Clopidogrel in addition to aspirin reduces in-hospital major cardiac and cerebrovascular events in unselected patients with acute ST segment elevation myocardial

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Summary

We sought to assess the effect of clopidogrel on in-hospital events in unselected patients with acute ST elevation myocardial infarction (STEMI). In a retrospective analysis of consecutive patients enrolled in the Acute Coronary Syndromes (ACOS) registry with acute STEMI we compared outcomes of either adjunctive therapy with aspirin alone or aspirin plus clopidogrel within 24 hours after admission. A total of 7,559 patients were included in this analysis, of whom 3,541 were treated with aspirin alone, and 4,018 with dual antiplatelet therapy. The multivariable analysis with adjustment for baseline characteristics and treatments showed that the rate of in-hospital MACCE (death, non-fatal reinfarction, non-fatal stroke) was significantly lower in the aspirin plus clopidogrel group, compared to the aspirin alone group in the entire cohort and all three reperfusion strategy groups (entire group odds ratio 0.60, 95% CI 0.49–0.72 , no reperfusion OR 0.69, 95% CI 0.51–0.94, fibrinolysis OR 0.62, 95% CI 0.44–0.88, primary PCI OR 0.54, 95% CI 0.39–0.74). There was a significant increase in major bleeding complications with clopidogrel (7.1% vs. 3.4%, p<0.001). In clinical practice early adjunctive therapy with clopidogrel in addition to aspirin in patients with STEMI is associated with a significant reduction of in-hospital MACCE regardless of the initial reperfusion strategy. This advantage was associated with an increase in major bleeding complications.

Keywords

Clopidogrel, reperfusion therapy, primary percutaneous coronary intervention, ST elevation myocardial infarction, prognosis, clinical practice

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Introduction

Platelets play an important role in the pathogenesis of acute coronary syndromes. It has been well established that antiplatelet therapy with aspirin improves the prognosis in patients with acute ST-segment elevation myocardial infarction (STEMI) and is therefore a standard treatment in these patients (1, 2). Aspirin only blocks the arachnidon-acid pathway of platelet aggregation, while clopidogrel blocks the $P2Y_{12}$ adenosine diphosphate receptor and acts synergistically with aspirin (3). In patients with acute coronary syndromes without ST elevations (4), and patients with elective percutaneous coronary intervention (PCI) (5), the therapy with clopidogrel in addition to aspirin further reduced platelet activation and thrombotic and ischemic complications after one year. Recently, the beneficial effect of clopidogrel in patients with STEMI treated with fibrinolysis has been shown in the CLopidogrel as Adjunctive Reperfusion TherapY (CLARITY-TIMI 28) study (6). Furthermore a large clinical study performed in patients with and without reperfusion therapy in China, the ClOpidogrel and Metoprolol in Myoycardial Infarction Trial (COMMIT) trial showed a reduction in four-week mortality with clopidogrel (7). In addition, clopidogrel pretreatment reduced ischemic complications before and after percutaneous coronary intervention (PCI) in the PCI-CLARITY substudy (8). However, little is known about the efficacy and safety of clopidogrel after STEMI in clinical practice. We there-

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fore analyzed data from the Acute COronary Syndromes (ACOS) registry to determine the impact of clopidogrel on in-hospital events in patients with STEMI treated with or without early reperfusion therapy.

Methods

The ACOS registry

The Acute Coronary Syndromes Registry (ACOS) is a prospective, multi-center, observational study on current treatment of acute coronary syndromes (STEMI, NSTEMI, and unstable angina pectoris) (9, 10). Consecutive patients were recruited within the period from June 2000 to December 2002. The 154 participating hospitals were located throughout Germany and included university hospitals, community hospitals and tertiary care centers all providing intensive care units and early reperfusion therapy. Two thirds (n=102) of the hospitals had interventional facilities. During the entire study period patients with acute coronary syndromes were registered prospectively over 12 months and followed during their clinical course to document patient characteristics, acute therapy and hospital course. The present study is an analysis of consecutive patients with STEMI treated with either aspirin monotherapy or dual platelet inhibition with aspirin and clopidogrel within 24 hours of admission.

