ORIGINAL ARTICLE

Long term clinical outcome and bleeding complications among hospital survivors with acute coronary syndromes

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Objective: To examine the 21 month clinical outcome and bleeding complications in hospital survivors with non-ST segment elevation acute coronary syndromes (NSTEMI) who were discharged with combined clopidogrel and aspirin anti-thrombotic therapy, and compare with those having ST segment elevation myocardial infarction (STEMI) who were discharged with aspirin alone.

Design: Observational study.

Setting: A large university hospital.

Patients: 224 patients were admitted to hospital with either NSTEMI or STEMI, and survived to discharge between 1 October 2001 and 31 December 2002.

Main outcome measures: Cardiovascular death, total death, new myocardial infarction, unstable angina requiring hospitalisation, stroke or transient ischaemic attack, coronary revascularisation; and fatal, life threatening, major and minor bleeding over 21 months after discharge.

Results: Despite having no or small infarct (median maximum creatine kinase 155 v 1295 u/l; $p < 0.001$) and taking more antianginal drugs, patients with NSTEMI had similar rates of cardiovascular death (9.5% v 8.3%; $p = \text{NS}$), new myocardial infarction (9.5% v 6.5%; $p = \text{NS}$) or unstable angina requiring hospitalisation (15.5% v 10.2%; $p = \text{NS}$) when compared with STEMI. Fatal, life threatening or major bleeding were $< 1\%$ in both groups ($p = \text{NS}$); and minor bleeding occurred in 4.3% NSTEMI and 2.8% STEMI patients respectively ($p = \text{NS}$).

Conclusions: Patients with NSTEMI had a similar and unfavourable long term outcome when compared with STEMI. There was no difference in serious bleeding complications between both groups.

Acute coronary syndromes comprise non-ST segment elevation acute coronary syndrome (NSTEMI) and ST segment elevation myocardial infarction (STEMI), and share in most cases, a common pathological process of atherosclerotic plaque rupture and erosion. NSTEMI can be further subdivided into unstable angina and non-ST segment elevation myocardial infarction, the latter being accompanied by a detectable rise in cardiac enzymes as a result of myocardial necrosis.¹ Over the past few years, a number of national and international guidelines have highlighted an evidence based approach in managing patients with NSTEMI²⁻⁵ and STEMI.^{6,7} Both NSTEMI and STEMI patients should be considered for aspirin, β blocker, and statin therapy. In addition, clopidogrel when added to aspirin has been shown to be effective in the short term management of NSTEMI, especially where an initial non-interventional management was favoured.⁴ In the CURE study,⁸ the addition of clopidogrel to the standard antiplatelet treatment of aspirin in NSTEMI has been shown to reduce combined cardiovascular mortality, non-fatal myocardial infarction, and stroke from 11.4% to 9.3% (absolute risk reduction 2.1%, relative risk reduction 20%). Although this risk reduction was evident in both low and high risk subgroups,⁹ there was a 37% excess in major bleeding among patients who received combined clopidogrel and aspirin therapy. The median study treatment duration was nine months, and the longer term benefits or bleeding risk of such combined treatment in these patients remain unclear.

We examine the management of a cohort of ACS patients who survived their hospital admission where all NSTEMI patients were discharged with combined clopidogrel and aspirin therapy, and all STEMI were discharged with aspirin alone, and compare their 21 month clinical outcome and bleeding complications.

METHODS

Patients who were admitted to University Hospital Aintree between 1 October 2001 and 31 December 2002 with either NSTEMI taking combined clopidogrel and aspirin, or STEMI taking aspirin alone as antithrombotic treatment upon hospital discharge were retrospectively identified. All patients were followed up for 21 months. All pharmacy discharge prescriptions containing clopidogrel were screened for inclusion eligibility for NSTEMI. Patients with STEMI formed part of an ongoing data collection for the myocardial infarction national audit project,¹⁰ and those discharged with aspirin alone were included in this study. Patients with NSTEMI or STEMI who died during their hospital admission, or survived but discharged with other antithrombotic regimens were excluded from the study.

