Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison
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CRD summary
This review concluded that the efficacy of antiplatelets differed for smokers and nonsmokers, with the benefit occurring mostly for smokers and less so for nonsmokers. The review did not evaluate adverse events, so the risk-benefit profiles of the drugs are unknown, and the usefulness of the results for informing clinical practice is limited.

Authors' objectives
To evaluate whether smoking status was associated with the efficacy of antiplatelet treatment in preventing cardiovascular events.

Searching
MEDLINE, EMBASE, CINAHL, and CAB Abstracts were searched, and Google Scholar was used to search the Internet, without language restrictions, to July 2013; search terms were reported. Four cardiology conference abstract databases, and the bibliographies of relevant reviews and studies, were searched.

Study selection
Randomised controlled trials (RCTs) that evaluated clopidogrel, prasugrel, or ticagrelor and reported smoking behaviour, more than as a baseline characteristic of the patients, were eligible for inclusion. The primary outcome was a composite of cardiovascular death, myocardial infarction (MI), and stroke.

Across the included trials, most patients had acute coronary syndrome and 31% were current smokers. The most common dose of clopidogrel was 75mg daily; prasugrel was given at 10mg daily and ticagrelor was given at 90mg daily. The overall incidence of the composite of cardiovascular death, MI, and stroke ranged from 4.3% to 14.9%.

Two reviewers independently selected trials for the review; disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias tool; it seems that this was done by two independent reviewers alongside data extraction.

Data extraction
The data for clopidogrel (with or without aspirin), compared with aspirin alone or a lower dose of clopidogrel plus aspirin, were extracted separately for smokers and nonsmokers. Hazard ratios and 95% confidence intervals, for each subgroup, were extracted or calculated by two independent reviewers. Where trials reported their results at multiple time points, data at the longest follow-up were extracted. Where trials reported the results for more than two smoking categories, these groups were combined to give two comparator groups.

Methods of synthesis
The trial data were combined using a fixed-effect model; relative risks and 95% confidence intervals were presented. Heterogeneity was assessed using Cochrane's Q and I².

Sensitivity analyses were conducted by omitting each trial in turn. Bucher's method was used to make indirect comparisons in a network meta-analysis. A sensitivity analysis was conducted, using the primary outcome from one trial that reported the composite of cardiovascular death, MI, and stroke as a secondary outcome.

Publication bias was investigated using a funnel plot.

Results of the review
Nine trials met the inclusion criteria (109,793 patients; range 2,080 to 25,074; 33,650 smokers). Six trials evaluated
Clopidogrel compared with aspirin, placebo or a different dose of clopidogrel; two evaluated prasugrel compared with clopidogrel; and one evaluated ticagrelor compared with clopidogrel. None of the trials was considered to be at a high risk of bias, and they were therefore considered to be of high quality. Follow-up ranged from up to 30 days, to up to three years.

Clopidogrel significantly reduced the risk of the composite outcome, in smokers (RR 0.75, 95% CI 0.67 to 0.83; six RCTS; $I^2=0$) and non-smokers (RR 0.92, 0.87 to 0.98; six RCTs; $I^2=0$), compared with controls. The results were consistent across sensitivity analyses.

For smokers, prasugrel significantly reduced the composite endpoint, compared with clopidogrel (RR 0.71, 95% CI 0.61 to 0.82; two RCTs), but ticagrelor did not (RR 0.83, 95% CI 0.68 to 1.00; one RCT). Prasugrel did not significantly reduce the incidence of the composite outcome, compared with ticagrelor (RR 0.85, 95% CI 0.67 to 1.09).

For non-smokers, neither prasugrel (RR 0.92, 95% CI 0.83 to 1.01; two RCTs) nor ticagrelor (RR 0.89, 95% CI 0.79 to 1.00; one RCT) significantly reduced the composite outcome, compared with clopidogrel, and there was no significant difference between prasugrel and ticagrelor (RR 1.03, 95% CI 0.88 to 1.20).

**Authors’ conclusions**
The efficacy of antiplatelets differed for smokers and non-smokers, with the benefit occurring mostly for smokers and less evidence of efficacy for non-smokers.

**CRD commentary**
This review addressed a clear question, supported by reproducible inclusion criteria. A range of relevant sources was searched, without language restrictions. Each stage of the review was conducted by two people, reducing the risks of error and bias. Appropriate criteria were used to assess trial quality. The method used to make the indirect comparison was straightforward; more sophisticated models are available, and might have been more suitable for data from heterogeneous trials.

The review did not analyse adverse events, so the risk-benefit profiles of the drugs are unknown. Therefore, the usefulness of the results of the review for informing clinical practice is limited.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should carefully consider the different benefits and risks of antiplatelet drugs for smokers and non-smokers; non-smokers were likely to derive less benefit, while smokers could have an increased risk of bleeding.

**Research:** The authors stated that the risk of bleeding in smokers should be evaluated, as should different doses of antiplatelets for smokers and non-smokers.

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