

## Indirect comparison meta-analysis of aspirin therapy after coronary surgery

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### Abstract

**Objectives** To evaluate the efficacy of low and medium dose aspirin therapy after coronary surgery by using an indirect comparison meta-analysis.

**Data sources** Systematic literature search of Medline, Embase, Cochrane controlled trials register, and trial register sites on the internet.

**Study selection** Outcome was evaluated by angiography and reported as graft occlusion and rate of events in patients. Trials that did not include aspirin as the sole therapy or did not have a placebo control arm were excluded. Articles were assessed for eligibility and quality and grouped according to dosage. The estimated difference in effect of low and medium dose aspirin on graft occlusion was obtained by combining the estimated log relative risks of low dose with placebo and medium dose with placebo.

**Results** For graft occlusion, the medium dose trials yielded a relative risk reduction of 45% compared with 26% for the low dose trials. The greater effect in the medium dose trials is summarised by a relative risk ratio of 0.74 (95% confidence interval 0.52 to 1.06;  $P=0.10$ ) for graft occlusion and 0.81 (0.57 to 1.16;  $P=0.25$ ) for events in patients.

**Conclusions** Medium dose aspirin may more successfully reduce graft occlusion than low dose regimens within the first year after coronary surgery.

### Introduction

The saphenous vein remains a widely used graft for coronary artery bypass, despite the increasing popularity of arterial grafts, and has an estimated occlusion rate of 15-30% in the first year.<sup>1</sup> In the past decade, beneficial effects of aspirin on graft patency were established by three meta-analyses that summarised trials from 1979 to 1993.<sup>2-4</sup> However, analyses took no account of the wide variation in doses (from 75 mg to 325 mg), and equivalent efficacy was assumed within this range. As a result, low dose aspirin (75-150 mg) is prescribed despite no direct comparisons against medium dose (300-325 mg) regimens.

We evaluated the efficacy of low dose aspirin with medium dose therapy on graft patency after coronary artery surgery using indirect comparison meta-analysis.

### Methods

#### Search strategy

We undertook a systematic literature search of the databases Medline and Embase, the Cochrane controlled trials register, the national research register, and trial sites on the internet for additional articles. The reference lists of relevant studies were reviewed, and investigators from previous trials consulted (see [bmj.com](http://bmj.com)).

#### Study selection

We included all randomised controlled trials that evaluated the efficacy of medium or low dose aspirin in preventing occlusion of vein grafts. Primary exclusion criteria included a total daily dose of aspirin less than 50 mg or more than 325 mg. We also excluded trials that did not include aspirin as sole therapy and studies that did not use a placebo control because placebo was the intermediary used for the indirect comparison. A given patient population was only used once and we selected the article that provided the most complete follow up data.

Three investigators independently assessed papers according to the predetermined eligibility criteria, and discordances were resolved by consensus review. Quality of the individual studies was assessed on the basis of randomisation, blind assessment of outcome, and number lost to follow up. Studies were grouped according to aspirin dosage; low dose was defined as 50-150 mg daily and medium dose as 300-325 mg daily.

#### Data abstraction

All the trials evaluated outcome by angiography and reported it as graft occlusion and event rates in patients. Grafts were considered occluded if the distal anastomosis could not be visualised by angiography. If the origin was occluded, all subsequent distal anastomoses were also considered to be occluded. If angiography was performed on more than one occasion we analysed data recorded closest to one year. An event in a patient was defined as one or more occlusions of a saphenous vein graft.

