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CLINICAL

Clopidogrel therapy in coronary heart disease: reviewing the evidence and assessing the practice

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ABSTRACT Since its introduction as a new anti-platelet agent a decade ago, clopidogrel has been shown to be a useful drug in the treatment of non-ST elevation acute coronary syndromes. Its use in such conditions has been advocated by national UK, European and international guidelines issued by a number of professional regulatory authorities. However, in the past few years, new evidence has emerged from a number of clinical trials supporting the expansion of clopidogrel use to include ST elevation myocardial infarction and patients undergoing both urgent and elective percutaneous coronary interventional procedures in the form of an initial loading dose followed by a daily maintenance dose, usually for a period of 12 months. This review paper aims to highlight areas in clinical practice where clopidogrel use does not follow the agreed guidelines. It also compares the published UK, European and international guidelines with the up-to-date evidence that recently became available from clinical trials. The paper also outlines some suggested recommendations to be considered when issuing any new clopidogrel-related guidance documents.

KEYWORDS Clopidogrel, dual anti-platelet therapy, ischaemic heart disease, percutaneous coronary intervention

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INTRODUCTION

Clopidogrel – first introduced in 1998 – is a potent, non-competitive inhibitor of adenosine diphosphate (ADP) induced platelet aggregation, irreversibly inhibiting the ADP binding to its platelet membrane receptors. Therefore, platelets exposed to clopidogrel are affected for the remainder of their approximately eight-day average lifespan. The inhibition is specific with no associated significant effect on either the cyclo-oxygenase (COX) or arachidonic acid metabolic pathways. Furthermore, clopidogrel indirectly inhibits the activation of glyco-protein (GP) IIb/IIIa receptors and their binding to fibrinogen, causing inhibition of further platelet aggregation.

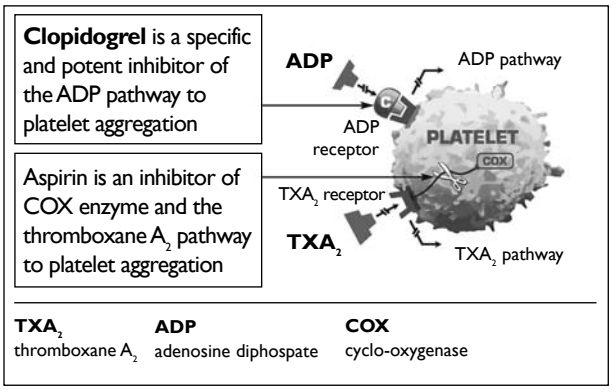

FIGURE 1 An illustration showing the mode of action of clopidogrel. (Reproduced with permission from Sanofi-Aventis.)

Evidence obtained from large randomised trials demonstrated a consistently beneficial effect of using clopidogrel in acute coronary syndromes (ACS). In consequence, the National Institute for Health and Clinical Excellence (NICE) issued detailed guidance in July 2004 recommending that clopidogrel be used in combination with low-dose aspirin for managing patients presenting with non-ST segment-elevation ACS (NSTE-ACS) who are at moderate to high risk of myocardial infarction (MI) or death. The guidance also states that the risk of MI or death in patients presenting with NSTE-ACS is determined by clinical signs and symptoms accompanied by the presence of new or dynamic ischaemic ECG changes – other than ST segment-elevation – and the detection of raised blood markers indicative of cardiac cell damage, such as troponin. The guidance recommends that dual anti-platelet therapy with clopidogrel and low-dose aspirin be continued for up to 12 months after the most recent acute episode of NSTE-ACS, and that standard care, including treatment with low-dose aspirin alone, is to resume thereafter.

In a further guidance document issued in May 2007, NICE recommended that after ST segment elevation myocardial infarction (STEMI), patients treated with a combination of aspirin and clopidogrel during the first 24 hours should continue such treatment for at least four weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual anti-platelet therapy. The

guidance further states that if the patient has not been treated with a combination of aspirin and clopidogrel during the acute phase of an MI, this combination should not routinely be subsequently initiated.