At 21 months after hospital discharge, general practitioners were contacted by post about their patients' status, and if appropriate, a questionnaire was sent to the patient requesting further information. Altogether 205 general practitioners were contacted and 174 (84.9%) replied; whereas 195 patients were contacted and 97 questionnaires (49.7%) were completed. In addition, all hospital records were searched for the occurrence of death, recurrent or new myocardial infarction, unstable angina requiring re-hospitalisation, coronary revascularisation, stroke or transient ischaemic attack, and bleeding. Vital status was available in 223 of the 224 patients. The study was approved by the local research ethics committee. Statistical analysis using Student's t , χ^2 , and Fisher's exact tests, and 95% confidence intervals (CI) were performed where appropriate.

Abbreviations: NSTEMI, non-ST segment elevation acute coronary syndromes; STEMI, ST segment elevation myocardial infarction

Table 1 Medical history, clinical characteristics, and discharge drugs

	NSTEACS (n = 116)	STEMI (n = 108)	p Value
Age, mean (SD)	65.8 (11)	63.4 (12)	NS
Female (%)	52 (44.8)	40 (37.0)	NS
Medical history			
Smoker (%)	53 (45.7)	63 (58.3)	NS
Diabetes mellitus (%)	23 (19.8)	14 (13.0)	NS
Hypertension (%)	66 (56.9)	38 (35.2)	<0.01
MI (%)	38 (32.6)	14 (13.0)	<0.001
CABG/PCI (%)	17 (14.7)	1 (0.9)	<0.001
CVA (%)	17 (14.7)	5 (4.6)	<0.02
PVD (%)	13 (11.2)	7 (6.5)	NS
Peptic ulcer or any bleed (%)	7 (6.0)	8 (7.4)	NS
ECG and cardiac markers			
ST depression	34 (29.3)		
T wave inversion	53 (45.7)		
Anterior ST elevation		35 (32.4)	
Inferior/posterior ST elevation		73 (67.6)	
Max CK, median (u/l)	155	1295	<0.001
Increased troponin T or I*	67 (57.8)	108 (100.0)	<0.001
Discharge drugs			
β blocker (%)	72 (62.1)	71 (65.7)	NS
Statin (%)	96 (82.8)	83 (76.9)	NS
ACEI or ARB (%)	68 (58.6)	85 (78.7)	<0.01
Calcium channel blocker (%)	75 (64.7)	17 (15.7)	<0.001
Nitrate (%)	81 (69.8)	47 (43.5)	<0.001
Nicorandil (%)	16 (14.0)	0 (0.0)	<0.001

*Increased troponin T ≥ 0.03 µg/l or troponin I > 1.0 µg/l.

Acute myocardial infarction was defined as the presence of at least two of the three following criteria: (a) cardiac ischaemic chest pain; (b) serial electrocardiographic changes; (c) increase of total creatine kinase to at least twice the upper limit of normal, or raised troponin T or I above the upper limit of normal. Stroke was defined as a new onset of focal or global neurological deficit, caused by ischaemia or haemorrhage within or around the brain lasting for more than 24 hours, or up to 24 hours in transient ischaemic attack. Major and life threatening bleeding were defined in accordance with the CURE study.⁸ Major bleeding was defined as substantially disabling bleeding, intraocular haemorrhage leading to the loss of vision, or bleeding necessitating the transfusion of at least two units of blood. Life threatening bleeding was defined as either fatal haemorrhage or one leading to a reduction in the haemoglobin concentration by at least 50 g/l, or to substantial hypotension requiring the use of inotropic agents, if it necessitated a surgical intervention, if it was a symptomatic intracranial haemorrhage, or if it necessitated the transfusion of four or more units of blood.