Data collection

Data on patient characteristics on admission were recorded, including age, gender, cardiovascular risk factors, concomitant diseases, prior myocardial infarction, prior stroke, prior cardiovascular interventions and chronic medical treatment, as well as data on symptoms and prehospital delay. Data on electrocardiografic findings, biochemical markers, reperfusion therapy, and adjunctive therapy were documented. Major cardiovascular and cerebrovascular adverse events until hospital discharge were recorded.

Every participating center was committed by written consent to include every consecutive patient with acute coronary syndrome. All patients gave informed consent for processing their anonymous data. Data were collected on three record forms by the treating physicians. Completed data sheets were sent to the central data processing center Institut für Herzinfarktforschung Ludwigshafen for uniform monitoring and registration. Source data verification was performed by comparison of the registry data with hospital records in randomly selected 800 patients in randomly chosen participating centers. The entire data were double keyed and regularly checked for inconsistencies and out of range errors. The study was approved by the ethical committee of Landesärztekammer Mainz.

Definitions

STEMI was diagnosed in the presence of the following two criteria: persistent angina pectoris for ≥ 20 min and ST-segment elevation of > 1 mm in ≥ 2 standard leads or ≥ 2 mm in ≥ 2 contiguous precordial leads, or the presence of a left bundle branch block and elevations of cardiac enzymes CK-MB or troponin. Successful PCI was defined as TIMI 3 patency and residual stenosis of < 50% after PCI. Reinfarction was diagnosed in case of recurrent angina with re-elevation of CK-MB or angiographic demonstration of occlusion of the infarct vessel. Stroke was defined as the occurrence of persistent specific neurologic deficits. Major adverse cardiac and cerebrovascular events (MACCE) were classified as death, non-fatal reinfarction and non-fatal stroke. Major bleeding was defined as bleeding needing blood transfusion, intracranial bleeding, bleeding needing surgical intervention or clinically relevant bleeding as judged by the treating physician.

Statistical methods

Data are presented as absolute numbers, percentage or medians with 25th and 75th percentiles as appropriate. Whenever possible, percentages were used to describe patient populations. The frequencies of categorial variables in two populations were compared by χ^2 test and by calculating odds-ratios (OR) and 95% confidence intervals (CI). Continuous variables were compared by two-tailed Wilcoxon rank sum test. The effect of clopidogrel on in-hospital death and MACCE was evaluated by a mutivariable regression model calculating the odds ratio and the 95% confidence interval. The following variables were included in the multivariable regression model: age, sex, diabetes mellitus, hypertension, hyperlipidemia, prior stroke, 3-vessel disease, renal insufficiency, anterior infarct location, cardiogenic shock, reduced left ventricular function, elective revascularization, acute treatment with GP IIb/IIIa inhibitors, beta-blockers, statins, ACE-inhibitors, fibrinolysis, primary PCI and stent implantation. In the subgroup of patients treated with primary PCI stent implantation and succesful PCI were included in the multivariate analysis. P-values <0.05 were considered significant. All p-values are the results of two-tailed tests. The analysis was performed with the SAS® system release 8.2 on a personal computer (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

From 2000 and 2002, a total of 16,814 consecutive patients from 154 hospitals with acute coronary syndromes were enrolled in the ACOS registry. Of these, 8,305 had STEMI. Seven hundred forty-six (0.8%) patients were excluded who had not been treated with aspirin within 24 hours after admission. Therefore, this analysis contains 7,559 patients; 3,541 (46.8%) were treated with aspirin alone and 4,018 (53.2 %) with aspirin and clopidogrel. Of these, 2,141 (28.3%) received no reperfusion therapy, 2,186 (28.9 %) fibrinolysis and 3,232 primary PCI (42.8%). The baseline characteristics of the patients of the entire cohort and in the three reperfusion strategy groups are shown in Table 1.

