

Clopidogrel in acute coronary syndromes

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Clopidogrel is well established in the treatment of acute coronary syndromes and is ubiquitous in cardiology practice. Landmark studies have established the importance of clopidogrel in the treatment of non-ST and ST elevation myocardial infarction and in percutaneous coronary intervention by reducing death, reinfarction, and adverse cardiac events. Knowledge of the benefits, risks, and duration of clopidogrel treatment is important for clinicians caring for patients presenting with and recovering from acute coronary syndromes. This review examines the recent key trials of clopidogrel in the treatment of acute coronary syndromes, as well as current cardiac guidelines from several professional societies.

What is clopidogrel and how does it reduce cardiac ischaemia?

Clopidogrel is a thienopyridine platelet antagonist that requires hepatic activation to form the active molecule. It selectively and irreversibly inhibits the binding of adenosine diphosphate to platelet receptors. Platelet activation plays a crucial role in the pathophysiology of arterial thrombosis and subsequent cardiac ischaemia.^{1,2} Inhibition of adenosine diphosphate receptor binding deactivates the platelet glycoprotein IIb-IIIa complex, thereby inhibiting platelet aggregation.³ Clopidogrel is often given together with aspirin because they work synergistically as platelet antagonists by inhibiting different receptor mediated

pathways that ultimately lead to platelet activation. Daily aspirin is indicated for patients who have already had or are at high risk for a cardiovascular event.

Who should be treated with clopidogrel?

Patients with non-ST elevation myocardial infarction

The CURE randomised trial established the role of clopidogrel in the treatment of patients with non-ST elevation myocardial infarction.⁴ In the trial, 12 562 patients with unstable angina or non-ST elevation myocardial infarction, who were largely medically managed, received aspirin and were randomly assigned to clopidogrel (300 mg loading dose, followed by 75 mg daily) or placebo. The absolute risk reduction in the composite end point of cardiovascular death, non-fatal myocardial infarction, and stroke for those who took both aspirin and clopidogrel was 2.1% ($P < 0.001$; relative risk 0.8, 95% confidence interval 0.72 to 0.9). This benefit of clopidogrel was also seen in patients who received subsequent coronary artery bypass surgery or percutaneous coronary intervention. Despite a 1% absolute increase in major bleeding with dual aspirin and clopidogrel treatment, such treatment has become standard clinical practice in the management of non-ST elevation myocardial infarction. The latest guidance from the American College of Cardiology, American College of Chest Physicians, and European Society of Cardiology on non-ST elevation myocardial infarction strongly recommends the use of clopidogrel (level I A recommendation; see box).⁵⁻⁷

Patients with ST elevation myocardial infarction

Two landmark trials established the role of clopidogrel in the treatment of patients with ST elevation myocardial infarction. CLARITY randomised 3491 patients who presented with ST elevation myocardial infarction within 12 hours of the onset of chest pain to receive a 300 mg clopidogrel loading dose, followed by 75 mg daily, or matching placebo for 30 days.⁸ All patients received aspirin, heparin, and fibrinolytics and then proceeded to coronary angiography. The

SOURCES AND SELECTION CRITERIA

We reviewed the most recent guidelines from the American College of Cardiology, National Institute for Health and Clinical Excellence, European Society of Cardiology, and American College of Chest Physicians on the use of clopidogrel in myocardial infarction. The landmark trials discussed in the above guidelines were retrieved for further review. We also searched for subsequent publications in this area by the key authors of the landmark trials. We searched Medline, Cochrane Library, and Embase using the terms "clopidogrel", "thienopyridine", "myocardial infarction", "acute coronary syndrome", "percutaneous coronary intervention", "coronary stent", and "coronary artery disease" for any additional landmark studies, reviews, or meta-analysis on the use of clopidogrel in myocardial infarction.

TIPS FOR NON-SPECIALISTS

Patients who are allergic to aspirin should take clopidogrel indefinitely

If the patient had a recent acute coronary syndrome, find out whether percutaneous coronary intervention was performed and what type of stent was used because this determines the optimal duration of clopidogrel treatment

Minimise the risk of bleeding in high risk patients (those on dual antiplatelet treatment or also taking anticoagulants or non-steroidal anti-inflammatory drugs) by reducing the dose of aspirin, targeting the lower range of the therapeutic international normalised ratio, minimising the duration of dual antiplatelet treatment, and prophylactically treating the patient with a proton pump inhibitor

Clopidogrel should be stopped five days before scheduled surgery or dental extraction. A cardiologist should be consulted first if a drug eluting stent has recently been inserted

Herbal remedies such as ginkgo should be avoided because they have antiplatelet activity and may increase the risk of bleeding in patients on dual antiplatelet treatment and warfarin

Tell the patient about the importance of adhering to dual antiplatelet therapy with aspirin and clopidogrel after stent implantation

primary composite end point (death, myocardial infarction, and infarct related occluded artery flow) was lower in the clopidogrel arm than in the placebo arm, with no difference in bleeding between the two groups.