RESULTS

Medical history and clinical characteristics (table 1)

A total of 224 hospital survivors were identified, of which 116 patients with NSTEMACS were discharged receiving combined

clopidogrel and aspirin antiplatelet treatment, and 108 patients with STEMI were discharged with aspirin alone. The mean age for NSTEMACS patients was 65.8 (SD 11) compared with 63.4 (SD 12) for STEMI patients. Among NSTEMACS patients, ST depression was present on the admission electrocardiogram in 29.3%, T wave inversion in 45.7%; and 57.8% had raised troponin concentration. Patients with NSTEMACS were more likely to have hypertension than those with STEMI (56.9% v 35.2%; $p < 0.01$). One third of NSTEMACS patients had previous myocardial infarction (32.6% v 13.0%; $p < 0.001$), and nearly a sixth of these patients had already experienced a prior cerebrovascular accident (14.7% v 4.6%; $p < 0.02$), which was significantly more frequent than in patients with STEMI. Prior coronary revascularisation was noted in 14.7% of NSTEMACS comparing with 0.9% in STEMI patients ($p < 0.001$). The potential for bleeding as suggested by previous occurrence of peptic ulcer disease or any serious bleeding was similar in both groups (6.0% v 7.4%; $p = NS$). Among STEMI patients, 35 had anterior infarction of whom 22 (62.9%) received fibrinolytic therapy; 73 had inferior and/or posterior infarction, and 57 (78.1%) received fibrinolytic therapy.

Drug treatment upon hospital discharge

β blocker and statin were used in similar proportions in both groups, with β blocker prescribed in 62.1% or more patients

Table 2 Clinical course and bleeding complications

Number (%; 95% CI)	NSTEMACS (n = 116)			STEMI (n = 108)			p Value
	1–21 m	1–9 m	10–21 m	1–21 m	1–9 m	10–21 m	
MI	11 (9.5; 5.4, 16.2)	8 (6.9)	3 (2.6)	7 (6.5; 3.2, 12.8)	5 (4.6)	3 (2.8)	NS
Unstable angina re-hospitalisation	18 (15.5; 10.0, 23.2)	15 (12.9)	3 (2.6)	11 (10.2; 5.8, 17.3)	7 (6.5)	4 (3.7)	NS
CABG/PCI	34 (29.3; 21.8, 38.2)	20 (17.2)	15 (12.9)	17 (15.7; 10.1, 23.8)	4 (3.7)	13 (12.0)	<0.02
CVA/TIA	4 (3.4; 1.3, 8.5)	3 (2.6)	1 (0.9)	0 (0.0; 0.0, 3.4)	0 (0.0)	0 (0.0)	NS
CV death	11 (9.5; 5.4, 16.2)	5 (4.3)	6 (5.2)	9 (8.3; 4.4, 15.1)	4 (3.7)	5 (4.6)	NS
Total death	16 (13.8; 8.7, 21.2)	8 (6.9)	8 (6.9)	11 (10.2; 5.8, 17.3)	4 (3.7)	7 (6.5)	NS
Fatal bleed	1 (0.9; 0.2, 4.7)	0 (0.0)	1 (0.9)	1 (0.9; 0.2, 5.1)	1 (0.9)	0 (0.0)	NS
Life threatening bleed	1 (0.9; 0.2, 4.7)	0 (0.0)	1 (0.9)	1 (0.9; 0.2, 5.1)	1 (0.9)	0 (0.0)	NS
Major bleed	1 (0.9; 0.2, 4.7)	0 (0.0)	1 (0.9)	2 (1.9; 0.5, 6.5)	1 (0.9)	1 (0.9)	NS
Minor bleed	5 (4.3; 1.9, 9.7)	5 (4.3)	0 (0.0)	3 (2.8; 0.9, 7.9)	2 (1.9)	1 (0.9)	NS

All p values compared 21 month data between NSTEMACS and STEMI.

and statin in at least 76.9% of these hospital survivors. NSTEMI patients were less likely to receive an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist than patients with STEMI (58.6% *v* 78.7%; $p < 0.01$), but they were more likely to receive additional antianginal drugs—calcium channel blocker, nitrate, or nicorandil ($p < 0.001$).

