Research Review

Clopidogrel (Plavix®) review

Acute Coronary Syndromes

Acute coronary syndromes (ACS), including conditions ranging from unstable angina to ST-segment-elevation myocardial infarction (STEMI) and non-STEMI, represent a considerable burden worldwide. Every year in Europe and the US, 3.4 million individuals experience an acute coronary accident[1,2] Over the last 30 years, the rate of mortality from cerebrovascular accidents and MIs has considerably decreased in industrialised countries, largely due to improvements in medical treatments.[3-5]

International and local guidelines support intensive medical treatment, and for many patients early revascularisation; this approach has proven beneficial and cost-effective in high-risk patient groups. [6] Scant data are available regarding the number and management of ACS cases in New Zealand, although one study indicates good adherence to the use of evidence-based management for ACS. [7]

Current Treatment Algorithm

New Zealand management guidelines have been issued for the optimal care of patients with ACS. [8,9] All patients undergoing reperfusion therapy for STEMI (PCI or fibrinolysis) should be given aspirin and clopidogrel unless these are contraindicated.[8] Antithrombin therapy should be given in combination with PCI or fibrinolytic therapy with fibrin-specific fibrinolytic agents, but antithrombin therapy in conjunction with streptokinase is optional.[8]

Patients who have had STEMI should be considered for early transfer to a tertiary cardiac centre with PCI facilities and links to cardiac surgical facilities.[8] If immediate transfer is not possible, patients should be transferred or referred as soon as is practicable for assessment of need for revascularisation (through PCI or coronary artery bypass grafting [CABG]). [8]

All patients with non-ST elevation ACS (NSTEACS) should have their risk stratified to direct management decisions.[9] All patients should receive aspirin, unless contraindicated.[9] High-risk patients with NSTEACS should be treated with aggressive medical management (including aspirin, clopidogrel, unfractionated heparin or subcutaneous enoxaparin, IV tirofibran or eptifibatide and a ß-blocker), and arrangements should be made for coronary angiography and revascularisation, except in those with severe comorbidities.[9]

Intermediate-risk patients with NSTEACS should undergo an accelerated diagnostic evaluation and further assessment to allow reclassification as low or high risk.[9] Low-risk patients with NSTEACS, after an appropriate period of observation and assessment, may be discharged on upgraded medical therapy for outpatient follow-up.[9] Before discharge, patients with an ACS should commence a medication regimen, including antiplatelet therapy (i.e. aspirin, clopidogrel), ß-blocker treatment, ACE inhibitor therapy, statin and other therapies as appropriate.[9]

Implantable cardiac defibrillators should be considered in some patients who, despite optimal medical therapy, have persistently depressed left ventricular function at >6 weeks after STEMI.[8] Patients should be advised on lifestyle changes that will reduce the risk of further coronary heart disease events, including smoking cessation, nutrition, alcohol, physical activity and weight management, as relevant.[8,9] Comprehensive ongoing prevention and cardiac rehabilitation services, as well as a written action plan for cardiac pain, should be provided for all patients.[8,9]

About the reviewer -
Dr Stewart Mann DM (Oxon), FRCP, FRACP, FCSANZ

Stewart Mann trained at Oxford University and Kings College Medical School, London. He undertook research at Northwick Park Hospital, Harrow especially in 24-hour ambulatory blood pressure monitoring leading to a doctorate. He trained in cardiology in Bristol, London and Sydney. He was a cardiologist at Wellington and Hutt Hospitals from 1986 until 2003 and then moved to his present post of Associate Professor of Cardiovascular Medicine at the University of Otago, Wellington. He continues clinical activity in the cardiology department, Wellington Hospital and in private practice at Wakefield Hospital and Ropata Village Medical Centre. His interests include preventive cardiology (especially hypertension), vascular biology and clinical information science.

This and other Research Review publications are intended for New Zealand medical professionals.