The revised guidance of the Scottish Medical Consortium (SMC) issued in August 2007 has similar recommendations for using clopidogrel in both STE-ACS and NSTE-ACS. The European Society of Cardiology (ESC) also issued broadly similar guidelines for the diagnosis and treatment of non-ST elevation myocardial infarction in 2007. However, the latest published ESC guidelines for STEMI treatment date back to 2003 and understandably do not contain any reference to clopidogrel use in STEMI. On the other hand, the American College of Cardiology/ American Heart Association (ACC/AHA) guidance update from 2007 has recommended using clopidogrel therapy for a duration of one year following both NSTE-ACS and STEMI. The same guidance advises omitting clopidogrel loading dose in elderly STEMI patients who receive fibrinolysis.

In line with some of the above NICE guidance, it is now routine practice in most UK district hospitals to commence clopidogrel at an initial dose of 300 mg, followed by a dose of 75 mg once daily, for the treatment of NSTE-ACS along with other standard therapy. However, new evidence – discussed below – has since emerged suggesting that clopidogrel use should be extended and, therefore, a review of the current practice and NICE guidance should be performed.

The aim of this review is to explore what the current evidence is with regard to the use of clopidogrel and to provide a set of recommendations to be considered prior to any new or revised NICE/ESC/SMC guidance. In the evidence we reviewed, we only included randomised placebo-controlled trials that investigated the use of clopidogrel in coronary disease. We have not included other trials that involved the use of clopidogrel in other clinical settings, such as stroke.

THE EVIDENCE

Clopidogrel was first investigated by the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events). This was a randomised, blinded, international trial involving 19,185 patients. It was designed to assess the relative efficacy and safety of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of ischaemic stroke, MI or vascular death in patients with recent MI, stroke or established peripheral vascular disease (PVD).[1] Although the result demonstrated marginal superiority of clopidogrel over aspirin with a relative risk reduction (RRR) of 8.7% (absolute risk reduction [ARR] = 0.51%) in the combined endpoint (p value = 0.045), CAPRIE formed the basis for the approval of clopidogrel as a therapeutic agent for the reduction of thrombotic events in patients with recent MI, recent stroke or established PVD.

TABLE 1 Effects of clopidogrel and aspirin in patients with non ST-segment elevation acute coronary syndromes. Adapted from the CURE study investigators. *N Engl J Med* 2001; 345:494–502.

Outcome	Clopidogrel	Placebo	Relative risk	p value
Cardio-vascular death	5.1%	5.5%	0.80	<0.001
Non-fatal MI	5.2%	6.7%	0.93	<0.001
Stroke	1.2%	1.4%	0.93	<0.001
Major bleeding	3.7%	2.7%	1.38	0.001
Minor bleeding	5.1%	2.4%	2.12	<0.001
All bleeding	8.5%	5.0%	1.69	<0.001

Clopidogrel in MI

Clopidogrel use in NSTE-ACS

The CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events trial) was another prospective randomised, placebo-controlled multi-centre trial that evaluated the efficacy and safety of clopidogrel when added to aspirin in 12,562 patients presenting acutely with NSTE-ACS. Patients were randomised to receive either clopidogrel (300-mg loading dose, followed by a maintenance dose of 75 mg daily) or a matching placebo for 3–12 months (mean 9 months). Both arms received standard ACS therapy including aspirin. The clopidogrel arm demonstrated a 20% RRR (p = 0.00009)[2] in the combined endpoints of MI, stroke or cardiovascular (CV) death. The absolute event rates were 9.3% and 11.4% in the clopidogrel and placebo groups respectively (ARR = 2.1%).

In addition, there was a further observed 1.9% ARR (RRR = 0.7) in patients from the clopidogrel arm who underwent percutaneous coronary intervention (PCI).[3] There was also a significant increase in the rates of both major and minor bleeding observed in the clopidogrel arm of 3.7% and 5.1% respectively, compared with 2.7% and 2.4% incidence in the placebo arm (Table 1). The superiority of clopidogrel over placebo observed in the CURE study has paved the way for the routine use of dual anti-platelet therapy in patients with NSTE-ACS who are not at an increased risk of bleeding complications.

Clopidogrel use in STEMI

Two more recent international, double-blinded, randomised multi-centre studies, CLARITY – TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy –

TABLE 2 CLARITY – TIMI 28: primary and angiographic outcomes (median 3.5 days)

Outcome	Clopidogrel	Placebo	p value
Primary endpoint	15%	21.7%	<0.001
TIMI flow grade 0–1	11.7%	18.4%	<0.001
MI	2.5%	3.6%	0.08
Death	2.6%	2.2%	0.49
TIMI flow grade 3	68%	61%	<0.001
TIMI myocardial perfusion	55.8%	51.2%	0.008
Thrombus	43%	50.8%	<0.001

Thrombolysis In Myocardial Infarction 28) and COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial) investigated the use of clopidogrel in patients with acute STEMI.