Subsequently, the COMMIT randomised trial enrolled 45 852 patients who presented with ST elevation myocardial infarction within 24 hours of onset of ischaemic pain but did not undergo percutaneous coronary intervention.⁹ Patients were randomised to clopidogrel 75 mg daily or matching placebo for four weeks or until hospital discharge. All patients received aspirin, and fibrinolytic agents were used if clinically appropriate. The clopidogrel group had a 0.9% absolute risk reduction in the composite end point of death, reinfarction, and stroke ($P=0.002$; odds ratio 0.91, 0.86 to 0.97) and a 0.6% reduction in absolute risk of death ($P=0.03$; 0.93, 0.87 to 0.99) compared with the placebo group at 28 days. Subgroup analysis of COMMIT showed that the effects of clopidogrel were consistent across a wide range of patients and independent of other drugs used. No excess major bleeding or cerebral haemorrhage was seen in the clopidogrel group.

The findings of the CLARITY and COMMIT trials have led to clopidogrel becoming standard treatment for ST elevation myocardial infarction. Guidelines from the American College of Cardiology strongly recommend the use of clopidogrel in addition to aspirin for the management of ST elevation myocardial infarction (level I A recommendation).¹⁰ A loading dose of clopidogrel 300 mg is encouraged in patients under 75 years, although this recommendation is based on expert opinion alone.

Patients undergoing percutaneous coronary intervention with coronary stenting

The CLASSICS trial established the role of clopidogrel after percutaneous coronary intervention by

showing that clopidogrel was equivalent to ticlopidine in reducing adverse cardiac events after coronary stenting but had a better safety and tolerability profile.^{11 12}

The PCI-CURE study, a subgroup analysis of the CURE trial, further established the role of clopidogrel after coronary stenting.¹³ In this trial, 2658 patients with non-ST elevation myocardial infarction who subsequently underwent percutaneous coronary intervention with stenting were randomised to a 300 mg loading dose of clopidogrel, followed by 75 mg daily clopidogrel or matching placebo. All patients received aspirin. The use of clopidogrel reduced the composite end point (death from cardiac disease, myocardial infarction, and target vessel revascularisation at 30 days) compared with the placebo group. The role of clopidogrel in reducing adverse cardiac events after coronary stenting is established, and treatment with clopidogrel has become standard clinical practice.

For how long should treatment with clopidogrel continue?

After acute coronary syndromes

The ideal duration of clopidogrel treatment for non-ST elevation myocardial infarction is unclear, although the average length of treatment in the CURE trial was nine months. The latest American College of Cardiology and American College of Chest Physicians guidelines for ST elevation myocardial infarction recommend a 14 day course of clopidogrel treatment (level I B recommendation) on the basis of the average duration of treatment in the COMMIT trial.^{10 14} These guidelines also suggest that up to one year of clopidogrel may be beneficial in ST elevation myocardial infarction, although this is based on extrapolation from other clopidogrel studies in coronary artery disease and expert opinion (level II C recommendation).

CHARISMA, a trial that randomised 15 603 patients with multiple cardiac risk factors and clinically evident cardiovascular disease to either clopidogrel

Classification of recommendations and levels of evidence

Recommendations

Level I: Evidence and agreement that treatment is beneficial

Level II: Conflicting evidence and divergence of opinion regarding benefits of treatment

Level III: Evidence and agreement that treatment is not beneficial, and may cause harm

Evidence

Level A evidence: Data derived from multiple randomised clinical trials or meta-analyses

Level B evidence: Data derived from a single randomised trial or non-randomised studies

Level C evidence: Consensus opinion or experts, case studies, or standard of care

75 mg daily or placebo plus background aspirin for two years, showed that prolonged treatment with clopidogrel did not reduce cardiac adverse events.¹⁵ This trial enrolled a heterogeneous group of patients with cardiac disease, so it is difficult to know whether patients with documented coronary artery disease would benefit from long term dual antiplatelet therapy with aspirin and clopidogrel. Routine prolonged treatment with clopidogrel beyond current recommendations is not warranted at this time.