Clinical course (table 2)

Over a period of 21 months, there was no significant difference in cardiovascular mortality (9.5% *v* 8.3%; $p = \text{NS}$), recurrent or new myocardial infarction (9.5% *v* 6.5%; $p = \text{NS}$) or unstable angina requiring re-hospitalisation (15.5% *v* 10.2%; $p = \text{NS}$) between NSTEMI and STEMI patients. The incidence of these ischaemic complications was further studied by dividing into two different time periods: (1) 1–9 months, and (2) 10–21 months. Recurrent or new myocardial infarction (6.9%, 2.6%) and unstable angina requiring re-hospitalisation (12.9%, 2.6%) were more frequently encountered in the first nine months after discharge than during the latter 10–21 months in NSTEMI patients, while cardiovascular death rates (4.3%, 5.2%) were similar in the two periods. Similar trends were seen in STEMI patients who experienced more recurrent or new myocardial infarction (4.6%, 2.8%) and unstable angina requiring re-hospitalisation (6.5%, 3.7%) in the first nine months than in the subsequent period, and cardiovascular death rates (3.7%, 4.6%) were similar in the two periods.

More NSTEMI patients received revascularisation than STEMI patients over the 21 months (29.3% *v* 15.7%; $p < 0.02$). Coronary angiography was performed during the index admission in seven NSTEMI patients and two STEMI patients. Of these, one NSTEMI patient received revascularisation during the index admission.

Bleeding complications

The incidence of fatal and life threatening bleed was low (0.9%) in both NSTEMI and STEMI patients ($p = \text{NS}$). Major bleeding occurred in 0.9% NSTEMI and 1.9% STEMI patients ($p = \text{NS}$). One NSTEMI patient died of an intracerebral and subarachnoid haemorrhage, and one STEMI patient died of a ruptured abdominal aortic aneurysm. Of the eight minor bleeds in the two groups, four were gastrointestinal in origin, of which two were attributable to peptic ulcer.

Antithrombotic treatment at 21 month follow up or time of death

Among 116 NSTEMI patients, 62 (53.4%) were taking combined clopidogrel and aspirin therapy, 31 (26.7%) aspirin alone, 16 (13.8%) clopidogrel alone, two (1.7%) no antithrombotic, two (1.7%) warfarin with or without aspirin, and in three (2.6%) patients antithrombotic drug was unknown. Whereas 82 (75.9%) STEMI patients remained taking aspirin

alone, an additional antithrombotic drug was used in 14 (13.0%), aspirin was stopped in nine and changed to another antithrombotic treatment (8.3%), and in three patients (2.8%) no information was available.

DISCUSSION

Over a 21 month period after hospital discharge, survivors with NSTEMI had similar rates of cardiovascular mortality, recurrent or new myocardial infarction, or unstable angina requiring re-hospitalisation when compared with STEMI survivors. Serious bleeding in NSTEMI patients taking combined clopidogrel and aspirin therapy, and STEMI patients taking aspirin alone was low in both groups.

Various acute coronary syndromes registries have published their findings recently, but few have compared the long term outcome of NSTEMI with STEMI. NSTEMI patients had a 5.9% six month post-discharge total mortality in the PRAIS-UK study.¹¹ In the GRACE registry UK cohort,¹² the six month post-discharge total mortality was 4.9% in NSTEMI and 6.1% in STEMI. Among these patients with NSTEMI, NSTEMI total mortality was higher at 6.4% compared with 3.9% in unstable angina, and the ratio of NSTEMI to unstable angina in the GRACE cohort was 0.62 to 1. In contrast, our NSTEMI patients had a much higher NSTEMI to unstable angina ratio (1.42 to 1), which would explain their higher 21 month cardiovascular mortality rate of 9.5%, when compared with 8.3% in STEMI patients. Moreover, cardiovascular mortality was evenly distributed (about 4%–5%) between the first nine months (1–9 m) and subsequent 12 months (10–21 m) in both NSTEMI and STEMI patients. Interestingly, the PRAIS-UK study¹³ showed that the proportion of cardiovascular deaths among all deaths decreased from 92% in the first six months to 69% over the 45 months' study duration. Our study showed 5 of the 16 deaths after discharge (31%) in NSTEMI patients were attributable to non-cardiovascular causes (four cancer, one septicemia). Likewise, 2 of the 10 deaths (20%) in STEMI were attributable to cancer.

