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REVIEW ARTICLE

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# Clinical use of clopidogrel in acute coronary syndrome

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**SUMMARY**

Several therapeutic approaches have been developed to improve the outcome among patients with acute coronary syndrome (ACS). However, treatment with antithrombotic therapies such as oral glycoprotein IIb/IIIa inhibitors has been limited by the lack of efficacy and excess bleeding complications. As the publication of the landmark study Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), the clinical benefit of early and intermediate-term use of combined antiplatelet agents – clopidogrel plus aspirin – in non-ST-segment elevation myocardial infarction (NSTEMI) patients became evident. Pretreatment and intermediate-term therapy with clopidogrel in NSTEMI ACS patients undergoing percutaneous coronary intervention (PCI) was further supported by the PCI–CURE trial. Recently, the results of two major trials Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28, Clopidogrel and Metoprolol in Myocardial Infarction Trial established the pivotal role of clopidogrel in the other spectrum of ACS–STEMI. Coupled with the results from previous multicentre trials, these two studies provide a guide for the early and long-term use of clopidogrel in the whole spectrum of ACS. A review summarising the results of the recent clinical trials and a discussion on its implications for the clinical management of ACS is presented.

**Review Criteria**

- A literature search of major trials on clopidogrel in acute coronary syndrome was performed between January 2001 and December 2005 on PubMed.
- Only randomised, double-blind, placebo-controlled trials were included in the review.

**Message for the Clinic**

- CLARITY–TIMI 28 and COMMIT trials have confirmed the role of clopidogrel in patients with ST-elevation myocardial infarction (STEMI).
- Clopidogrel is a safe and effective 'add-on' therapy in the treatment of STEMI across a broad range of STEMI patient demographics with no excess of bleeding events.

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## Introduction

The pathophysiology of acute coronary syndrome (ACS) is plaque disruption because of either atherosclerotic plaque rupture or endothelial erosion, leading to acute thrombotic occlusion of the coronary artery (1). From the time of first presentation, ACS patients are at high risk of life-threatening atherothrombotic events, including myocardial infarction (MI) and stroke. Ongoing research on ACS has been aiming at reducing these cardiovascular risks and improving clinical outcome. Thus, antithrombotic therapies have been the focus of various research studies, particularly those targeting on platelet activation and aggregation.

The efficacy of aspirin as an antiplatelet agent has been widely accepted in various settings. The efficacy of clopidogrel as an adjunct antiplatelet agent in ACS patients without ST-segment elevation has been well established in aspirin-treated patients in the large Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study (2). Recent clinical trial results have also provided an evidence base for the use of clopidogrel concomitantly with aspirin to reduce further the risk of thrombotic events in ACS patients with ST-segment elevation. This review summarises those results and discusses their implications for clinical practice.

## Pathophysiology of ACS

Acute coronary syndrome is caused by an acute or subacute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombus formation, vasoconstriction and microembolisation (3). Thrombosis is induced at the site of plaque rupture or erosion that leads to rapid compromise of coronary blood flow. Different degrees of the superimposed thrombus formation at the site of plaque disruption are associated with different clinical presentations of ACS. Thus, platelet activation, aggregation and associated inflammation play a key role in the transformation of a stable atherosclerotic plaque to an unstable lesion.

## Mechanisms of action of antiplatelet agents

All mediators of platelet activation cause conformational changes in the glycoprotein IIb/IIIa surface receptor of platelets, allowing it to bind to circulating

fibrinogen and to form platelet–fibrin aggregates. Inhibitors of the glycoprotein IIb/IIIa receptor are expected to be the most potent antiplatelet agents, as they block the final common pathway for platelet aggregation.

Aspirin permanently acetylates platelet cyclooxygenase 1, blocking the synthesis of thromboxane $A_2$. Thromboxane $A_2$ promotes activation of other platelets and is a potent vasoconstrictor. Aspirin has no effect on other platelet activators, such as adenosine diphosphate (ADP), thrombin or serotonin.

