Triple therapy rather than triple threat: a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment


CRD summary
The authors concluded that triple antithrombotic therapy was superior to dual antiplatelet therapy in reducing cardiovascular events and mortality, although with a higher rate of major bleeding. Potential biases in the search and selection of studies and unclear details about study design and quality made the reliability of the conclusions unclear.

Authors' objectives
To evaluate the benefits and risks of triple antithrombotic therapy compared with dual antiplatelet therapy after stent implantation in patients under long-term oral anticoagulation treatment.

Searching
Electronic searching was conducted in PubMed and The Cochrane Library, along with reviews and the reference lists of relevant papers. Reference lists were further searched manually. Field experts were contacted. Search dates and terms were not reported. It appeared that the review was restricted to published studies in English.

Study selection
Clinical controlled trials that compared triple antithrombotic therapy (combined aspirin, clopidogrel and oral anticoagulation) with dual antiplatelet therapy (combined aspirin and clopidogrel) in adult patients with an indication for long-term oral anticoagulation who underwent percutaneous coronary intervention (PCI) with stent implantation were eligible for inclusion. Retrospective studies were eligible where local physicians had decided on treatment combinations according to perceived risks and benefits. Studies of patients with bare metal stents (BMS) were eligible if follow-up was three months or longer; studies of patients with drug-eluting stents (DES) were eligible with follow-up six months or longer. Studies with short-term follow-up and those with insufficiently described bleeding events were excluded.

The mean age of patients ranged from 63 to 72 years. Participants had various indications (including atrial fibrillation, left ventricular thrombus, mechanical heart valve, peripheral artery disease, pulmonary embolus and venous thromboembolism) for oral anticoagulation. Studies were generally grouped into those at high or low risk of bleeding or thrombotic events and those that received triple antithrombotic therapy and dual antiplatelet therapy. Control groups (where reported) comprised age- and sex-matched patients with no indication for oral anticoagulation. The outcomes of interest were major bleeding in the first six months of follow-up, minor bleeding, ischaemic stroke, major adverse cardiac events (MACE) and all-cause mortality. Outcome definitions were presented in the paper. Mean follow-up ranged from six months to more than 12 months.

Two reviewers independently selected the studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
There was no reported formal quality assessment of included studies.

Data extraction
Data were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI). Authors were contacted for missing data.

Two reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Odds ratios were pooled in a fixed-effect or random-effects meta-analysis and 95% CIs were reported. A random-effects model was used where statistical heterogeneity ($I^2>50\%$) existed. Publication bias was assessed using a funnel plot.
Results of the review
Nine studies (1,996 participants, range 82 to 515) were included in the review. The authors reported that methodological features varied and larger trials demonstrated higher quality. No further details of study quality were presented.

Triple antithrombotic therapy was superior to dual antiplatelet therapy in the prevention of MACE (OR 0.60, 95% CI 0.42 to 0.86, I²=33%; seven studies) and reduction of all-cause mortality (OR 0.59, 95% CI 0.39 to 0.90, I²=0%; six studies). There were no significant differences in incidence of ischaemic stroke, but a trend towards higher incidence was noted for dual antiplatelet therapy (four studies).

Risk of major bleeding in the first six months was significantly higher with triple antithrombotic therapy (OR 2.12, 95% CI 1.05 to 4.29, I²=45%; five studies). A trend was noted for triple antithrombotic therapy and higher incidence of minor bleeding (four studies).

There was no evidence of publication bias.

Authors' conclusions
Compared with dual antiplatelet therapy, triple antithrombotic therapy was substantially more efficacious in reducing the occurrence of cardiovascular events and mortality in PCI-stent patients with an indication for long-term oral anticoagulation treatment, although there was a higher rate of major bleeding in the first six months.

CRD commentary
The review question was clear and supported by potentially reproducible inclusion criteria for all aspects apart from outcomes. However, the authors excluded studies without justification in the study selection criteria. The search was incompletely reported with no search dates and terms. It appeared that only published papers in English were included in the review, so language and publication biases were possible. No evidence of publication bias was found. There was no formal quality assessment of the included studies. The authors referred to limitations in the study designs, but gave no indication of the study designs included and did not discuss the comparability of intervention groups. Study selection and data extraction were carried out with sufficient efforts to minimise error and bias. Study details were limited, but the chosen method of synthesis appeared to be appropriate and statistical heterogeneity was taken into account.

The authors' conclusions reflect the evidence presented, but concerns about the application of study selection criteria, the possibility of language and publication biases, absence of detail on study quality or design and questionable comparability of study groups made the reliability of the conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated that triple antithrombotic therapy was a better choice for patients with a high risk of thrombotic events and low risk of bleeding. Treatment should be individualised, depending on the risk of bleeding and ischaemic complications.

Research: The authors did not state any implications for further research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.