CLARITY[4] enrolled 3,491 patients – presenting with acute STEMI within 12 hours of symptoms – to study the hypothesis that the addition of clopidogrel to standard fibrinolytic therapy improves the infarct-related artery patency and minimises ischaemic complications in such patient cohorts. Patients were randomised to receive either clopidogrel with a loading dose of 300 mg, followed by 75 mg daily, for 30 days or to placebo. Patients underwent coronary angiography two to eight days post randomisation, after which the drug was discontinued. For patients undergoing PCI, it was recommended that they receive open-label clopidogrel with a loading dose. The results demonstrated statistically significant improved patency rate of the infarct-related artery in the clopidogrel arm compared with placebo (Table 2).

COMMIT/CCS-2[5,6] studied the effect of clopidogrel plus aspirin versus aspirin alone in 45,852 patients – in 1,250 hospitals – presenting with acute STEMI within 24 hours of symptoms onset. All patients were given 162 mg aspirin daily and, in addition, 75 mg clopidogrel daily or matching placebo for four weeks or until prior discharge or death. Allocation to clopidogrel produced a highly significant 9% proportional reduction in the primary composite outcome of death, re-infarction or stroke (2,121 [9.2%] clopidogrel versus 2,310 [10.1%] placebo; ARR = 0.9%, p = 0.002). This indicates that the addition of daily 75 mg of clopidogrel to other standard treatment of acute STEMI reduces mortality and major vascular events in hospital. There was no observed increase in major bleeding in the clopidogrel arm.

TABLE 3 CHARISMA: Composite and individual primary and secondary endpoints

Endpoint	Clopidogrel + aspirin (n = 7,802), n (%)	Placebo + aspirin (n = 7,801), n (%)	RR	p value
Efficacy endpoints				
Primary endpoint	534 (6.8)	573 (7.3)	0.93	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99	0.90
Death from any cardio-vascular cause	238 (3.1)	196+	1.04	0.68
MI (non-fatal)	147 (1.9)	159 (2.0)	0.92	0.48
Ischaemic stroke (non-fatal)	132 (1.7)	160 (2.1)	0.82	0.10
Secondary efficacy endpoint	1,301 (16.7)	1,395 (17.9)	0.92	0.04
Hospitalisation for UA, TIA or revasculari-sation	866 (11.1)	957 (12.3)	0.90	0.02
Safety endpoints				
Severe bleeding	130 (1.7)	104 (1.3)	1.25	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53	0.17
Moderate bleeding	164 (2.1)	101 (1.3)	1.62	<0.001

Clopidogrel and stable coronary disease

On the other hand, another large randomised placebo controlled study, CHARISMA (Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilisation, Management and Avoidance),[7,8] investigated the efficacy of clopidogrel in preventing the occurrence of major CV complications (MI, stroke, CV death) in high-risk stable patients who received daily low-dose aspirin. The study also looked at the long-term safety profile of clopidogrel in the studied cohort of patients. A total of 15,603 patients – with either clinically evident CV disease (n = 12,398) or multiple risk factors (n = 3,205) – were randomised to receive clopidogrel 75 mg daily or placebo and were followed up for a median of 28 months, the primary endpoint being a composite of MI, stroke or CV death. The results showed no significant difference between the two trial arms in reducing the primary endpoint (Table 3). However, in the patients

with known CV disease, there was a trend towards benefit with clopidogrel, but it was not statistically significant. There was a significant increase in the incidence of moderate bleeding in the clopidogrel arm.