When released from red blood cells, activated platelets and damaged endothelial cells, ADP induces platelet adhesion and aggregation (4,5). The platelet ADP receptor effects dense and α-granule release, thromboxane $A_2$ generation, glycoprotein IIb/IIIa receptor activation and P-selectin expression (6).

Clopidogrel is a thienopyridine derivative that selectively and irreversibly inhibits the $P2Y_{12}$ component of the platelet ADP receptor (7) and has no direct effect on other mediators of platelet aggregation such as cyclooxygenase, thromboxane synthetase or adenoside. A thienopyridine derivative, clopidogrel is a prodrug which is metabolised by the hepatic cytochrome P450-1A enzyme system to a short-lived thiol that binds to the $P2Y_{12}$ receptor. By blocking the ADP-dependent mechanisms of platelet activation, clopidogrel also limits the activation by other agonists and results in markedly decreased platelet recruitment and aggregation. Maximal inhibition of ADP-induced platelet aggregation by clopidogrel ranges from 40% to 60%. This steady state is reached in 3–5 days in healthy subjects at a standard dose of 75 mg/day or in 2–5 h after a 300 mg loading dose (8). The antiplatelet effects of clopidogrel and aspirin are thus synergistic (9,10).

## Rationale for the use of clopidogrel in ACS

The benefit of the use of aspirin was shown in the Second International Study of Infarct Survival, which enrolled 17,187 subjects with acute ST-segment elevation MI (STEMI). Aspirin was shown to safely reduce vascular mortality by about 25% and recurrent non-fatal infarction by about 50% in the study (11). Subsequently, the Antithrombotic Trialists' Collaboration Group reviewed 287 studies which involved a wide variety of high-risk vascular patients to compare the ability of various antiplatelet regimens ($n = 77{,}000$) vs. control ($n = 135{,}000$) in reducing adverse cardiovascular events (12). Antiplatelet therapy (usually aspirin) reduced the risk of vascular death, MI or stroke by about 25%. However, there was still a substantial risk of death from cardiovascular events, reinfarction and ischaemia in ACS patients routinely treated with aspirin, in both the short and long term.

Long-term treatment of ACS patients with oral glycoprotein IIb/IIIa inhibitors has been associated with increased mortality, no change in the incidence of MI and increased bleeding complications (13). The addition of intravenous glycoprotein IIb/IIIa inhibitor (abciximab) to fibrinolytic therapy (together with aspirin and heparin) in STEMI patients was reported, in a meta-analysis of trials involving 23,166 patients. The reinfarction rates were 2.3% and 3.6% for the abciximab and the control groups ($p < 0.001$) respectively, and 30-day mortality rates were 5.8% for both groups (14). However, the rate of major bleeding complications was significantly higher among those treated with abciximab (5.2%) compared with placebo (3.1%) ($p < 0.001$). This suggests that there is an additional role for antiplatelet therapy apart from the use of oral glycoprotein IIb/IIIa inhibitors.

Conversely, the use of clopidogrel has been shown to be safe and efficacious in the long term. Compared with aspirin 325 mg, clopidogrel was shown to provide a relative risk reduction of 8.7% [absolute risk reduction, 0.5% (NNT (number needed to treat) = 200); $p = 0.043$] for ischaemic stroke, MI or vascular death among 19,185 patients with recent MI or ischaemic stroke or peripheral artery disease (15). This benefit extended beyond the 25% relative risk reduction provided by aspirin, and was associated with fewer bleeding complications during a follow-up period of 1.91 years (15). Subsequently, early and intermediate-term (9 months–1 year) use of clopidogrel (300 mg loading dose, then 75 mg/day for a mean duration of 9 months) plus aspirin in non-ST-segment elevation MI (NSTEMI) patients ($n = 12{,}562$) was shown being able to reduce the relative risk of death from cardiovascular causes, non-fatal MI or stroke by 20% ($p < 0.001$) compared with aspirin alone in the CURE study (Figure 1) (2). Subgroup analysis of the trial results revealed that the rates of each component of the composite outcome also tended to be lower in the clopidogrel group, with the greatest difference observed for rates of reinfarction (5.2% in the clopidogrel group vs. 6.7% in the placebo group). Although there were significantly more patients with major bleeding in the clopidogrel group (3.7% vs. 2.7%; relative risk, 1.38; $p = 0.001$), there were not significantly more patients with life-threatening bleeding or haemorrhagic strokes.