#### Statistical methods

In the absence of randomised trials making head to head comparisons, an indirect comparison is possible using a common comparator.<sup>5-9</sup> We performed a meta-analysis combining trials of low dose aspirin versus placebo to obtain the estimated relative risk,  $RR_{LP}$ . A

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Results of trials on aspirin treatment after coronary surgery

Trial and regimen	No with distal anastomosis	No with occlusion	Occlusion rate	Relative risk (95% CI)	No who had angiography*	Patients with events	Event rate	Relative risk (95% CI)
<b>Medium dose</b>								
Gavaghan <sup>11</sup> :								
Aspirin 324 mg	362	19	0.05	0.48	119	14	0.12	0.39
Placebo	328	36	0.11	(0.28 to 0.82)	100	30	0.30	(0.22 to 0.70)
Goldman <sup>12</sup> :								
Aspirin 325 mg	340	45	0.13	0.59	104	36	0.35	0.79
Placebo	345	78	0.23	(0.42 to 0.82)	107	47	0.44	(0.56 to 1.11)
<b>Low dose</b>								
Lorenz <sup>13</sup> :								
Aspirin 100 mg	57	11	0.19	0.56	29	9	0.31	0.44
Placebo	81	28	0.35	(0.30 to 1.03)	31	20	0.65	(0.21 to 0.92)
Sanz <sup>14</sup> :								
Aspirin 150 mg	745	106	0.14	0.79	373	91	0.24	0.82
Placebo	750	135	0.18	(0.63 to 1.00)	371	122	0.33	(0.66 to 1.03)
Hockings <sup>15</sup> :								
Aspirin 100 mg	128	6	0.05	0.52	50	5	0.10	0.61
Placebo	145	13	0.09	(0.20 to 1.34)	52	9	0.17	(0.22 to 1.67)

\*Not all patients randomised underwent angiography.

separate meta-analysis of trials comparing medium dose aspirin versus placebo yielded an estimated relative risk, RR<sub>MP</sub>. We obtained the estimated difference in effect of low and medium dose aspirin, RR<sub>ML</sub>, by combining the two estimated log relative risks. These were then back transformed to give the estimate of RR<sub>ML</sub> with a 95% confidence interval (see bmj.com for details).

The statistical analysis of graft patency presents a particular difficulty as patients typically receive several grafts, and it cannot be assumed that grafts within patients act independently. To avoid such cluster sampling error we also analysed graft patency in terms of rates of events in patients.<sup>10</sup>

**Results**

*Trial flow and trial characteristics*—Of 32 publications identified for review, we identified five published trials as eligible for overview and included them in the meta-analysis. Three trials used low dose aspirin whereas two used medium dose regimens (see bmj.com).

*Meta-analysis*—The table shows the rates of graft patency and events in patients for each trial. The pooled relative risk reduction for graft occlusion was 45% in the medium dose trials (0.55, 95% confidence interval 0.41 to 0.73) compared with 26% in the low dose trials (0.74, 0.60 to 0.91), a relative risk ratio of 0.74 (0.52 to 1.06; P=0.10). However, this analysis is per vein and thus includes patients more than once, so the results are overprecise. The results for event rate in patients were broadly similar (see table and figure) but with a relative risk ratio of 0.81 (0.57 to 1.16; P=0.25).

**Discussion**

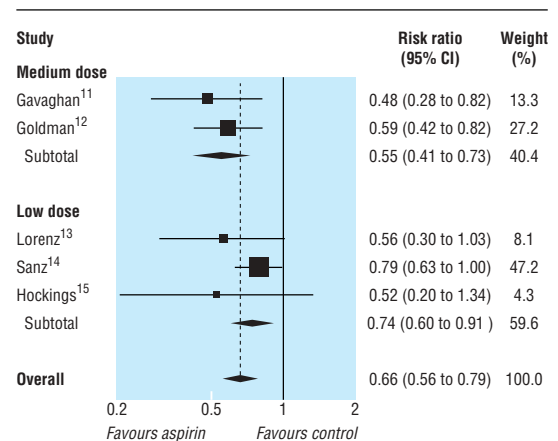
The concept of a minimally effective dose of aspirin is attractive and is currently under evaluation for the prevention of stroke and myocardial infarction.<sup>16</sup> Existing limited evidence showed that medium rather than low dose regimens were more effective in reducing vein graft occlusion and event rates in patients. Although these results are not statistically significant, this possibility of a dose effect needs consideration; the

wide confidence intervals reflect the scarcity of aspirin trials at these doses.