Clopidogrel

Clopidogrel, a thienopyridine antiplatelet agent, selectively and irreversibly inhibits adenosine diphosphate (ADP)-induced platelet aggregation mediated by the P2Y12 purinoceptor on the platelet surface and has been shown to have a synergistic antiplatelet effect when combined with aspirin.[10,11]

Inhibition of platelet aggregation occurs within 2 hours of administration of clopidogrel.[11,12] The time to achieve maximal inhibition of platelet aggregation is significantly reduced by the use of a loading dose of clopidogrel.[11,12] Platelet aggregation and bleeding times gradually return to baseline values approximately 5 days after discontinuation of the drug.[11,12] However, there is substantial individual variability in the onset and offset of the antiplatelet effect of clopidogrel.[11]

Generally, no dosage adjustment is required in patients who are elderly or who have renal or hepatic impairment, although as experience is limited in patients with severe hepatic impairment, clopidogrel should be used with caution in these patients.[11,12] Gender has no effect on plasma levels of the inactive primary metabolite.[12] Some issues remain unresolved regarding the use of clopidogrel, such as the optimal loading dose in patients undergoing PCI and the optimal treatment duration following drug-eluting intracoronary stent placement.[11]

Data from several large, randomised, double-blind clinical trials have shown that clopidogrel has beneficial effects in patients with STEMI and that the combined use of clopidogrel with a statin has a synergistic effect on clinical outcomes in non-STEMI or unstable angina.[11] Data on the overall tolerability profile of clopidogrel, including bleeding complications, are similar to that of aspirin, although the incidence of haemorrhagic complications is generally increased when clopidogrel and aspirin are used concurrently.[11]

In New Zealand, clopidogrel is indicated in combination with aspirin for patients with (1) unstable angina or non-STEMI. In this population, clopidogrel is indicated for early and long-term reduction of atherothrombotic events whether or not patients undergo cardiac revascularisation and (2) STEMI.[12] In such patients, clopidogrel has been shown to reduce the rate of all-cause mortality and the rate of a combined endpoint of death, re-infarction or stroke.[12]

For current funding criteria of clopidogrel in New Zealand, go to www.pharmac.govt.nz [13]

Major studies on safety and efficacy of clopidogrel

A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)[14]

Authors: CAPRIE Steering Committee

Summary: Treatment with clopidogrel for 1–3 years was associated with a modest but statistically significant advantage over aspirin in reducing adverse cardiovascular outcomes in patients with atherosclerotic vascular disease in this randomised, double-blind, parallel-group study.

Method: 19,185 patients from 16 countries, aged ≥21 years with a recent MI, recent ischaemic stroke or symptomatic peripheral vascular disease were randomised to 1–3 years' treatment with clopidogrel (75mg) or aspirin (325mg) once daily. The primary outcome was the time to first occurrence of new ischaemic stroke (fatal or not), new MI (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Results: An intention-to-treat analysis of 1960 first events included in the outcome cluster revealed that clopidogrel was associated with a lower incidence of outcome events of every kind. The annual risk of ischaemic stroke, MI, or vascular death was 5.32% in the clopidogrel group and 5.83% in the aspirin group, reflecting a statistically significant relative-risk reduction of 8.7% in favour of clopidogrel. Similar results were obtained with clopidogrel when the outcomes were predominantly vascular events, but the relative-risk reduction was smaller for all-cause mortality (6.9%). Among patients who survived an on-study stroke or MI, the incidence of subsequent events was again lower in the clopidogrel group. No major between-group differences were seen in terms of safety. Aspirin was associated with more clinically relevant bleeding than clopidogrel and there was a trend for more severe upper gastrointestinal discomfort with aspirin and more gastrointestinal haemorrhage (2.7% vs 2.0%).

Comment: The CAPRIE Trial result showed a small but significant benefit for clopidogrel over aspirin in patients with a variety of pre-existing vascular disease over a period of 1-3 years. 99% confidence limits ranged from negligible difference to a 20% benefit for clopidogrel. There was an analysis of subgroups (which were not prespecified) and, not surprisingly, there were some where the difference between aspirin and clopidogrel was small and another (the small subgroup who had had prior surgical revascularisation) where the benefit appeared larger (absolute risk reduction of 6.4%). Interpretation of such subgroup analysis is hazardous and should be regarded as "hypothesis-generating" rather than definitive.

An overall conclusion was that clopidogrel was at least as good as aspirin and could certainly be used as an alternative where patients were allergic to aspirin. The small benefit did not, however, suggest that clopidogrel should be widely advocated as a superior alternative to aspirin.