Coronary stenting has improved the outcome of percutaneous coronary intervention (PCI). However, stent thrombosis was a major limitation (16). Dual antiplatelet therapy has been shown to be consistently better than anticoagulation in preventing this

 

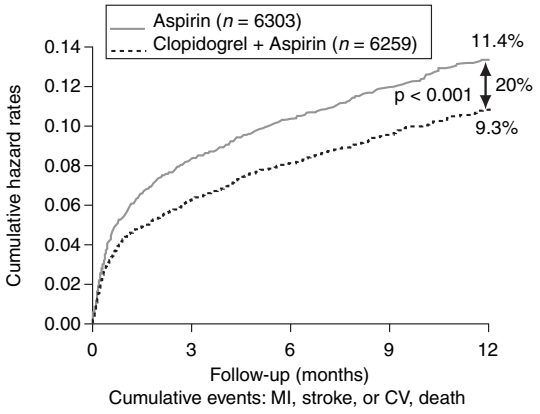


**Figure 1** Early and long-term benefits of clopidogrel in unstable angina (CURE study) (2). (Reproduced with permission from the Publishing Division of the Massachusetts Medical Society)

complication. Indeed, clopidogrel plus aspirin treatment (4 weeks) has become standard care for preventing stent thrombosis in patients who received bare metal stents implantation (17–20). The PCI–CURE trial results demonstrated that extending clopidogrel use to include pretreatment and long-term treatment (mean 8 months) in NSTEMI ACS patients ($n = 2658$) undergoing PCI reduced the risk of cardiovascular death or MI by about one-third (21). These findings corroborated the results of the prospective, randomised, placebo-controlled Clopidogrel for the Reduction of Events During Observation trial ($n = 2116$), which showed that a pretreatment dose of 300 mg clopidogrel 6–24 h before PCI afforded the greatest effect (relative risk reduction, 38.6%; $p = 0.51$) (22).

The results from the Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty study which demonstrated that pretreatment with a higher (600 mg) loading dose of clopidogrel significantly reduced the risk of MI by 50% (odds ratio 0.48, $p = 0.044$) in patients undergoing PCI, suggests that there is potential benefit of using a higher loading dose (600 mg) of clopidogrel in clinical practice (23).

Although clopidogrel had established a record of reducing ischaemic events without significantly increasing bleeding complications in a number of settings, its role in STEMI patients remained undefined until the results of the CLARITY–TIMI 28 and COMMIT trials were published in 2005.

## Clopidogrel reduces mortality in ST-segment elevation myocardial infarction

Platelet activation and aggregation are key processes in the initiation and propagation of coronary-artery thrombosis. In patients with STEMI, clinical practice guidelines recognise the importance of promptly restoring normal epicardial blood flow and myocardial perfusion in the infarct zone (24,25). The most effective pharmacological reperfusion regimen appears to be concurrent fibrinolytic therapy and platelet inhibition and, up until recently, aspirin was the only antiplatelet agent routinely used in this setting.

## Clopidogrel reduces the risk of death, recurrent MI and stroke (COMMIT/CCS-2 trial results)

The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) was a highly powered, randomised, double-blind, placebo-controlled trial jointly co-ordinated by the Clinical Trial Service Unit of Oxford University, UK and the Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, China (26). Spanning 5 years, patients ($n = 45,852$) in this study of the emergency treatment of acute MI were recruited from 1250 hospitals throughout China. The objectives of the antiplatelet arm of the trial were to investigate whether adding clopidogrel (75 mg/day) to aspirin and standard fibrinolytic and anticoagulant therapy would further reduce the composite risk of death, recurrent MI or stroke, or improve mortality, compared with placebo.