The best way to answer the question is by a prospective randomised trial. Unfortunately, this has never been done. We therefore performed indirect comparison meta-analysis with placebo as an intermediary. The validity of this statistical method is built on the assumption that no important differences exist between trials examining medium or low dose regimens. If the two sets of trials differ with respect to a feature (clinical or methodological) that modified the treatment effect, then the comparisons of medium and low dose aspirin would be confounded. In our series, a notable difference was the shorter time to angiography in the low dose aspirin trials. In particular, this investigation was performed at a mean of 10 days (compared with one year in the medium dose trials) in the study by Sanz, the largest of the five trials. Although graft occlusion this early is often attributed to surgical technique,<sup>17</sup> a beneficial effect of aspirin compared with placebo on graft patency was already evident in this early time frame.

**Clinical implications**

The financial implications of converting from low to medium dose therapy are marginal. Twenty 75 mg tab-



Relative risk of each aspirin regimen compared with placebo for graft occlusion (see bmj.com for complete data)

lets cost £0.10 (\$0.17, €0.15) and twenty 300 mg tablets cost £0.19 (\$0.32, €0.28). Reluctance to convert to medium dose therapy is possibly due to concerns about bleeding, even though most postoperative prescription occurs on the first postoperative day as the risk of bleeding is then reduced.<sup>18</sup> A large prospective study of 5065 patients after coronary surgery reported a lower incidence of all bleeding complications in those who had received aspirin compared with patients who did not receive aspirin,<sup>19</sup> thus supporting the safety of early postoperative aspirin administration. Long term use is associated with established risks of bleeding. Recent meta-analyses however, established that the proportional increase in major extracranial haemorrhage and gastrointestinal bleeding was not attenuated by using lower doses.<sup>20 21</sup>

What are the benefits of preventing graft occlusion? Angiographic follow up showed that death, myocardial infarction, and revascularisation rates were associated with the progression of vein graft disease.<sup>22</sup> But the clinical picture is far from clear because comparative trials on aspirin therapy have not reported on survival, rates of recurrent angina, or need for a further operation that could potentially be altered by improved graft patency.

### Biological plausibility

It is generally accepted that aspirin is useful in the first month after surgery when vein graft attrition is caused mainly by thrombotic occlusion.<sup>19</sup> Although low dose aspirin is sufficient to inhibit production of platelet thromboxane in patients with atherosclerosis,<sup>23</sup> aggregometry after coronary bypass surgery showed that low dose aspirin (100 mg) did not inhibit early post-operative platelet aggregation.<sup>24</sup> Why the biological effects of aspirin should be modified under these conditions is uncertain and may be due to the effects of cardiopulmonary bypass or surgical trauma. Similar comparative studies have not been performed to evaluate the biological effects of aspirin at higher doses. Later phases of intimal hyperplasia and vein graft atherosclerosis are not influenced by aspirin therapy,<sup>25</sup> and this is reflected by the attenuation of the beneficial effects on vein graft patency after the first year.<sup>26</sup>

### Conclusions

The results of our meta-analysis show that medium dose aspirin may more successfully reduce graft occlusion than low dose regimes within the first year after coronary surgery. With a proved safety profile in hospital, no substantial increase in cost, and no proportional increase in major haemorrhage, clinicians could consider 325 mg as the optimum dose in the first year.

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## What is already known on this topic

Early use of aspirin after coronary surgery is safe and is associated with reduced risk of death and major vascular events

Low to medium dose aspirin (75-325 mg) is equivalent or superior to high dose aspirin (500-1500 mg) in preventing vein graft occlusion

## What this study adds

Compared with low dose aspirin regimens (75-150 mg), medium dose regimens (300-325 mg) may be more effective in preventing graft occlusion and events in patients

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