In-hospital events

The total in-hospital mortality was lower in the patients treated with clopidogrel and aspirin compared to the group treated with aspirin alone (12.4% versus 5.1%, p< 0.001) (Table 2). However, in the multivariable analysis a significant reduction in mortality with clopidogrel was no longer observed, only a trend towards reduced mortality in the entire group and patients treated with primary PCI (Table 3). MACCE were observed significantly less often in the clopidogrel groups (Fig. 1). The absolute reduction in MACCE was higher in patients with higher baseline risk as-

Table 1: Baseline characteristics and treatments during the index hospitalisation in the entire group and subgroups according to the initial reperfusion strategy.

Patients	Entire group (n=7559)			Without early reperfusion therapy (n=2141)			Treated with fibrinolysis (n=2186)			Treated with primary PCI (n=3232)		
	Aspirin N=3541	Aspirin + clopidogrel n=4018	p- value	Aspirin n=1604	Aspirin + clopidogrel n=537	p- value	Aspirin n=1448	Aspirin + clopidogrel n=738	p-value	Aspirin n=489	Aspirin + clopidogrel n=2743	p-Value
Baseline characteristics												
Age (years), median	68.2 (58.3–77.0)	63.8 (53.8–72.4)	<0.001	73.5 (63.4–80.6)	70.3 (61.6–78.7)	0.001	64.3 (54.2–72.7)	60.9 (51.1–68.0)	<0.001	63.8 (54.8–72.5)	63.5 (53.4–71.8)	0.2
Women	1196 (33.8 %)	1098 (27.1 %)	<0.001	678 (42.3 %)	193 (35.9%)	0.01	376 (26.0 %)	170 (23.0 %)	0.1	142 (29.0 %)	726 (26.5 %)	0.2
Medical history												
Prior myocardial infarction	633 (17.9 %)	565 (14.1 %)	<0.001	347 (21.6 %)	129 (24.0 %)	0.2	202 (14.0 %)	93 (12.6 %)	0.4	84 (17.2 %)	342 (12.5 %)	0.005
Prior PCI or CABG	295 (8.3 %)	439 (10.9 %)	<0.001	132 (8.2 %)	84 (15.6 %)	<0.001	102 (7.0 %)	69 (9.3 %)	0.06	61 (12.5 %)	286 (10.4 %)	0.2
Prior Stroke / TIA	241 (6.8 %)	193 (4.8 %)	<0.001	155 (9.7 %)	45 (8.4 %)	0.4	61 (4.2 %)	23 (3.1 %)	0.2	25 (5.1 %)	125 (4.6 %)	0.6
Risk factors												
Hypertension	2129 (60.1 %)	2326 (57.9 %)	0.05	1037 (64.7 %)	362 (67.4 %)	0.2	780 (53.9 %)	401 (54.3 %)	0.8	312 (63.8 %)	1562 (56.9 %)	0.005
Diabetes mellitus	1038 (29.3 %)	953 (23.7 %)	<0.001	588 (36.7 %)	186 (34.6 %)	0.4	314 (21.7 %)	157 (21.3 %)	0.8	136 (27.8 %)	610 (22.2 %)	0.007
Hypercholesterolemia*	2166 (61.2 %)	2538 (63.2 %)	0.08	929 (57.9 %)	313 (58.3 %)	0.9	917 (63.3 %)	482 (65.3 %)	0.4	320 (65.4 %)	1742 (63.5 %)	0.4