Patients were enrolled if they presented with suspected acute MI within 24 h of the onset of symptoms, and the scheduled treatment period was 4 weeks or prior hospital discharge. There were no age limits for inclusion in the study: patients had a mean age of 61 years and 26% of patients were 70 years of age or older. The use of other therapies was balanced between the clopidogrel and placebo groups. About 55% of patients received fibrinolytic drugs (typically urokinase), which may not be comparable with the rate of thrombolysis in other Western countries. The average time from symptom onset to presentation was just over 10 h, and the mean treatment duration was 15 days.

The COMMIT study results (Figure 2) showed that the addition of clopidogrel to aspirin significantly reduced the relative risk of in-hospital death by 7% [absolute risk reduction, 0.6% (NNT = 167); $p = 0.03$] and the risk of composite cardiovascular events (death, reinfarction or stroke) by about 10% [absolute risk reduction, 0.9% (NNT = 111); $p = 0.002$]. These benefits appeared to be independent of, and therefore additional to, those of other standard treatments. There was no apparent increase in major bleeding, even when clopidogrel was administered with fibrinolytic agents or to older patients.

 

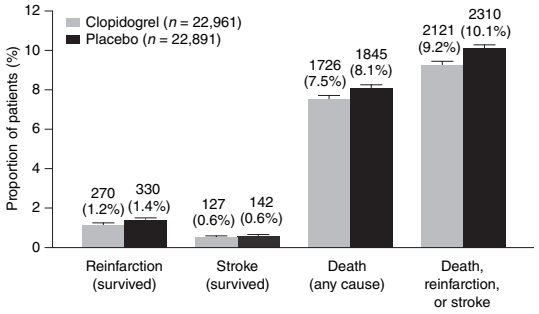


**Figure 2** Absolute effects of clopidogrel on death, reinfarction, or stroke (COMMIT study) (26). (Reproduced with permission from Elsevier)

This represents the first change in pharmacological reperfusion therapy for patients with STEMI in more than 10 years that has achieved mortality benefit. Earlier studies have shown that fibrinolytic therapy failed to restore coronary flow in approximately 20% of STEMI patients (27–29). Among those who did not achieve reperfusion, mortality rates were doubled. Furthermore, angiographic reocclusion occurred in 5–8% of patients during index hospitalisation and these patients had an associated threefold increase in mortality (30). These adverse outcomes may have been overcome in the COMMIT study group by the synergistic effects of clopidogrel and aspirin. Together, they may have sufficiently reduced platelet activity so that the threshold of aggregation was not exceeded, shifting the balance in favour of sustained reperfusion rather than reocclusion.

The benefits of adding clopidogrel were seen in a wide range of patients (Figure 3), even in older patients aged over 70 and those presenting many hours after the onset of symptoms. The findings derived from the large population studied using a simple protocol, which allows management of patients to approximate real world clinical practice, are likely to be applicable to STEMI patients in many other countries of the world.

An unexpected observation during COMMIT was that the benefit of clopidogrel emerged as early as the first day of therapy (Figure 4) even without a loading dose. In the absence of a loading dose, maximal antiplatelet effects with clopidogrel are expected to be seen days after initiation. No loading dose was given to patients in the COMMIT study because of concerns about potential bleeding complications. Some antiplatelet activity does develop within a few hours of administering a 75 mg oral dose and may be adequate to provide the beneficial effect (31). It is possible that the results might have been more favourable had the patients received a 300 mg loading dose of clopidogrel.

## Clopidogrel improves the patency rate in the infarct-related artery and reduces ischaemic complications (CLARITY trial results)

Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY–TIMI 28) was designed to determine whether the addition of clopidogrel is beneficial in STEMI patients who are receiving a standard fibrinolytic regimen, including aspirin (32). Patients ($n = 3491$) aged between 18 and 75 years were randomised to receive either clopidogrel (300 mg loading dose followed by 75 mg once daily) or placebo in a double-blind setting.

The average time from symptom onset to fibrinolytic administration was 2.7 h. Study medication was administered up to and including the day of coronary angiography or, for patients who did not undergo angiography, up to and including day 8 or hospital discharge, whichever came first. The protocol specified that coronary angiography be performed during index hospitalisation, 48–192 h after the start of study medication (or earlier if clinically indicated), to assess for late patency of the infarct-related artery. Patients were followed up for 30 days for clinical events.