Clopidogrel in PCI

The benefit of long-term (12-month) treatment with clopidogrel after PCI was investigated by the CREDO trial (Clopidogrel for the Reduction of Events During Observation),[9] a randomised, double-blind, placebo-controlled study conducted among 2,116 patients enrolled at 99 North American centres. Long-term clopidogrel therapy was found to be associated with a 26.9% RRR in the combined risk of death, MI or stroke (95% confidence interval [CI] 3.9–44.4; p = 0.02; ARR = 3%). There was no significant increase in the risk of major bleeding at the end of one year compared with the placebo. In this study, patients who received a clopidogrel loading dose of 300 mg ≥6 hours before PCI had a statistically non-significant trend towards benefiting for the combined endpoint (RRR = 38.6%; 95% CI -1.6–62.9; p = 0.051). No such trend was observed in the sub-group of patients who received clopidogrel loading ≤6 hours before PCI. The addition of GP IIb/IIIa inhibitors such as abciximab to dual anti-platelet therapy during urgent PCI was shown in a number of studies to be beneficial, albeit at a cost of higher bleeding complications. Therefore GP IIb/IIIa use is mainly reserved for high-risk ACS patients undergoing urgent PCI.

Optimal dosing

Patti et al[10] conducted a smaller study aiming to determine the optimal clopidogrel loading dose required prior to PCI by randomising 255 patients to receive either a 600-mg (n = 126) or 300-mg (n = 129) loading dose, four to eight hours before PCI. The primary endpoint was 30-day mortality, MI or target vessel revascularisation (TVR). The primary endpoint occurred in 4% of patients in the high loading dose versus 12% of those in the conventional loading dose group (p = 0.041), and was due entirely to peri-procedural MI. Peak values of cardiac markers (CK-MB, Troponin I) were significantly lower in patients treated with the 600-mg regimen (p = 0.038). This is a relatively small study, but its results have led many interventional centres to adopt a policy of using a 600-mg loading dose of clopidogrel, usually six hours before PCI.

Duration of treatment

In another sizeable study, Spertus et al[11] used prospectively collected data of 500 MI patients to examine the prevalence and predictors of thienopyridine – mainly clopidogrel – discontinuation 30 days after drug eluting stent (DES) treatment. Patients who stopped thienopyridine therapy after 30 days were found to be much more at risk of dying during the next 11 months (7.5% versus 0.7%, p <0.0001; adjusted hazard ratio = 9.0; 95% CI 1.3–60.6). In line with such findings, it is now routine practice in most UK cardiac interventional units to prescribe dual anti-platelet therapy for at least 12 months following PCI treatment with DES, in order to maintain patency of the stented artery.

Cessation of treatment

The BASKET-LATE study[12] (Basel Stent Kosten Effektivitäts Trial) examined the incidence of late stent thrombosis in patients treated with DES versus bare-metal stents (BMS) within one year after the discontinuation of clopidogrel therapy in a consecutive series of 746 non-selected patients with a total of 1,133 stented lesions. Although the rates of 18-month cardiac death/MI were found not to be different between DES and BMS patients, following discontinuation of clopidogrel (between months 7 and 18), these events occurred in 4.9% after DES versus 1.3% after BMS implantation (between 15 and 362 days after the discontinuation of clopidogrel). These results suggest that patients who receive DES are more at risk of late stent thrombosis compared with those with BMS. Therefore, in some higher risk groups, clopidogrel therapy may need to be given for much longer than 12 months or even indefinitely following DES implantation. There are no other completed studies that examined this issue, although more studies are expected to emerge with clearer outcome results in due course.

Recent developments and other related studies

The latest TRITON – TIMI 38 study[13] (Trial to assess Improvement in Therapeutic outcomes by Optimizing Platelet Inhibition with prasugrel) compared the role of a new thienopyridine, prasugrel, with clopidogrel. A total of 13,608 patients with moderate- to high-risk ACS and scheduled PCI were randomly assigned to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6–15 months. The primary efficacy endpoint was death from CV causes, non-fatal MI or non-fatal stroke. The key safety endpoint was major bleeding. The primary efficacy endpoint occurred in 12.1% of the clopidogrel group and 9.9% of the prasugrel group (p <0.001). The rate of MI was 9.7% for clopidogrel versus 7.4% for prasugrel (p <0.001), the rate of urgent TVR was 3.7% versus 2.5% (p <0.001) and the rate of stent thrombosis was 2.4% versus 1.1% (p <0.001). However, major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio = 1.32; 95% CI 1.03–1.68; p = 0.03). Fatal bleeding was significantly higher in the prasugrel group (0.4% vs. 0.1%; p = 0.002).