Smoker	1142 (32.3 %)	1604 (39.3 %)	<0.001	370 (23.1 %)	150 (27.9 %)	0.02	604 (41.7 %)	331 (44.9 %)	0.2	168 (34.4 %)	1123 (40.9 %)	0.006
Renal impairment‡ (%)	143 (4.0 %)	81 (2.0 %)	<0.001	86 (5.4 %)	23 (4.3 %)	0.4	34 (2.3 %)	7 (0.9 %)	0.02	23 (4.7 %)	51 (1.9 %)	<0.001
Findings on admission												
Prehospital delay > 3 h	1835 (54.8 %)	1941 (50.3 %)	<0.001	1117 (74.9 %)	340 (69.1 %)	0.01	429 (30.8 %)	248 (34.4 %)	0.09	289 (62.0 %)	1353 (51.2 %)	< 0.001
Cardiogenic shock	410 (11.6 %)	318 (7.9 %)	<0.001	202 (12.6 %)	40 (7.4 %)	0.001	158 (10.9 %)	72 (9.8 %)	0.4	50 (10.2 %)	206 (7.5 %)	0.04
Heart rate > 100 bpm	748 (21.1 %)	546 (13.6 %)	< 0.001	460 (28.7 %)	122 (22.7 %)	0.007	207 (14.3 %)	93/737 (12.6 %)	0.3	81 (16.6 %)	330 (12.0 %)	0.005
Anterior infarct location	648/1278 (50.7 %)	1187/2465 (48.2 %)	0.1	293/549 (53.4 %)	207/361 (57.3 %)	0.2	273/549 (49.7 %)	214/442 (48.4 %)	0.7	82/180 (45.6 %)	765/1661 (46.1 %)	0.9
Revascularization procedures during administration												
PCI > 48 hours	542/2966 (18.3 %)	239/3901 (6.1 %)	<0.001	215/1308 (16.4 %)	112/482 (23.2 %)	0.00096	504 (34.8 %)	597 (80.9%)	< 0.001	14/470 (3.0 %)	41/2710 (1.5 %)	0.02
Total stent rate (< and > 48 hours)	499 (14.1 %)	2994 (74.5 %)	<0.001	67 (4.1 %)	68 (12.6 %)	<0.001	202 (13.9 %)	497 (67.3 %)	< 0.001	83 (29.1 %)	2144 (88.5 %)	< 0.001
CABG	162 (4.6 %)	102 (2.5 %)	<0.001	100 (7.6 %)	43 (8.8 %)	0.40330	39 (3.4 %)	15 (2.3 %)	0.2	23/433 (5.3 %)	44/2561 (1.7 %)	< 0.001
Medication< 48 hours												
Beta-Blockers	2732 (77.2 %)	3433 (85.4 %)	<0.001	1147 (71.5 %)	433 (80.6 %)	<0.001	1207 (83.4 %)	649 (87.9%)	0.005	378 (77.3 %)	2350 (85.7 %)	< 0.001
ACE-inhibitors	2150 (60.7 %)	2582 (71.0 %)	<0.001	1012 (63.1 %)	371 (69.1 %)	0.01	847 (58.5 %)	507 (68.7 %)	< 0.001	291 (59.5 %)	1973 (71.9 %)	< 0.001
Statins GP IIb/IIIa Inhibitors	1973 (55.7 %) 2347 (58.4)	3019 (75.1 %) 632 17,6 %	<0.001 <0.001	789 (49.2 %) 206 (12.8%)	369 (68.7 %) 164 (32.4%)	< 0.001 <0.001	875 (60.4 %) 140 (9.7%)	549 (74.4 %) 112 (15.0%)	< 0.001 <0.05	309 (63.2 %) 277 (56.6%)	2100 (76.6 %) 1849 (67.4%)	< 0.001 <0.001

* LDL cholesterol >130 mg/dl and/or history of hypercholesterolemia and/or actual medication for hypercholesterolemia; ‡ creatinine > 2 mg/dl.