Intention-to-treat analysis primary and secondary outcome clusters

Outcome event cluster and treatment group	Event rate per year	Relative-risk reduction (95% CI)	p
Ischaemic stroke, MI, or vascular death (primary cluster)			
Clopidogrel (nyrs=17636*)	5.32%	8.7% (0.3 to 16.5)	0.043
Aspirin (nyrs=17519)	5.83%		
Vascular Death			
Clopidogrel (nyrs=17482)	1.90%	7.6% (-6.9 to 20.1)	0.29
Aspirin (nyrs=18354)	2.06%		
Death from any cause			
Clopidogrel (nyrs=18377)	3.05%	2.2% (-9.9 to 12.9)	0.71
Aspirin (nyrs=18354)	3.11%		

nyrs – patient years at risk

Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation[15]

Authors: The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators

Summary: Clopidogrel treatment reduced the risk of cardiovascular death, non-fatal MI, or stroke in patients with NSTEACS receiving aspirin in this randomised, double-blind, placebo-controlled trial.

Method: 12,562 patients were randomised within 24 hours of the onset of a NSTEACS to receive clopidogrel (300 mg loading followed by 75 mg daily) or placebo in addition to aspirin 160–360 mg daily for 3–12 months.

Results: The primary outcome of cardiovascular death, non-fatal MI, or stroke occurred in 9.3% of patients treated with clopidogrel and in 11.4% of patients in the placebo group (risk reduction [RR], 0.80). The second primary outcome – the first primary outcome or refractory ischaemia – occurred in 16.5% of patients in the clopidogrel group and in 18.8% of patients in the placebo group (RR, 0.86). The benefits of clopidogrel were evident within the first 24 hours of randomisation and the major absolute benefit was in the first 3 months with continuing benefits throughout the study period. Major bleeding events were more common in the clopidogrel group (3.7% vs 2.7%; RR, 1.38) but there was no excess in life-threatening bleeding or intracranial haemorrhage. The risk of major bleeding was increased in patients undergoing Coronary Artery Bypass Graft (CABG) within 5 days of stopping clopidogrel (9.6% vs 6.3%; RR, 1.53).

Comment: The frequent use of composite endpoints in such trials can be problematic as it gives equal weighting to both severe outcomes (e.g. death from myocardial infarction within 30 days) and less important clinical events (e.g. minor stroke with no residual disability). Mortality was not significantly reduced whether calculated as cardiovascular, non-cardiovascular or total. The first co-primary outcome (death, MI or CVA) was reduced with an absolute risk reduction (ARR) of 2.1%. The group studied comprised a wide cross section of patients at variable degrees of risk and capacity to benefit. The group with highest risk (TIMI score 5-7) had an ARR of 4.8% for events (number needed to treat to prevent one event – NNT = 21). Even the lowest risk group showed a reasonable reduction – NNT = 63.

Most benefit from treatment was achieved early, an ARR of 0.7% was achieved within 24 hours of the loading dose (300mg) of clopidogrel, 1.1% by 30 days and approximately 90% of the total benefit by 3 months. There was some further benefit with more prolonged treatment but the cost-effectiveness of this becomes arguable. Bleeding was more of a problem with the combination of aspirin and clopidogrel but subgroup analysis suggested this could be minimised by using low doses (75-100mg daily) of aspirin. Benefits were apparently exactly similar whether or not patients had been taking aspirin prior to their enrolment. (Some of the information here was obtained from papers and comments subsequently published by the CURE authors).

Incidence of selected important study outcomes

Outcome	Clopidogrel Group (N=6259)	Placebo Group (N=6303)	Relative Risk (95%CI)	P Value
First primary outcome: nonfatal myocardial infarction, stroke, or death from cardiovascular causes	582	719	0.80 (0.72-0.90)	<0.001
Second primary outcome: first primary outcome or refractory ischemia	1035	1187	0.86 (0.79-0.94)	<0.001
Death from cardiovascular causes	318	345	0.93 (0.79-1.08)	
Myocardial infarction	324	419	0.77 (0.67-0.89)	
Death from noncardiovascular causes	41	45	0.91 (0.60-1.39)	
Stroke	75	87	0.86 (0.63 – 1.18)	

Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study[16]

Authors: Mehta SR et al

Summary: The addition of clopidogrel to aspirin prior to PCI and then continued on a long-term basis after the procedure reduced the incidence of major ischaemic events compared with no clopidogrel pretreatment and only short-term thienopyridine therapy afterwards, according to the results from this prospective study in the subgroup of patients undergoing PCI in the CURE trial.[17]

Method: A total of 2658 patients with NSTEACS undergoing PCI in the CURE study were randomised to double-blind therapy with clopidogrel (n=1313) or placebo (n=1345). Patients were pretreated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, the 2172 patients with intracoronary stents received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2–4 weeks after PCI then continued with the randomly assigned study drug until the end of the trial. The primary endpoint was a composite of cardiovascular death, MI, or urgent target vessel revascularisation (UTVR) within 30 days of PCI.

Results: Events in the primary outcome cluster occurred in 4.5% of patients in the clopidogrel group and in 6.4% of patients in the placebo group (relative risk [RR], 0.70). Long-term administration of clopidogrel after PCI was associated with a significantly lower incidence of cardiovascular death or MI than placebo (6.0% vs 8.0%; RR, 0.75) and also with a lower rate of cardiovascular death, MI, or any revascularisation (18.3% vs 21.7%; RR, 0.83). The overall rate of the combined endpoint of cardiovascular death or MI (including event before and after PCI) was significantly lower with clopidogrel than with placebo (8.8% vs 12.6%; RR, 0.69). Fewer glycoprotein IIb/IIIa inhibitors were used in the clopidogrel group than in the placebo group (20.9% vs 26.6%; RR, 0.79). The need for a second revascularisation procedure was lower in the clopidogrel group than in the placebo group (14.2% vs 17.1%; RR, 0.82), primarily because of a reduced need for a repeat PCI (12.9% vs 10.7%; RR, 0.83). No increase in major or life-threatening bleeding was observed with clopidogrel compared with placebo.

Comment: This was a separate analysis of some 21% of patients in the CURE study who underwent percutaneous coronary intervention (PCI). Clinical choice to use PCI was not influenced by randomised therapy. (Other parallel trials - "CREDO"[17] and "CLARITY"[18] - also examined this question with slightly differing treatment regimens and reached similar conclusions).

As the use of thienopyridines shortly before and for a limited period after PCI was already established, some 25% of patients in PCI-CURE were preloaded with these on open label and >80% received them for a limited period post-procedure before returning to their originally randomised treatment. This introduces some potential confounding and allows accurate analysis of only the preloading with clopidogrel. However, the benefits were significant, the ARR for MI being 1.5% and for refractory ischaemia being 1.7%. Benefits were also greater than for the other subjects in CURE not undergoing PCI although patients would probably have also been selected for PCI because of higher clinical risk which itself might have predicated greater capacity to benefit.

This trial, along with others, established the routine need for use of clopidogrel (in addition to aspirin) as preloading before and continuous therapy after stenting for a period of at least around 3 months. The trial was performed before the introduction of drug-eluting stents which are known to be associated with delayed re-endothelialisation and are presumed to require more prolonged thienopyridine therapy.

Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial[19]

Authors: Chen ZM et al

Summary: All-cause mortality was reduced by 7% in patients treated with clopidogrel compared with those who were not, and there were no life-threatening bleeds in this randomised, placebo-controlled, multicentre trial, which studied patients with STEMI in an emergency setting.

