidogrel upon discharge from hospital was strongly correlated with the performance of cardiac catheterization and percutaneous coronary intervention (PCI), whereas usage remains low in patients not receiving these procedures.

Data from a recent laboratory study by Lau *et al.*[16] suggest that the desired decrease in platelet aggregation from clopidogrel treatment is adversely affected by the concomitant use of atorvastatin. This antagonistic effect was not present in patients treated with pravastatin. The authors postulated that this was caused by a drug–drug interaction between clopidogrel and atorvastatin, which may involve the CYP3A4 metabolic pathway. However, this study was limited to the assessments of platelet aggregation *in vitro* and did not evaluate relevant implications of the drug interaction on clinical events.

Our analysis of more than 15 000 patients shows that, in general, patients receiving clopidogrel and statins do not exhibit any increase in overall clinical events that would suggest that this drug interaction observed in laboratory studies is clinically significant. In fact, patients who were discharged on aspirin, clopidogrel, and a statin (group IV) had the lower mortality over the 6 months following hospital discharge, even after adjustment for several confounding variables and treatment assignment bias. Thus, our data do not support a clinically meaningful antagonistic interaction between statins and clopidogrel, but on the contrary suggest important synergism between the two drugs on clinical outcomes when used on a background of aspirin therapy. Even in diabetics and patients on prior clopidogrel that have been shown to be high-risk,[21,22] the point estimate favoured the combination therapy of clopidogrel and statin, although this was not statistically significant. Whether longer term clopidogrel use and/or follow-up may have shown more robust reduction in

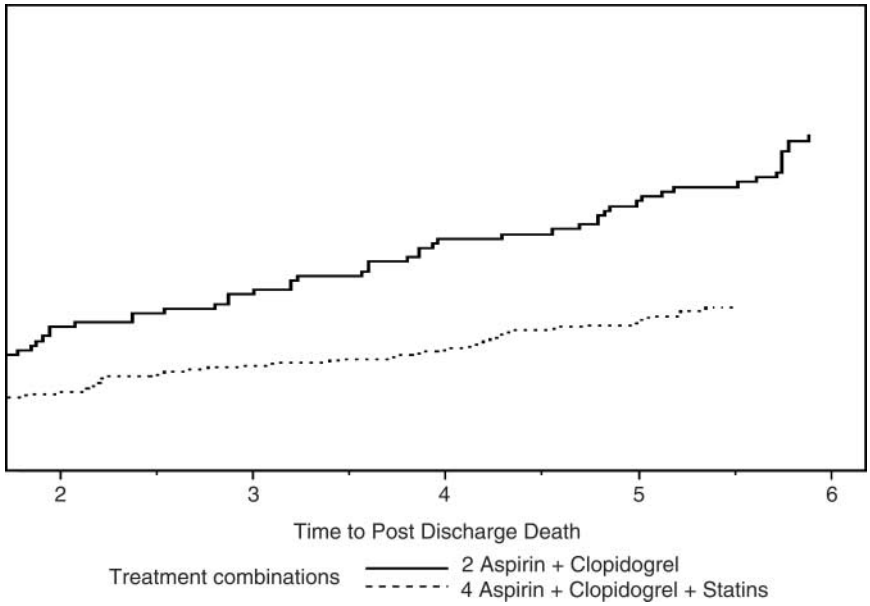

Figure 2 Kaplan–Meier estimates of unadjusted mortality at follow-up in group II vs. group IV.

Table 3 Propensity analysis predicting the use of group IV vs. group II

Predictors	OR	95% CI
Age (per 10 years increase)[a]	0.81	0.77–0.85
Initial serum creatinine	0.88	0.81–0.95
History of hyperlipidaemia	3.27	2.88–3.70
History of renal dysfunction	1.3	1.03–1.73
In-hospital GP IIb/IIIa	0.63	0.56–0.72
c-statistic = 0.69		

[a]As age increases the OR decreases.

Table 4 Subgroup analysis

Variable (Group IV)	Crude HR (95% CI)	Adjusted HR (95% CI)
Diabetic patients	0.33 (0.23–0.63)	0.60 (0.30–1.02)
Non-diabetic patients	0.50 (0.29–0.86)	0.60 (0.31–1.08)
Chronic clopidogrel use	0.52 (0.24–1.17)	0.58 (0.21–1.57)
Non-chronic clopidogrel	0.42 (0.30–0.61)	0.53 (0.35–0.80)

Reference group, group II (aspirin + clopidogrel). Adjusted GRACE risk score[20] and propensity score.

mortality in these groups remains to be seen. Clearly, our data suggest that more research is needed to evaluate strategies to improve the outcomes of diabetics and those with clopidogrel 'treatment failure' with ACS.

As noted earlier, within the present study, we noted a strong correlation between the prescription of clopidogrel on patient discharge and the performance of PCI. This is not surprising, because the initial therapeutic value of clopidogrel in clinical practice has been the prevention of subacute stent thrombosis. This has fueled a strategy for all post-stent patients to receive $\geq$ 1 month of clopidogrel therapy. Despite this close association of clopidogrel use with PCI, our restriction of the comparison to group II and IV where PCI use was similar, combined with adjustment for baseline confounders including treatment assignment bias, allowed us to provide insight into the clinical effects of drug interaction between clopidogrel and statin in these two groups when minimizing the role played by PCI on outcomes. Thus, our data suggest with reasonable certainty that the combination of clopidogrel and statin when used along with aspirin has no significant drug interaction that adversely affect clinical outcomes.

Strengths and limitations

GRACE is the largest multinational registry study to include the complete spectrum of ACS patients. In addition, this registry employs standardized criteria for defining ACS and hospital outcomes and the most rigorous quality control and audit measures of any current or previously published registry datasets. Our results are subject to limitations that are similar in any retrospective observational study. Although we have demonstrated a correlation between medication use and mortality, causality cannot be assumed. Furthermore, we cannot address patient compliance to medications at follow-up that may affect their outcomes. We also were unable to assess the influence of the combination of clopidogrel and specific statins on patient outcomes.

Conclusion

Our data suggest that the combination of clopidogrel with a statin has significant synergistic effects on the

clinical outcomes of patients with non-ST-elevation ACS. Thus, despite evidence of adverse drug interaction *in vitro*, our findings are that the concomitant use of these drugs improves the outcomes of patients with ACS.

Acknowledgements

The authors would like to express their gratitude to the physicians and nurses participating in GRACE. Further information about the project, along with the complete list of participants, can be found at www.outcomes.org/grace. GRACE is supported by an unrestricted educational grant from Aventis Pharma (Bridgewater, NJ, USA) to the Center for Outcomes Research (Worcester, MA, USA).

Appendix

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