After coronary stenting

The optimal duration of clopidogrel after coronary stenting was still unclear at the end of the PCI-CURE study, which looked at the use of clopidogrel only up to 30 days after stenting. The CREDO trial randomised 2116 patients who underwent percutaneous coronary intervention with stenting to a 300 mg loading dose of clopidogrel, followed by 75 mg daily for 12 months or a placebo loading dose, followed by clopidogrel 75 mg daily for 28 days.¹⁶ The composite end point of death, myocardial infarction, and stroke at 12 months was lower in the 12 month clopidogrel arm than in the 28 day clopidogrel arm. This showed that a longer rather than shorter course of treatment with clopidogrel is best after coronary stenting. Major bleeding at 12 months was not significantly different between the 12 month and 28 day clopidogrel groups. On the basis of PCI-CURE and CREDO, the most recent guidance from the American College of Cardiology, European Society of Cardiology, and American College of Chest Physicians on percutaneous coronary intervention strongly recommends clopidogrel for at least one

RESEARCH QUESTIONS

Ongoing research

The OASIS 7 trial is investigating the benefits of a 600 mg loading dose of clopidogrel, followed by 150 mg daily for one week, then 75 mg daily compared with the current standard of a 300 mg loading dose and 75 mg daily

The DAPT trial is investigating the optimal duration of clopidogrel after placement of a drug eluting stent

Other thienopyridine agents are in development

Questions for future research

What advantages do newer thienopyridine platelet antagonists, such as prasugrel, have compared with clopidogrel?

What is the optimal dose of clopidogrel for patients with diabetes?

month after bare metal stent insertion (level I A recommendation), with an ideal duration of one year (level I B recommendation).¹⁷⁻¹⁹

After drug eluting coronary stent placement

A longer duration of dual antiplatelet treatment with aspirin and clopidogrel is needed after placement of a drug eluting stent than a bare metal stent. Previous percutaneous coronary intervention guidelines recommended six to 12 months of such treatment, largely on the basis of randomised clinical trials of drug eluting stent studies and registry data.²⁰ Concerns have recently emerged about late stent thrombosis and subsequent adverse cardiac events with drug eluting stents. Several small observational studies and registry data suggest that mortality and the incidence of myocardial infarction may be higher with drug eluting stents than with bare metal stents, probably because of the greater chance of late stent thrombosis with drug eluting stents.^{21,22} Observational studies and analysis of registry data show that premature discontinuation of clopidogrel is the biggest risk factor for late stent thrombosis.^{22,23} The possibility of higher cardiac event rates associated with drug eluting stents has sparked much concern and debate.²⁴

Because of these concerns, the American College of Cardiology has recommended that patients receive at least one year of dual antiplatelet treatment with aspirin and clopidogrel after implantation of any drug eluting stent. These recommendations are based largely on observational data and expert opinion (level I B recommendation).²² The use of dual antiplatelet treatment is crucial and patients should be told about the importance of adhering to treatment with clopidogrel before implantation of a drug eluting stent.

The optimal treatment beyond one year is unknown, but studies to determine the optimal duration of clopidogrel after placement of a drug eluting stent are under

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

American College of Chest Physicians (www.chestjournal.org/content/vol133/6_suppl/)—Latest guidelines from the ACCP on antithrombotic treatment

American College of Cardiology (<http://www.acc.org/qualityandscience/clinical/statements.htm>)—ACC guidelines on non-ST elevation myocardial infarction, ST elevation myocardial infarction, and percutaneous coronary interventions

European Society of Cardiology (www.escardio.org/guidelines-surveys/esc-guidelines/Pages/GuidelinesList.aspx)—ESC guidelines on acute coronary syndromes

Emmons KL, Taylor NT. Contemporary issues in clopidogrel therapy: new evidence shaping clinical practice. *Pharmacotherapy* 2007;27:553-63

Galla JM, Lincoff AM. The role of clopidogrel in the management of ischemic heart disease. *Curr Opin Cardiol* 2007;22:273-9

RESOURCES FOR PATIENTS

NHS Direct (http://cks.library.nhs.uk/patient_information_leaflet/anti_platelets_clopidogrel#)—Clopidogrel drug monograph

NHS Direct (http://cks.library.nhs.uk/patient_information_leaflet/heart_attack)—Information about heart attacks

NHS Choices (www.nhsdirect.nhs.uk/articles/article.aspx?articleId=112§ionId=145)—Information about percutaneous coronary intervention

SUMMARY POINTS

All patients presenting with acute coronary syndromes should be given a 300 mg loading dose of clopidogrel, then 75 mg daily

Patients not undergoing percutaneous coronary intervention should receive clopidogrel for nine to 12 months for non-ST elevation myocardial infarction and 14 days for ST elevation myocardial infarction

Patients given a bare metal stent should receive clopidogrel, in addition to aspirin, for at least one month and ideally for one year

Patients given a drug eluting stent should receive clopidogrel, in addition to aspirin, for at least one year

The duration of clopidogrel treatment must take into account the patient's risk of bleeding

way. Patients who are allergic to aspirin should take clopidogrel indefinitely.

What about bleeding?