In a recent small study (ISAR-CHOICE-2), von Beckerath et al[14] tested whether increasing the daily clopidogrel maintenance dose had any added effect on platelet function in 60 patients following successful PCI and pre-treatment with a 600-mg loading dose. Patients were randomised to receive a daily dose of either 75 or 150 mg for 30 days, at which point platelet function was

TABLE 4 A summary of the large randomised trials that have investigated the use of clopidogrel in coronary heart disease

TRIAL NAME	PATIENTS (N)	MANAGEMENT STRATEGY	OTHER AGENTS USED	RESULTS
ISAR-REACT 2 Kastrati *JAMA* 2006	2,022 NSTE-ACS undergoing PCI	Loading 600 mg Clopidogrel 2 hours prior PCI + 325–500 mg ASA. Abciximab 0.25 mg/kg bolus followed by IV 0.125 mcg/kg/min for 12 hours + 70 U UFH/kg bolus, followed by infusion. Placebo group received 140 U heparin/kg bolus, followed by infusion (European practice). Post PCI: ASA 200 mg indefinitely. Clopidogrel 75 mg bd for max 3 days, followed by 75 mg/day for 6 months		No difference in incidence of ischaemic events between the two groups in patients without an elevated troponin level. Events significantly lower in patients with elevated troponin (RRR = 29%). No significant difference in bleeding risk between the groups. 600-mg clopidogrel loading associated with better protection during PCI.
COMMIT Chen *Lancet* 2005	45,852	Clopidogrel + ASA versus ASA alone	Placebo, metoprolol	RRR = 9% for primary endpoint in favour of clopidogrel + ASA. ARR = 0.9% for primary endpoint
CLARITY Sabatine *N Engl J Med* 2005	3,491	Clopidogrel + ASA and fibrinolytics	GP IIb/IIIa, LMWHs, UFH, fibrinolytics	36% RRR in primary endpoint with clopidogrel. 30% RRR in MI. Urgent revascularisation need reduced by 20%, recurrent MI reduced by 24%. ARR = 6.7% for primary endpoint
ISAR REACT Kastrati *N Engl J Med* 2004	2,159 Follow-up for 30 days	600-mg loading dose clopidogrel 2 hours prior to PCI + 325–500 mg ASA. Abciximab bolus, followed by IV infusion for 12 hours + 70 U Heparin/kg bolus, followed by infusion. Placebo group received 140U heparin/kg bolus followed by infusion. Post PCI: ASA 75–325 mg indefinitely. Clopidogrel 75 mg bd for max. 3 days, followed by 75 mg/day for 30 days		Use of abciximab was associated with no benefit in the 30 days after procedure. It was associated with an increased frequency of thrombocytopenia. In patients with low and intermediate risk undergoing PCI after pre-treatment with 600 mg clopidogrel loading at least 2 hours pre-procedure, the additional use of abciximab is associated with no clinically measurable benefit within the first 30 days.
CREDO Steinhubl *JAMA* 2002	2,116 Follow-up 28 days and one year	300-mg loading dose clopidogrel 3–24 hours prior to PCI, followed by 75 mg/day	All received stents. ASA, beta blocker, statin, ACEI, CCB	Clopidogrel loading: • 3–6 hours pre-procedure: no benefit • 6–12 hours: 35.5% RRR • 12–24 hours: 40% RRR • Clopidogrel + GP IIb/IIIa: 30% RRR No significant difference in major/minor bleeds in 28 days
CURE Yusuf *N Engl J Med* 2001	12,562, 3–12 months, mean 9 months	Effect of clopidogrel + ASA. Clopidogrel 300mg loading, then 75 mg/day. ASA 75–325 mg/day	Placebo	RRR = 20% and 14% for primary and secondary endpoints in favour of clopidogrel. ARR = 2.1% for primary endpoint
CAPRIE Gent *Lancet* 1996	19,185 for 3 years, mean 1.9 years	Clopidogrel versus ASA	Placebo	RRR of 8.7% in favour of clopidogrel. ARR = 0.51%

evaluated by two different assay techniques. Both assays revealed that a clopidogrel dose of 150 mg results in larger platelet numbers being inhibited compared with the conventional maintenance dose of 75 mg. No clinical endpoints were measured in the study.