Since the publication of the CURE study,⁸ combined clopidogrel and aspirin therapy have been widely used in the acute management of NSTEMI. However, the optimal duration of clopidogrel therapy remains unclear. The key issues are its efficacy, cost, and risks, particularly bleeding risk when combined with aspirin. The efficacy of combined clopidogrel and aspirin treatment was a 20% reduction in the composite end points of cardiovascular mortality, myocardial infarction, and stroke over the median study duration of nine months. This risk reduction was achieved mainly through a reduction in myocardial infarction (5.2% *v* 6.7%; RR 0.77; CI 0.67 to 0.89; an absolute difference of 1.5%). There was no significant difference in the reduction of cardiovascular mortality alone (5.1% *v* 5.5%; RR 0.93; CI 0.79 to 1.08). The cost of clopidogrel therapy is £459.03 per patient-year.¹⁴ Incidence of fatal, life threatening, major and minor bleeding in the CURE study were 0.2%, 2.2%, 3.7%, and 5.1% respectively. In the MATCH study,¹⁵ the equivalent bleeding rates in patients suffering from ischaemic stroke or transient ischaemic attack who received combined clopidogrel and aspirin therapy at 18 months were 0.4%, 2.6%, 1.9%, and 3.2% respectively. Our 21 month bleeding rates in NSTEMI patients discharged with combined clopidogrel and aspirin therapy were 0.9%, 0.9%, 0.9%, and 4.3% respectively. It is possible that bleeding events could have been missed among our patients as they were not followed up as vigorously as otherwise for participants of a clinical trial. Nevertheless, patients who developed serious bleeding (fatal or life threatening) would still be detected as a consequence of their hospitalisation or death. Our result would suggest that for every 1000 NSTEMI patients treated with 21 months of

Key points

- Acute coronary syndromes comprise NSTEMI and STEMI
- NSTEMI patients had no or small infarct when compared with those having STEMI
- 21 month clinical outcome including cardiovascular death was similar in both groups
- Serious bleeding was uncommon in NSTEMI patients taking combined clopidogrel and aspirin, and STEMI patients taking aspirin alone

combined clopidogrel and aspirin therapy, nine patients (95% CI 2 to 47) may die as a result of their bleeding. Fatal bleeding occurred at a comparable rate over the same period in STEMI patients treated with aspirin alone. Besides NSTEMI, recent studies have also shown benefits of combining clopidogrel with aspirin in the acute phase management of ST segment elevation myocardial infarction¹⁶ and Chen on behalf of the COMMIT/CCS-2 investigators (presented at the American College of Cardiology 2005 scientific sessions). However, there is no current evidence to support the combined use of clopidogrel and aspirin beyond the hospitalisation period in patients with STEMI.

Despite having no or small myocardial damage, patients with NSTEMI continued to experience high rates of cardiovascular death and other ischaemic complications after their hospital discharge, and were comparable with STEMI patients who had bigger infarct. Given their unfavourable long term clinical outcome, risk of serious bleeding with combined clopidogrel and aspirin therapy, and cost, it would seem logical to recommend an evidenced based strategy of early coronary revascularisation in all suitable high risk NSTEMI patients to improve their prognosis.²⁻⁵ Until longer term evidence becomes available as in the case of aspirin,¹⁷ clopidogrel should be withdrawn as a long term combined antiplatelet therapy with aspirin in NSTEMI patients who are stable and conservatively managed, as benefits are unclear and there is a small but definite risk of serious bleeding.

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