Treatment with clopidogrel resulted in a 36% relative reduction [absolute risk reduction, 6.7% (NNT = 15); $p < 0.001$] in the composite odds of an occluded infarct-related artery on the predischarge angiogram or death or recurrent MI by the time of angiography. This benefit was consistent across a broad range of subgroups (Table 1). At 30 days, clopidogrel therapy led to a significant 20% relative reduction in the odds of death from cardiovascular causes, recurrent MI or ischaemia leading to the need for urgent revascularisation ($p = 0.03$). Treatment with clopidogrel was not associated with an increased rate of major bleeding or intracranial haemorrhage.

In a subgroup of patients from the CLARITY–TIMI 28 study, investigators sought to determine whether clopidogrel pretreatment before PCI in patients with recent STEMI was superior to clopidogrel initiated at the time of PCI in preventing major adverse events (PCI–CLARITY) (33). Patients were randomised to receive clopidogrel as a 300 mg loading dose, followed by 75 mg/day ($n = 933$), or placebo ($n = 930$) in addition to a fibrinolytic agent and aspirin, for 2–8 days until angiography. PCI was performed, at the discretion of the investigator, at an average of 3 days after randomisation. Patients who underwent coronary stenting received a loading dose of at least 300 mg clopidogrel, followed by 75 mg daily.

Pretreatment with clopidogrel significantly reduced the odds of cardiovascular death, reinfarction or stroke by 46% before and within 30 days following

 