Concerns about the risk of bleeding when using clopidogrel in addition to a fibrinolytic and aspirin still remain. Clopidogrel monotherapy has a similar risk of bleeding to that of aspirin monotherapy. Prolonged dual antiplatelet treatment carries a risk of increased bleeding. The CURE and CHARISMA trials showed around a 1% absolute increase in moderate to major bleeding with combined aspirin and clopidogrel versus aspirin alone. No increase in intracranial haemorrhage was seen with combined aspirin and clopidogrel treatment compared with aspirin alone in all the landmark trials. Dual antiplatelet treatment caused bleeding mostly in the gut. The risk is higher with increasing age, concurrent use of anticoagulant and anti-inflammatory drugs, a history of gastrointestinal bleeding, and other risk factors for bleeding.

An ongoing dilemma is the use of aspirin and clopidogrel in patients who also need warfarin. The addition of warfarin puts patients at further risk of significant bleeding. Little literature is available to guide clinicians, although expert consensus opinion recommends reducing the dose of aspirin (to 75-80 mg daily), targeting a lower international normalised ratio, and minimising the duration of dual antiplatelet treatment in these patients.¹⁷ Temporary discontinuation of warfarin or use of one antiplatelet agent only may be considered if the risk of bleeding is deemed to exceed the benefits of treatment. Gastrointestinal prophylactic treatment should be initiated in all patients at high risk for gastrointestinal bleeding who are on dual antiplatelet treatment. These risks should be considered before placement of drug eluting stents and when determining the duration of treatment for individual patients.

What is the optimal loading dose of clopidogrel?

The optimal loading dose of clopidogrel is still unclear. Although the landmark studies in myocardial

infarction and percutaneous coronary intervention used a 300 mg loading dose, higher doses have recently been shown to produce faster and greater platelet inhibition, thereby reducing the risk of further cardiac events. The ARMYDA-2 randomised study showed that, in patients undergoing percutaneous coronary intervention, a 600 mg loading dose of clopidogrel was superior to 300 mg in reducing periprocedural myocardial infarction.²⁵ On the basis of emerging clinical trial data, the current American and European guidelines recommend 600 mg in patients undergoing percutaneous coronary intervention (level I C recommendation) and 300 mg in patients presenting with acute coronary syndromes.^{17 18}

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Mental illness—not a laughing matter

Part of every introduction in small talk is the discussion of what one does for a living. Most people, on finding out that I am a psychiatrist, will cast a pitying glance at my husband, giggle nervously, and edge away from me saying something to the effect that, "Oh, I had better watch what I say and do then." All of this, of course, is meant to imply that I have, by virtue of my training, some sort of psychic or mind reading abilities and that mere mortals had better beware. It's mostly done in jest, and I sometimes play along. After all, psychic powers would make my job a lot easier and would make parties far more interesting.

What I find much more difficult to deal with are the declarations, often accompanied by much winking and guffawing, that someone I have been introduced to would benefit from my professional expertise. This kind of statement has been made not only by laypeople but also by colleagues within the medical profession. Implying that someone has a mental illness seems to be widely accepted as the basis for a joke, and I find this rather disturbing. After all, if I joked with an oncologist or orthopaedic surgeon that my colleague needed their attention, the result would be a kind of speechless horror and accusations of insensitivity. Cancer and broken bones are obviously not funny. So why is it considered acceptable to joke about mental illness?

I have seen first hand how much suffering mental illness can cause. The patients have to live through frightening and bewildering experiences that are debilitating and can result in alienation from those they care about, loss of employment, and destruction of their sense of self worth. Friends and family of those with mental illness witness dramatic changes in the behaviour and personality of

those they love while feeling helpless and unable to share their pain with wider acquaintances. Mental illness does not come with open wounds or scars to show others how much suffering it causes, but it can be more devastating than many chronic physical illnesses.

Perhaps people joke about it to distance themselves from mental illness—it thereby becomes something abstract that could never happen to you or someone close to you. But anyone can have mental illness, regardless of age or profession. It is not a sign of "mental weakness," and its sufferers, like all patients, should be treated with respect, empathy, and understanding. How can we expect to combat the stigma of mental illness when medical professionals treat psychiatric problems with derision and as being less worthy of attention and sympathy? And bear in mind that the medical professions, along with the armed forces, have the highest incidence of work related mental illness, with some 1 in 4 health service workers reporting significant levels of minor psychiatric disorder.

The charity Rethink, with its 2009 campaign, is saying that it's "Time to Change" the way the general public looks at mental illness (www.rethink.org/how_we_can_help/campaigning_for_change/time_to_change/index.html). This is even more important for doctors—we owe it to those we work with as well as those we look after.

"Mental illness is nothing to be ashamed of, but stigma and bias shame us all."—Bill Clinton

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