	Aspirin	Aspirin+ Clopidogrel	P-value	Odds ratio (95% CI)
Entire group	n=3541	n=4018		
Death	438 (12.4 %)	206 (5.1 %)	< 0.001	0.38 (0.32–0.45)
Non-fatal reinfarction	110 (6.6 %)	206 (2.9 %)	< 0.001	0.42 (0.33–0.53)
Non-fatal stroke	32 (1.0 %)	18 0.5 %	0.006	0.46 (0.26–0.81)
No reperfusion	n=1604	n=559		
Death	15.6 %	9.3 %	0.0002	0.55 (0.40–0.76)
Non-fatal reinfarction	7.8 %	3.9 %	0.003	0.48 (0.29–0.79)
Non-fatal stroke	1.0 %	0.8 %	0.8	0.85 (0.28–2.63)
Fibrinolysis	n=1448	n=738		
Death	9.7 %	5.6 %	0.0008	0.55 (0.38–0.78)
Non-fatal reinfarction	5.7 %	3.0 %	0.006	0.51 (0.31–0.84)
Non-fatal stroke	1.0 %	0.4 %	0.17	0.43 (0.12–1.52)
Primary PCI	n=489	n=2743		
Death	45 (9.4 %)	115 (4.2 %)	< 0.0001	0.42 (0.30–0.60)
Non-fatal reinfarction	25 (5.6 %)	70 (2.7 %)	0.008	0.46 (0.29–0.73)
Non-fatal stroke	6 (1.4 %)	11 (0.4 %)	0.01	0.31 (0.11–0.83)

Table 2: In-hospital mortality and non-fatal events in patients with dual antiplatelet therapy compared to aspirin alone in the univariate analysis.

Table 3: Odds ratios for in-hospital mortality and MACCE (death, non-fatal reinfarction and non-fatal stroke) in the multivariable analysis in the entire group and in-patients treated with and without early reperfusion therapy treated with dual antiplatelet therapy compared to aspirin alone.

	Odds ratio	95 % Confidence interval
Mortality		
Entire group	0.65	0.42–1.00
No reperfusion	0.84	0.58–1.23
Fibrinolysis	0.83	0.52–1.33
Primary PCI	0.65	0.42–1.00
MACCE		
Entire group	0.61	0.51–0.73
No reperfusion	0.69	0.51–0.94
Fibrinolysis	0.62	0.44–0.89
Primary PCI	0.50	0.35–0.72

sesed with the TIMI risk score (11) (Fig. 2). The multivariable analysis of MACCE after adjustment for baseline characteristics and adjunctive therapies showed that the rate of MACCE were significantly lower with dual antiplatelet therapy (Table 3). This significant advantage persisted when successful PCI defined as TIMI 3 flow and less than 50% stenosis after PCI was included in the mutivariable analysis in the PCI group.

Bleeding complications

There was a significant increase in major bleeding complications with clopidogrel (7.1% versus 3.4%, odds ratio 2.2, 95% CI 1.5–3.1,p < 0.0001). The rate of in-hospital major bleeding complications in the subgroups is shown in Table 4 and showed a significant increase in major bleeding complications in the patients without early reperfusion and fibrinolysis. The rate of intracranial hemmorrhage was 0.2% versus 0.4% with and without clopidogrel, while the rate of tranfusions was 3.2% versus 1.8%, respectively. The rate of patients with MACCE and major bleeding in patients with and without clopidogrel was 0.6% versus 1.0% in the total population ((p=0.2), 1.0% versus 0.7% in the group without reperfusion therapy (p=0.6), 0.9% versus 0.9% in the group with fibrinolysis (p=0.9) and 0.5% versus 2.2% in the group with primary PCI (p< 0.01), respectively

Net clinical benefit

The incidence of the combined endpoint MACCE or major bleeding in patients with and without clopidogrel was 12.5 % versus 21.0% in the total population (p < 0.001), 15.6 % versus 24.9% in the group without reperfusion therapy (p < 0.001), 13.9 % versus 17.1 % in the group with fibrinolysis (p=0.1) and 11.4% versus 19.4 % in the group with primary PCI (p < 0.01), respectively.