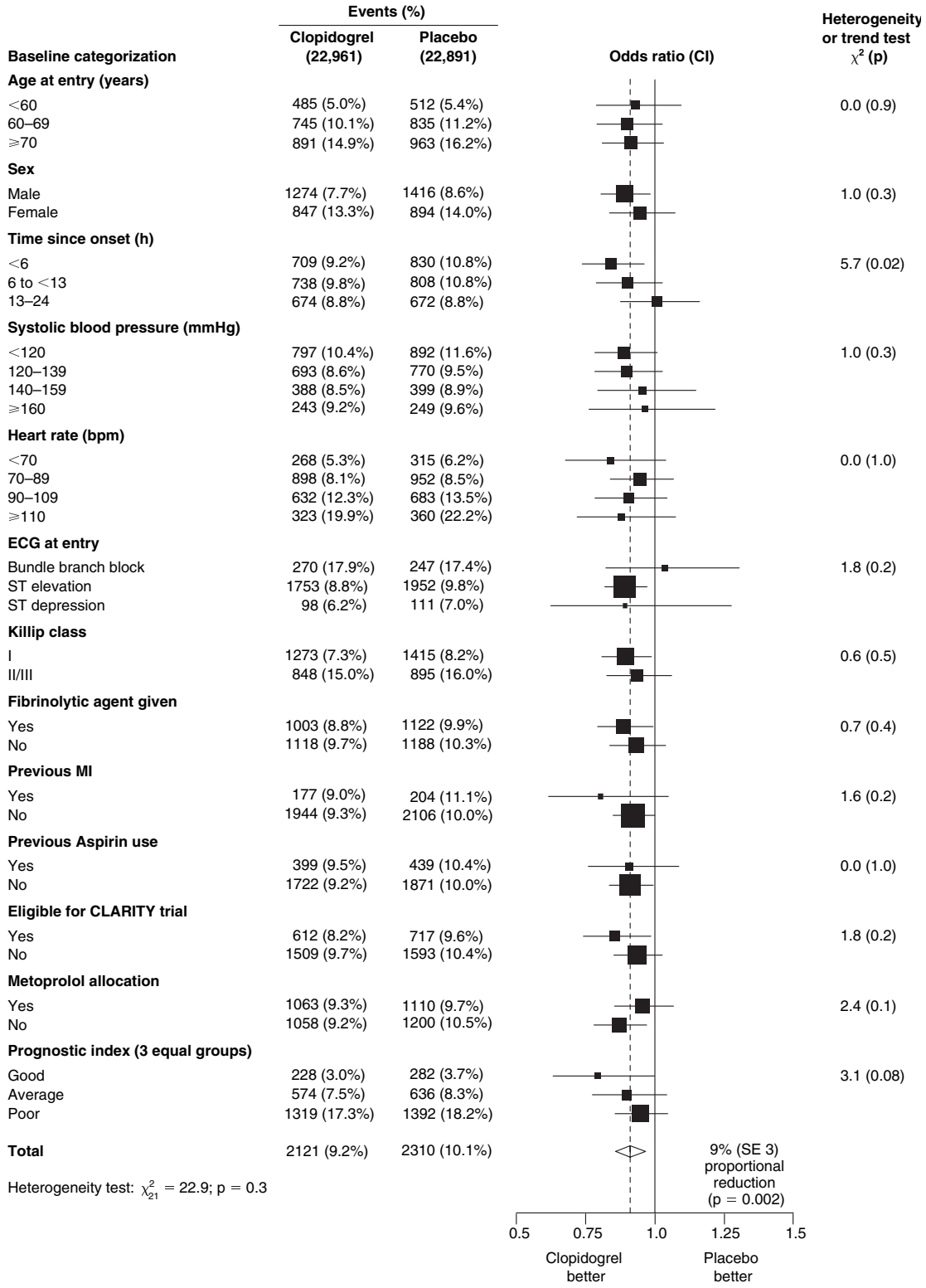


**Figure 3** Effects of clopidogrel allocation on death, reinfarction, or stroke in different categories of patient (COMMIT study) (26). (Reproduced with permission from Elsevier)

PCI, irrespective of the timing of PCI relative to randomisation (Table 2). Clopidogrel pretreatment was consistently beneficial regardless of patient age, gender, the presence of diabetes mellitus or infarct location. The benefit of pretreatment was also similar whether patients had PCI urgently for recurrent

 

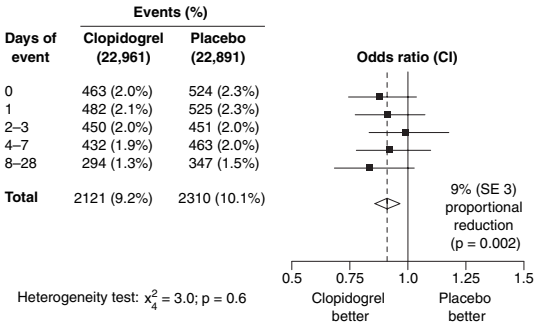


**Figure 4** Effects of clopidogrel allocation on death, reinfarction, or stroke by day of event in COMMIT study. Odds ratio in each period (black square with area proportional to number of events) and 99% CI (horizontal line); broken vertical line indicates oversall result, and diamond indicates its 95% CI (26). (Reproduced with permission from Elsevier)

ischaemia or electively, and whether or not they received glycoprotein IIb/IIIa inhibitor or a loading dose of open label clopidogrel at the time of PCI. There was no significant increase in the risk of major or minor bleeding, even though these patients had received intensive antiplatelet therapy.

## Implications for future management of ACS

Increasingly, clopidogrel is included in the long-term therapy for unstable angina (UA) and during coronary artery procedures (PCI or stenting). The benefits demonstrated by the Clopidogrel vs Aspirin In Patients at Risk of Ischemic Events (CAPRIE) and CURE studies led to the current recommendations for clopidogrel use in the American Heart Association (AHA)/American College of Cardiology (24,34) and European Society of Cardiology (3) guidelines on ACS management.

The improved mortality and reduced risks of reinfarction and stroke seen in patients with acute MI in the COMMIT trial were achieved with short treatment duration at fairly low cost. Clopidogrel could therefore be used widely in populations with limited resources as well as in developed countries. According to the COMMIT results, early clopidogrel therapy has the potential to prevent about 5000 deaths and 5000 non-fatal reinfarctions and strokes if it were given to 1 million of the 10 million patients worldwide who have an MI each year. The COMMIT trialists recommended starting clopidogrel [probably with a loading dose as in the CURE study (2)] in almost all patients presenting with suspected acute MI, irrespective of age, gender and the use of other treatments (provided there are no strong contraindications). They also suggested that continuing clopidogrel therapy after hospital discharge might lead to further gains (35). Long-term benefit of dual antiplatelet therapy with clopidogrel plus low-dose aspirin was recently shown in subgroups of patients with prior MI from a recent analysis of the Clopidogrel