Clopidogrel in coronary artery bypass grafting (CABG)

The American College of Chest Physicians (ACCP) 2004 guidelines recommend 9–12 months of clopidogrel in addition to aspirin for patients undergoing CABG for NSTE-ACS. This is based on sub-analyses of the CURE and CAPRIE studies that showed significant reductions in the incidence of death, MI and stroke in patients who had CABG during those trials.[15] However, another large study, CASCADE (Clopidogrel After Surgery for Coronary Artery Disease),[16] is currently in the recruitment stage and is designed to test the effect of long-term clopidogrel use on saphenous vein graft intimal hyperplasia following CABG. The results are expected to help redefine modern anti-platelet management of CABG patients. Clopidogrel has been shown to increase the risk of post-CABG bleeding if taken within three days prior to surgery but not if taken before that.[17,18]

The optimum platelet inhibition after CABG was investigated by Lim et al, who randomised 54 patients to receive 100 mg aspirin, 325 mg aspirin or 75 mg clopidogrel tablets daily for five days post elective CABG, after which period assessment of platelet aggregation was performed. Compared with baseline, the mean percentage aggregations with collagen on day five were found to be an average of 56% for both doses of aspirin and 99% for clopidogrel. The mean difference between the two arms was 42% (95% CI = 27–56) in favour of aspirin. It was concluded that clopidogrel, unlike aspirin, did not inhibit platelet aggregation in the first five postoperative days and therefore should not be used as a sole anti-platelet agent early after CABG.

Many other studies have investigated the use of clopidogrel in different clinical settings, such as cerebro-vascular disease. These are not discussed here as those topics are beyond the scope of this article.

DISCUSSION

Clopidogrel in MI

The above outlined clinical trials provide useful evidence of the benefit that clopidogrel may – or may not – achieve in different cohorts of patients with coronary disease. Both types of ACS, STE and NSTE, seem to benefit prognostically from the addition of clopidogrel therapy in the form of an immediate initial loading dose of 300 mg, followed by a 75-mg maintenance daily dose. Therefore, unless clearly contraindicated, all patients admitted with ACS should receive such doses of clopidogrel in addition to aspirin, plus the other appropriate cardiac medications. Although the COMMIT trial has shown a beneficial effect of clopidogrel at the end of 28 days post STEMI, the study has not continued any further to investigate the presence or absence of any longer-term benefit of dual anti-platelet therapy.

On the other hand, evidence extrapolated from the CURE study shows clear long-term benefit of clopidogrel in NSTE-ACS patients. As concluded by the ACC/AHA guidelines detailed in the introduction, it may be more appropriate that clopidogrel therapy continues for up to one year following STEMI. However, we still agree that there is limited direct evidence for longer-term dual anti-platelet therapy post STEMI, and both the bleeding risk and cost of such therapy need to be carefully considered. Further trials may be necessary to assess the benefit versus risk of longer-term dual anti-platelet therapy post STEMI.

At present, there is no NICE guidance to cover the use of clopidogrel prior to or after coronary intervention. Using a loading dose of 600 mg is shown to improve 30-day survival and reduce the risk of MI and TVR within 30 days post PCI compared with a lower dose of 300 mg. Although these data are obtained from a small study, it is still widely accepted that the higher dose be administered routinely to patients prior to PCI procedures, as indeed has become the practice in most UK interventional centres. A larger randomised multi-centre study involving a total of 14,000 patients (OASIS-7) is currently evaluating this issue of clopidogrel optimal loading dose prior to PCI and presented its preliminary results at the American College of Cardiology conference this year.

Furthermore, a daily maintenance clopidogrel dose of 75 mg for at least 12 months post PCI was shown to reduce effectively the risk of acute stent thrombosis. There is now evidence to suggest that the incidence of late stent thrombosis after clopidogrel discontinuation is higher in patients receiving DES,[11] although hard evidence is still lacking as to which sub-group of those patients is at highest risk.

However, until evidence to the contrary is available, it is appropriate to assume that those with more complex coronary lesions receiving DES would require longer duration, or even indefinite use, of clopidogrel therapy along with aspirin. This is a cause for concern as a number of patients may inevitably stop clopidogrel at some stage, either due to side effects or to undergo non-cardiac surgery. In such circumstances, it is recommended that advice from an interventional cardiologist is sought by the GP prior to any plans for drug discontinuation. This concern is outlined in more details in Dr Gershlick's letter to the *BMJ*.[19]

In response to further primary care concerns regarding clarification of duration of clopidogrel therapy, treatment information cards were recently introduced. These cards are recommended to be used for all patients commenced on clopidogrel and require the dose, date treatment started and intended duration of therapy to be clearly stated. This move was endorsed by both the British Cardiovascular Intervention Society and the UK Clinical Pharmacy Society.