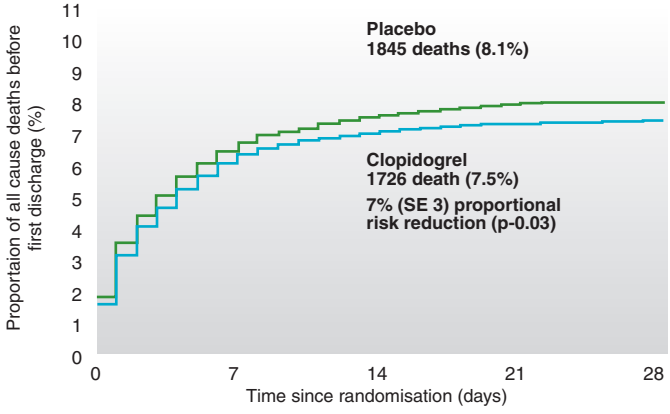
Method: From August 1999 to February 2005, COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) studied 45,852 patients with left bundle branch block, ST-segment elevation or ST-segment depression within 24 hours of suspected acute MI symptom onset. Patients were randomised to daily treatment with aspirin 162 mg and clopidogrel 75 mg (n=22,961), or aspirin 162 mg and placebo (n=22,891). Both treatment regimens were continued for 4 weeks, unless the patient had died or had been discharged from hospital, at which point the treatment was stopped. The two joint primary outcomes were all-cause death, and the composite of reinfarction, stroke or death.

Results: Significantly fewer reinfarctions, strokes and deaths occurred in the clopidogrel group than in the placebo group (9.2% vs 10.1%; 9% proportional risk reduction). Furthermore, all-cause mortality was significantly lower in the clopidogrel group than in the placebo group; 7.5% of patients died in the clopidogrel group compared with 8.1% of the placebo group (7% proportional risk reduction). Although the subgroup analysis was not sufficiently powered, the beneficial effect of clopidogrel on the joint primary outcomes did not differ between patient subgroups. Clopidogrel did not significantly increase the risk of bleeding in the overall treatment period, in patients aged >70 years or in those given fibrinolytic therapy (overall, 0.58% of clopidogrel recipients compared with 0.55% of placebo recipients).

Comment: This was a huge trial co-ordinated from Oxford, UK, but carried out entirely in China (known both as COMMIT and the Second Chinese Cardiac Study – CCS-2). All patients with suspected myocardial infarction without a clear need for, or contraindication to, the trial therapies were eligible. The trial reflected the simplicity of design and cross-randomisation of the landmark study – ISIS-2 – which examined effects of streptokinase and aspirin in a factorial 2X2 design In COMMIT, the treatments under test were clopidogrel and metoprolol continued for 28 days and compared with equivalent placebos.

The large size proved necessary to power for an analysis of effects of the interventions on mortality and recruitment had to be extended when the expected event rate (14%) proved to be an overestimate. In the end result, the ARR of the primary endpoint (death, reinfarction or stroke by 28 days) was reduced by 0.9% in the clopidogrel group and for all-cause mortality from by 0.6% adding 6 deaths prevented per 1000 patients to the 40 seen in the ISIS-2 trial with aspirin. Reassuringly, there was no excess of bleeding in the group given clopidogrel whatever other therapy was used. The trial established the benefit and safety of adding clopidogrel to standard therapy given for myocardial infarction, including (where appropriate) thrombolysis and anticoagulation.

Effects of clopidogrel on all cause death before first discharge from hospital



Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events[20]

Authors: Bhatt DL et al

Summary: Dual antiplatelet therapy with clopidogrel and aspirin in patients with stable cardiovascular disease or multiple cardiovascular risk factors was not associated with a significant benefit versus aspirin alone, and dual antiplatelet therapy was associated with an increased risk of moderate to severe bleeding, in this randomised, double-blind, placebo-controlled, multicentre trial.

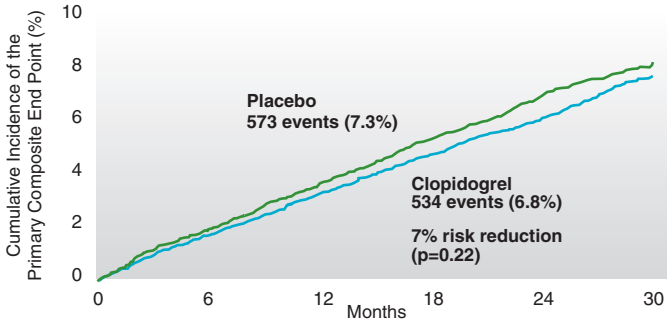
Method: A total of 15,603 patients with either clinically evident cardiovascular disease or multiple atherothrombotic risk factors were randomised to receive clopidogrel 75 mg/day (n=7802) or placebo (n=7801), both with concomitant aspirin 75–162 mg/day. The primary efficacy endpoint was a first occurrence of MI, stroke or cardiovascular death.