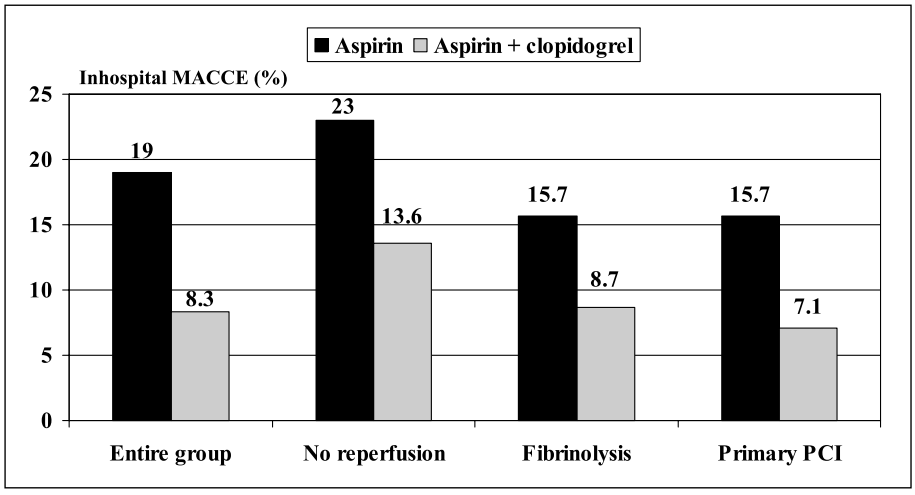

Figure 1: In-hospital MACCE in the entire group and subgroups according to the initial reperfusion strategy.

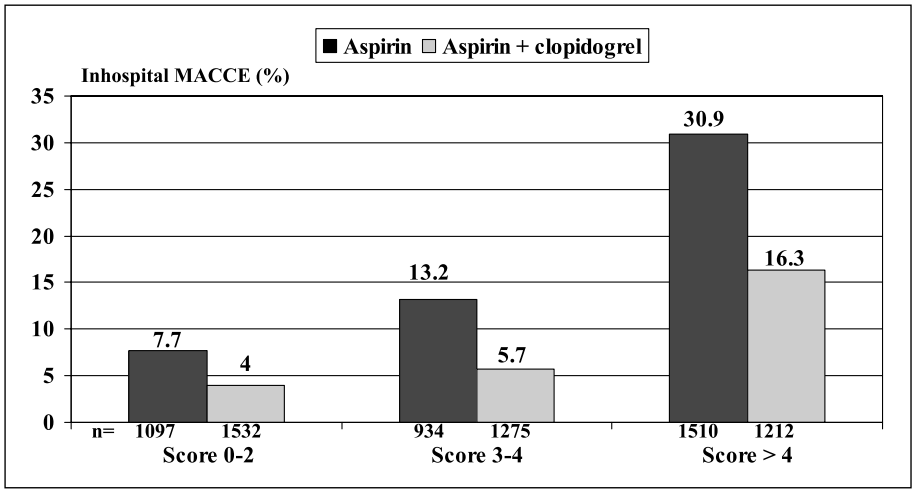

Figure 2: Rate of of in-hospital MACCE according to the baseline risk of the patients as assessed by the TIMI risk score.

Table 4: In-hospital major bleeding complications.

