Safety and efficacy of triple antithrombotic therapy after percutaneous coronary intervention in patients needing long-term anticoagulation
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CRD summary
The review addressed a clear question. Inclusion criteria were stated for population, intervention and outcomes, but not for study design. Several relevant databases were searched. The search was restricted to articles in English. It did not appear that attempts were made to identify unpublished articles. Therefore, language and publication biases could not be ruled out. Appropriate steps to minimise reviewer error and bias were taken during data extraction; it was unclear whether similar steps were taken during study selection and so reviewer error and bias could not be ruled out. No validity assessment was carried out, so it was not possible to ascertain the quality of included studies. All studies were a non-randomised design and this may have affected the reliability of the findings. Statistical heterogeneity was assessed, but potential sources of heterogeneity were not investigated. This and the varying definitions of outcomes made it unclear how appropriate it was to combine studies.

The unclear quality of the included studies and the presence of statistical heterogeneity mean the authors’ conclusions should be treated with caution.

Authors’ objectives
To compare the safety and efficacy of triple antithrombotic therapy with dual therapy in patients undergoing percutaneous coronary intervention (PCI).

Searching
EMBASE, CINAHL, PubMed and The Cochrane Library were searched up to January 2009 for articles published in English. Search terms were reported. Reference lists of relevant articles were handsearched.

Study selection
Studies that compared antithrombotic triple therapy (low-dose aspirin, clopidogrel and warfarin) with dual therapy (aspirin and clopidogrel) in patients who underwent PCI were eligible for inclusion. Outcomes eligible for inclusion were bleeding complications and one or more of all-cause mortality, nonfatal myocardial infarction, coronary artery revascularisation and stroke/transient ischaemic event.

Patients in the included studies had ST-elevation myocardial infarction, non ST-elevation myocardial infarction or angina. Reason for anticoagulant therapy was atrial fibrillation, deep vein thrombosis, prophylaxis for left ventricle thrombus, pulmonary embolism, prosthetic valve, atrial flutter and total knee replacement. Mean age ranged from 59 years to 74 years. The mean proportion of males ranged from 37% to 75%. Follow-up ranged from six to 84 months. Definition of major and minor bleeding varied between studies.

More than one author selected the studies for review. It was unclear whether this was performed in duplicate or independently.

Assessment of study quality
It appeared that a validity assessment was not carried out. The authors commented on some aspects of study quality in the discussion.

Data extraction
Two reviewers independently extracted the number events in each group and calculated relative risks (RR) with corresponding 95% confidence intervals (CI) for individual studies. Disagreements were resolved by consensus.

Methods of synthesis
The studies were combined using a Mantel-Haenszel fixed-effect model in the absence of significant statistical heterogeneity. A random-effects model was used where there was significant heterogeneity. Statistical heterogeneity was assessed using the Cochran's Q and $I^2$ statistics.

**Results of the review**

Six studies were included for review (n=1,482 participants): one prospective non-randomised study (n=515) and five retrospective non-randomised studies (n=967).

Triple therapy was associated with significantly increased risk of major bleeding compared to dual therapy (RR 2.75, 95% CI 1.08 to 6.99; six studies, n=1,472). There was evidence of significant statistical heterogeneity ($I^2$=63.9%) and a random-effects model was used.

Triple therapy was associated with significantly fewer major adverse cardiac events (MACEs) compared to dual therapy (RR 0.72, 95% CI 0.56 to 0.94; three studies, n=992). Statistical heterogeneity was low ($I^2$=21.9%) and a fixed-effect model was used. The results reported for risk of MACEs differed between the text and the tables.

**Authors’ conclusions**

Triple therapy may be superior to dual therapy in reducing MACEs in patients needing long-term anticoagulant therapy after PCI, but it significantly increased risk of major bleeding compared to dual therapy.

**Implications of the review for practice and research**

Practi ce: The authors stated that triple therapy should be individualised based on considerations of appropriateness, duration and safety. The review did not address the conditions under which triple therapy may be appropriate.

Research: The authors stated that a randomised controlled trial was needed to compare triple therapy and dual therapy in patients undergoing PCI.

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