**Table 1** Benefits of clopidogrel across subgroups in the CLARITY study: Reduced odds and event rates for the composite of an occluded infarct-related artery on the pre-discharge angiogram, death, or recurrent MI by the time of angiography [32].

| | | | Event rates (%) | |
|---|---|---|---|---|
| **Characteristic** | **Number of patients** | **Odds reduction (%)** | **Clopidogrel** | **Placebo** |
| Overall | 3491 | 36 | 15.0 | 21.7 |
| Age | | | | |
| <65 years | 2466 | 42 | 13.2 | 21.0 |
| >65 years | 1015 | 22 | 19.0 | 23.1 |
| Gender | | | | |
| Male | 2796 | 35 | 14.5 | 20.8 |
| Female | 685 | 38 | 16.9 | 24.7 |
| Infarct location | | | | |
| Anterior | 1416 | 33 | 15.0 | 20.7 |
| Non-anterior | 2065 | 38 | 15.0 | 22.0 |
| Fibrinolytic agent | | | | |
| Fibrin-specific | 2397 | 31 | 14.7 | 20.1 |
| Non-fibrin-specific | 1084 | 44 | 15.7 | 24.9 |
| Predominant heparin | | | | |
| Low molecular weight | 1429 | 31 | 11.4 | 15.7 |
| Unfractionated | 1431 | 42 | 17.8 | 27.1 |
| None | 621 | 26 | 17.1 | 21.9 |

 

**Table 2** Major cardiovascular outcomes according to allocation of clopidogrel pretreatment before PCI (PCI-CLARITY study) [33].* (Reproduced with permission from American Medical Association)

| Outcome | No. (%) | | Adjusted odds ratio (95% CI)† | p Value |
|---|---|---|---|---|
| | Clopidogrel pretreatment ($n = 933$) | No pretreatment ($n = 930$) | | |
| Outcomes before PCI | | | | |
| MI or stroke | 37 (4.0) | 58 (6.2) | 0.62 (0.40–0.95) | 0.03 |
| MI | 37 (4.0) | 57 (6.1) | 0.60 (0.38–0.95) | |
| Stroke | 0 | 1 (0.1) | – | |
| Outcomes after PCI | | | | |
| Cardiovascular death, MI, or stroke | 34 (3.6) | 58 (6.2) | 0.54 (0.35–0.85) | 0.008 |
| Cardiovascular death or MI | 31 (3.3) | 50 (5.4) | 0.58 (0.36–0.94) | 0.03 |
| Cardiovascular death | 13 (1.4) | 24 (2.6) | 0.49 (0.24–1.03) | |
| MI | 18 (1.9) | 29 (3.1) | 0.60 (0.33–1.11) | |
| Stroke | 4 (0.4) | 11 (1.2) | 0.35 (0.11–1.11) | |
| Overall outcomes before and after PCI | | | | |
| Cardiovascular death, MI, or stroke | 70 (7.5) | 112 (12.0) | 0.59 (0.43–0.81) | 0.001 |
| Cardiovascular death or MI | 67 (7.2) | 103 (11.1) | 0.62 (0.45–0.86) | 0.004 |
| Cardiovascular death | 13 (1.4) | 24 (2.6) | 0.49 (0.24–1.03) | |
| MI | 55 (5.9) | 83 (8.9) | 0.64 (0.44–0.92) | |
| Stroke | 4 (0.4) | 12 (1.3) | 0.32 (0.10–1.01) | |

Abbreviations: CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Patients may have had more than 1 outcome. Patients with cardiovascular events before and after PCI are counted in each category, but counted only once for overall event rates.
†Variables controlled for in adjusted analysis included type of fibrinolytic, initial type of heparin, infarct location, and a propensity score for PCI.

for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial (36). The study had a median follow-up of 28 months. However, as with all subgroup analyses, the results should be interpreted with caution. Nevertheless, in STEMI patients, it is clear that current data supports the use of clopidogrel for up to 28 days postevent.