The recent TRITON – TIMI 38 study[13] suggests that prasugrel may be superior to clopidogrel in ACS patients scheduled for PCI, in terms of reducing acute events and TVR. However, the trial showed no primary endpoint mortality difference between the two groups and appeared to show a significant increase in fatal bleeding in the prasugrel arm. Furthermore, the study drugs were only administered after the angiograms were performed, hence clopidogrel concentrations may have been sub-therapeutic at the time of PCI. This may limit future use of prasugrel to high-risk ACS patients who are at low risk of haemorrhage, whereas it should be avoided in others with lower-risk ACS who may be at a relatively higher risk of bleeding complications.

Although there is now evidence to show that a clopidogrel daily maintenance dose of 150 mg results in more intense platelet inhibition compared with a 75-mg dose, it is still not clear if this translates into improved clinical outcomes in terms of mortality and morbidity. For the time being, using a dose of 75 mg daily appears to be both safe and beneficial. Using a higher maintenance dose does not have supportive evidence and may result in an increase in the side effects profile.

Clopidogrel and CABG

Clopidogrel should be discontinued at least three days prior to CABG as this appears to limit post-CABG bleeding complications. For the use of clopidogrel post CABG, there are no available data at present other than the sub-group analyses obtained from the CURE and CAPRIE studies. Until results from the CASCADE study are available, dual anti-platelet therapy with clopidogrel and aspirin should continue to be given for 9–12 months to NSTE-ACS patients who undergo CABG.

As shown by Lim et al,[20] the immediate use of clopidogrel following CABG does not seem to add any benefit over aspirin therapy. However, the study was too small to be powered for any meaningful outcome endpoints and the long-term use of clopidogrel post-CABG is currently being evaluated by the CASCADE study, which was due to complete in November 2007 but is currently still recruiting. It will then become clearer as to whether clopidogrel plays any role in preventing the process of intimal hyperplasia of saphenous vein grafts.

The long-term use of clopidogrel in conjunction with aspirin in patients who have stable coronary disease – and in patients with multiple risk factors of the condition – was shown not to be associated with any significant prognostic benefit but rather with a significant increase in bleeding complications. At present, many patients tend to be left on clopidogrel for much longer than a year following either an ACS attack or non-complex PCI treatment. This practice should be discouraged as it lacks supportive evidence and worsens the risk of bleeding complications.

SUMMARY

Since its introduction in 1998, clopidogrel has proven to be an invaluable anti-platelet agent for the treatment of coronary heart disease. In particular, its benefit is well established in acute coronary syndromes (both ST and non-ST elevation) in the form of an initial loading dose followed by a daily maintenance dose usually for a period of 12 months. It is also beneficial when given as a loading dose prior to elective or emergency PCI followed by a daily maintenance dose for a year. We expect any revised future UK or ESC guidance to expand the indications for clopidogrel use to accommodate the evidence that is currently available. The set of recommendations below may be used as a framework for future guidance.

RECOMMENDATIONS

1. Following an ACS event – either STE or NSTE – an immediate clopidogrel loading dose of 300 mg should be administered, along with the usual aspirin loading dose.

2. Following STEMI, it is more appropriate to continue clopidogrel maintenance therapy for up to a year rather than just four weeks. However, direct evidence to confirm such benefit needs to be clarified by a clinical trial and therefore it is still acceptable, although not ideal, to discontinue clopidogrel four weeks after STEMI.

3. NICE needs to develop clear guidance as to the use of clopidogrel in PCI. An initial loading dose of either 300 mg or 600 mg should be given ideally >6 hours before the procedure, followed by a daily maintenance dose of 75 mg for 12 months. The awaited OASIS-7 trial may further clarify the optimum pre-PCI loading dose.

4. In sub-groups that receive DES for complex coronary lesions, we recommend long-term dual anti-platelet therapy. In those patients, clopidogrel should not be discontinued without prior discussion with an interventional cardiologist.

5. Clopidogrel should be discontinued at least three days prior to CABG, as this appears to limit post-CABG bleeding complications. There are no available data to support the use of clopidogrel post CABG.
6. Long-term use of clopidogrel – along with aspirin – in stable coronary heart disease appears not to be beneficial and should be avoided.

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