

RAPID APPRAISAL

Name of Trial: Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome.

Reference: Ho PM, Peterson ED, Wang L et al. Journal of the American Medical Association 2008;299:532-9

Question: Is the risk of death or acute myocardial infarction greater in the 90-day period following cessation of clopidogrel therapy compared to the period beyond 90 days in patients having had a recent myocardial infarction?

Summary: The risk of death or myocardial infarction is approximately doubled in the first 90 days following clopidogrel cessation compared to the 90-day period following that for patients medically treated for a mean of 302 days, or 278 days for patients treated with percutaneous coronary intervention. However this risk has not been proven with longer duration of clopidogrel treatment, as is the case in UK practice. The results of this study are interesting but do not warrant any changes to current practice in the use of clopidogrel in patients with acute coronary syndrome treated either medically or with percutaneous coronary intervention.

Did the study ask a clearly focussed question?

Yes – The study investigated the incidence of acute myocardial infarction (MI) or death from any cause following cessation of clopidogrel therapy.¹

Was the study design appropriate?

Yes – Although it was a retrospective observational study, which may be affected by bias and confounding, a prospective study would not be practicable or ethical in this scenario. Patients with a diagnosis of acute MI or unstable angina/acute coronary syndrome (ACS) were identified from a large American database. Patients were selected if they were discharged from hospital following these events, received a prescription for clopidogrel and remained event-free during the period that they were assumed to be taking clopidogrel.¹

Were participants appropriately allocated to intervention and control groups?

No control group was included in the study. However patient groups were distinguished between those treated only medically for ACS (n = 1568) and those who received percutaneous coronary intervention (PCI), or a 'stent', (n = 1569).

How were participants followed up and data collected?

Clopidogrel use was assessed using an American health database with records of the quantity and dates on which clopidogrel was dispensed. The last day of clopidogrel use was assumed to be the date of dispensing of the last prescription recorded plus the number of day's treatment supplied on that prescription. The duration of clopidogrel treatment was calculated from the date of hospital discharge until the last day of clopidogrel use. Endpoints of acute MI or all-cause mortality were identified from databases linked to the American Veterans Association, therefore it is possible that

treatment of events received outside of this association could be missing from the study.¹ It is worth noting that of all potentially eligible patients only 29% were included in analyses.¹

Was the study large enough?

The study involved over 3100 patients. Although no indication is provided of its power to detect the size of the observed effects, 95% confidence intervals around the final results demonstrate acceptable precision for the major findings.¹

How are the results presented, and what is the main result?

Of medically treated patients 17.1% experienced subsequent death or acute MI after cessation of clopidogrel (n = 268) and most of these events (60.8%) occurred in first 90 days after ceasing therapy. For patients treated with PCI, subsequent death or acute MI occurred in 7.9% (n = 124) after cessation of clopidogrel and again most of these events (58.9%) occurred in the first 90 days after ceasing therapy. Multivariable analysis demonstrated a nearly two-fold increase in the risk of death or acute MI during the first 90 days after ceasing treatment with clopidogrel compared to the following 90 day period in both medically and PCI-treated patients. Adjusted incident rate ratios were 1.98 (95% confidence interval [CI] 1.46 to 2.69) and 1.82 (95% CI 1.17 to 2.83) respectively. Although the relative risk is increased substantially in the first 90 days following clopidogrel cessation compared to the 90 days that follow this, the absolute increase in risk remains small, being 0.62 for medically treated patients and 0.24 for PCI treated patients per 1000 patient days of follow-up.¹

The results are also stratified according to the cumulative duration of clopidogrel treatment for medically-treated patients (≤ 90 , ≤ 180 , ≤ 270 , or > 270 days). The size of effect was significant and

consistent at about 2-fold for analyses up to 270 days, but for patients treated > 270 days the adjusted incidence rate ratio was not significant at 1.79 (95% CI 0.96 to 3.34). The subgroup sizes for these analyses were small and they should be interpreted with caution.¹

How safe were the regimens?

Apart from the primary outcome measures, which are themselves safety-orientated outcomes, other adverse effects were not reported.

Combination therapy with aspirin and clopidogrel is not without risk, most notably bleeding episodes. In the pivotal CURE study with mean treatment duration of nine months the incidence of any bleeding complication was 5.0% with aspirin alone compared to 8.5% with aspirin and clopidogrel.²

How precise are the results?