Reperfusion strategy	Aspirin	Aspirin + Clopidogrel	P-value	Odds ratio (95 % CI)
Entire group	3.4 %	7.1 %	< 0.001	2.2 (1.5–3.1)
No reperfusion	2.0 %	5.1 %	0.01	2.6 (1.2–5.8)
Fibrinolysis	4.1 %	9.4 %	0.002	2.4 (1.3–4.4)
Primary PCI	6.3 %	7.1 %	0.7	1.1 (0.6–2.3)

Discussion

In our analysis clopidogrel, when given in addition to aspirin, significantly reduced the odds for mortality, recurrent myocardial infarction and stroke in unslected patients with STEMI in clinical practice, regardless of the initial reperfusion strategy. Our analysis is the first evaluation of a large prospective registry with STEMI patients, which investigates the effect of early administration of clopidogrel in patients with STEMI. Two recent randomised trials have evaluated the role of clopidogrel in addition to aspirin in patients with STEMI: the CLARITY-TIMI 28 trial showed the safety and efficacy of clopidogrel in addition to fibrinolysis in patients < 75 years (6). Patents with STEMI receiving a standard fibrinolytic regimen including aspirin were randomised to receive a loading dose of 300 mg clopidogrel and 75 mg daily thereafter or placebo. The primary endpoint of an occluded infarct vessel after 2–8 days, death and reinfaction was significantly reduced with clopidogrel. In addition, the composite endpoint of death, reinfarction and urgent revascularization until day 30 occurred significantly more often in the placebo group. There was no increase in major bleeding complications with clopidogrel, especially the rate of intracranial bleedings was similar. In addition, clopidogrel reduced cardiovascular death and reinfarction in patients in CLARITY treated with PCI during

the index hospitalisation (8). The beneficial effect of a short-term therapy up to four weeks with clopidogrel has been demonstrated in the COMMIT study (7), which included a large number of patients with STEMI treated with fibrinolysis or without early reperfusion therapy. Here, clopidogrel given in addition to aspirin lead to a 0.7% reduction in all causes of mortality. Again there was no increase in the rate of major bleeding complications.

In the ACOS registry consecutive patients were enrolled, including high risk patients with advanced age, renal insufficiency, cardiogenic shock and resuscitated patients. In these unselected patients we observed a reduction in MACCE with clopidogrel. As shown in Figure 2 the absolute reduction in MACCE was more pronounced in patients with higher baseline risk as indicated by a higher TIMI risk score. That might indicate that an improved antiplatelet therapy is especially beneficial in high risk groups. The reduction in mortality seen in the univariate analysis was no longer significant in the multivariable analysis. However, the MACCE rate was significantly lower, even after adjustment for baseline variables and concomitant therapies. This is consistent with the findings of the CLARITY-TIMI 28 and the COMMIT trials. In contrast to the results in the randomized clinical trials we observed a significant increase in bleeding complications with dual antiplatelet therapy. This is certainly due to the inclusion of unselected patients with higher risk for bleeding complications compared to randomised trials and therefore not unexpected. On the other hand it assures that a more effective platelet inhibition was achieved with dual antiplatelet therapy, which was not only associated with less ischemic events but with more bleedings. However, the net clinical benefit incorporationg bleeding complications into outcome was in favour of clopidogrel in the total patient population and patients without reperfusion therapy and with primary PCI.

Limitations

The present report is not a randomized, controlled study evaluating the effect of clopidogrel in addition to aspirin in patients with STEMI. In the ACOS registry, treatment with clopidogrel was left to the discretion of the physician. This could result in selection bias, which can not be fully eliminated by a multivariable analysis. In the PCI group, stenting was less often used in the aspirin alone group. This might explain that clopidogrel was not given during the early phase after STEMI. Another reason might be the need for oral anticoagulation. In addition we have no information about the initial loading dose of clopidogrel and can therefore not evaluate the effect of different dosing strategies.

Our definition of bleeding did not exactly correspond to one of the established definitions. However, the definition was very close to the GUSTO severe and moderate bleeding, which has been shown to correlate closely with clinical outcome (12).

Conclusion

In conclusion, our data suggest that clopidogrel improves the clinical course of patients with STEMI. This benefit is observed regardless of the initial reperfusion strategy. This advantage was associated with a significant increase in major bleeding complications.

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