The CLARITY–TIMI 28 study, which enrolled STEMI patients mainly in western Europe and North America, was different in design to the COMMIT study, in that it incorporated a loading dose of clopidogrel, a fibrin-specific lytic agent was given to more than two-thirds of patients with an average time from symptom onset to fibrinolytic administration of $< 3$ h, and angiography 2–8 days after the start of study medication followed by PCI in more than half the patients. Nevertheless, current evidence showed that the addition of clopidogrel to aspirin represents a major advance in the care of STEMI patients, with clear benefit across a broad range of patient demographics and practice patterns and no excess of bleeding events.

The use of clopidogrel plus aspirin in acute MI requires no extra monitoring compared with aspirin alone. In practice, few patients presenting with STEMI undergo urgent surgery (e.g. coronary artery bypass grafting) during the index hospitalisation. Therefore, there is no need to delay clopidogrel administration because of the risk of major bleeding during a surgical procedure and should be safe to administer to suspected acute MI patients during the early acute phase.

Moreover, a recent extension of the CLARITY–TIMI 28 study has shown that it is feasible to treat STEMI patients with fibrinolytic agents, heparin, aspirin and clopidogrel in medically-equipped ambulances without an increase in major bleeding complications (37). Preliminary results indicate that prehospital administration of clopidogrel significantly reduced the risk of an occluded infarct artery (TIMI flow grade 0/1), death and reinfarction prior to angiography.

The benefit of clopidogrel pretreatment in the PCI–CLARITY study was consistently maintained across pretreatment periods ranging from 6 h to 8 days, suggesting that even brief periods of pretreatment with clopidogrel before PCI improved patient outcomes. The event curves for the study and control

 

groups continued to diverge following PCI, suggesting that the benefit of clopidogrel pretreatment may extend beyond the prevention of platelet aggregation during the procedure. According to the PCI–CLARITY data, adopting a strategy of clopidogrel pretreatment in 100 patients undergoing PCI should prevent two MIs before PCI and two cardiovascular deaths, MIs or strokes in the 30 days following PCI.

For those ACS patients who do not undergo PCI, their reperfusion will be managed pharmacologically. In this context, clopidogrel has been shown to reduce the reoccurrence of thrombotic events without significantly increasing major bleeding complications with treatment of up to 30 days (STEMI patients) and much longer (UA and NSTEMI patients). The fact that the COMMIT trial was conducted in China is noteworthy in that there was always a concern over increased bleeding risk in Asians compared with Caucasians after intensive antiplatelet therapy.

The results of both the COMMIT and CLARITY–TIMI studies have led to the approved extended use of clopidogrel in STEMI patients from the US Food and Drug Administration and the European Medicines Evaluation Agency in August 2006. In future, clopidogrel may be included as part of the long-term medical management of all ACS patients.

## Conclusions

Both the COMMIT and the CLARITY–TIMI 28 trials have shown that clopidogrel is a safe and effective 'add-on' therapy in the early treatment of STEMI. Considering all the evidence, it may be reasonable to prescribe clopidogrel 300 mg for patients < 75 years old with STEMI upfront and clopidogrel 75 mg for patients > 75 years old with STEMI. Initiating clopidogrel therapy in the ambulance may further reduce ischaemic times and promote faster and better reperfusion.

The 2005 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care have developed an algorithm for stabilisation of patients with ACS (38). The recommendations include giving:

- a 300 mg loading dose of clopidogrel, in addition to standard care, to emergency department patients with ACS with elevated cardiac markers or new ECG changes consistent with ischaemia (excluding STEMI) in whom a medical approach or PCI is planned (class I);
- a 300 mg oral dose of clopidogrel to emergency department patients with suspected ACS (without ECG or cardiac marker changes) who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (class IIa);
- a 300 mg oral dose of clopidogrel to emergency department patients up to 75 years of age with STEMI who receive aspirin, heparin and fibrinolysis.

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