Results: After a median follow-up of 28 months, the rate of the primary endpoint was 6.8% for the clopidogrel plus aspirin group and 7.3% for the placebo plus aspirin group (RR, 0.93). There was a statistical advantage for clopidogrel for the main secondary endpoint, which was a composite of first occurrence of MI, stroke, death from cardiovascular causes, or hospitalisation for unstable angina, transient ischaemic attack or revascularisation procedure; respective rates were 16.7% and 17.9% (RR, 0.92). A modest reduction in the primary endpoint with clopidogrel versus placebo was seen in the subgroup with clinically evident atherothrombosis (6.9% vs 7.9%; RR, 0.88). In the subgroup of patients with multiple atherothrombotic risk factors without documented cardiovascular disease, the rate of the primary endpoint was higher in the clopidogrel group compared with the placebo group (6.6% vs 5.5%; RR, 1.2). Moreover, in this subgroup of asymptomatic patients, clopidogrel was associated with a significant increase in the rate of death from all causes (5.4% vs 3.8%) or from cardiovascular causes (3.9% vs 2.2%). Clopidogrel was also associated with an increased risk of moderate to severe bleeding; the rate of intracranial haemorrhage was similar in the two treatment groups.

Comment: This trial examined the possible benefits of long-term (mean over 2 years) clopidogrel treatment (in addition to aspirin) in patients with stable cardiovascular disease or multiple risk factors. The composite endpoint (again of death, myocardial infarction or stroke) was not significantly reduced. Subgroup analysis of a secondary composite endpoint which included several other less severe cardiovascular endpoints did appear to indicate some possible benefit with marginal significance but an accompanying leading article suggested this could not be regarded as clinically significant. Further prespecified subgroup analysis also suggested that the group at highest risk might benefit slightly while those at lower risk (those with risk factors but no manifest disease) were disadvantaged by clopidogrel. There was a significantly increased rate of moderate bleeding with clopidogrel (2.1% v 1.3%); severe bleeding rate being non-significantly higher (1.7% v 1.3%).

This trial established with some certainty that there is little net benefit obtained from long-term use of clopidogrel in stable cardiovascular disease except where aspirin is not tolerated, a condition affecting about 5-10% of the population.

Cumulative incidence of the Primary End Point



CONCLUSION – Dr Stewart Mann

Although the benefits of clopidogrel (as an addition to aspirin) are quantitatively much less than the effects of earlier interventions (such as aspirin therapy itself or thrombolysis), these have been established in several large clinical trials to reach both statistical and clinical significance.

- CAPRIE established a role for clopidogrel in those unable to take aspirin.
- CURE and COMMIT showed its benefit (as an addition to aspirin) when used for a few weeks or months after an acute coronary syndrome.
- PCI-CURE, CREDO and CLARITY confirmed particular benefit for clopidogrel given as preloading before and longer term therapy after stenting.
- CHARISMA showed negligible benefit when given to stable patients with cardiovascular disease or multiple risk factors

Some uncertainties remain. Since long-term therapy is apparently unhelpful, the ideal duration of therapy after an acute coronary syndrome is unclear. While the CURE study showed some continuing additional benefit with therapy out to up to 10 months, absolute risk reduction after 3 months was minimal.

Stenting provides another ongoing conundrum. There is logic for additional protection here given the potentially thrombogenic surface of the stent until it has been endothelialised. For traditional "bare-metal" stents, this will mostly take place in the first month after placement although some patients have been known to have the potential to rethrombose on later withdrawal of the thienopyridine. The more widespread recent use of drug-eluting stents where both restenosis and re-endothelialisation are inhibited clearly suggests a need for more prolonged therapy. Recent alarm over a small but definite increase in the rate of late (even >3 years) thrombosis within such stents (leading to substantial myocardial damage or death) has posed the question of whether treatment for 1 year or longer with clopidogrel should be considered.

Clopidogrel does increase the propensity to bleeding which seems to be equivalent and additional to the bleeding seen with aspirin. This offsets small vascular benefits in patients at lower cardiovascular risk. Accepting the ongoing requirement for clearer optimum treatment periods, the place of the drug in cardiovascular protection is now well established.

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