Some important assumptions have been made in the method of this study. Firstly, the date of cessation of clopidogrel therapy is calculated with reference to dispensing dates and quantities. Secondly, only acute MI that resulted in or occurred during hospitalisation was recorded. Thirdly, it is not clear why clopidogrel was stopped and any assumption that the decision to stop is based only on clinical judgement may obscure links between the decision to stop and the risk of an event, i.e. confounding by indication. Even with these constraints the study was large enough to produce relatively narrow confidence intervals and the results can be considered to have a high degree of precision, even though the absolute differences are small, whilst taking into consideration the constraints of this particular study and retrospective studies in general.

Can the results be applied to the local population?

Possibly not because there is no distinction between non-ST segment elevated MI (non-STEMI) and STEMI events, or the type of stent, factors that influence the duration of clopidogrel therapy.³ For medically treated patients the mean duration of treatment was 302 days (≈ 10 months) with only 52% taking clopidogrel for more than nine months. In the case of non-STEMI this may not reflect UK practice with the National Institute for health and Clinical Excellence recommending that patients are treated for up to 12 months with clopidogrel and aspirin.⁴ In the case of STEMI the mean duration observed in the study exceeds that generally used for treating STEMI in UK practice as the evidence base only demonstrates a benefit for the combination of aspirin and clopidogrel

treatment for one month's duration.^{4,5} In the case of PCI-treated patients the mean duration of clopidogrel treatment was 278 days (≈ 9 months) which, depending on the type of stent used, is less than the 12 months often indicated in UK practice.⁶ These potential differences in the duration of clopidogrel therapy make the results of this study less relevant to UK populations.¹

Additionally there are demographic characteristics that may also affect the relevance of the data to a UK population: 98% of the study population were male, the mean age was 66 years and 53% were of white race. The population was a high risk group with a high incidence of co-morbidities and risk factors: smoking (34%) heart failure (23%), diabetes (21%), prior MI (26%), prior heart bypass (23%), peripheral vascular disease (26%), renal disease (16%), chronic pulmonary disease (15%), and other conditions. There is also some evidence of sub-optimal use of other therapies with significant proportions of patients not receiving at discharge: beta-blocker (7%), aspirin (9%), a statin (19%) or an ACE inhibitor (25%).¹

Is the risk of death or acute MI greater in the 90-day period following cessation of clopidogrel therapy compared to the period beyond 90 days in patients who have had a MI?

Yes – In patients administered clopidogrel daily as part of post-MI treatment, the risk of death or MI was approximately doubled in the first 90 days following clopidogrel cessation compared with the 90 day period following this. This effect was demonstrated in patients treated medically (mean duration of clopidogrel therapy = 302 days) and in those treated with PCI (mean duration of clopidogrel therapy = 278 days). However this risk might not be apparent with variations in duration of clopidogrel treatment, as is the case in UK practice.

Is a change in practice recommended?

The results of this study are not sufficiently robust to recommend any change in current practice for clopidogrel in patients with ACS treated either medically or with PCI. It is reasonable to expect that the risk of an event, in this case death or MI, decreases with time since the original cardiac event. The absence of a control group would have served to reduce the effect of this potentially confounding factor. However, as the authors themselves state, the results do generate an intriguing hypothesis which requires further investigation. For some groups of patients it is not known whether the long-term benefits of aspirin plus clopidogrel treatment are outweighed by the risks.

REFERENCES

1. Ho PM et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA 2008;299:532-9
2. The CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502 (RCT)
3. sanofi-aventis & Bristol Myers Squibb. Summary of product characteristics. Plavix® tablets. 20th Feb 2008
<http://emc.medicines.org.uk>
4. National Institute of health and Clinical Excellence. Secondary prevention in primary and secondary care for patients following a myocardial infarction. Clinical Guideline 48. May 2007 (G)
5. Regional Drug & Therapeutics Centre. Clopidogrel in ST-elevation myocardial infarction. Drug Update No. 55, June 2007 (R)
6. Gershlick AH, Richardson G. Drug eluting stents. BMJ 2006;333:1233-4 (E)

KEY: E-editorial, G-Guidance, RCT - randomised controlled trial, R-review

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