

## 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

What do we really know about the effect of treatment with aspirin after coronary artery bypass surgery? In the United Kingdom over 25 000 such procedures are performed annually.<sup>1</sup> Despite the increasing popularity of arterial grafts, the saphenous vein remains widely used and has an estimated occlusion rate of 15-30% in the first year.<sup>2</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>3-5</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 major bibliographic databases—Medline (1966 to April week 3, 2003) and Embase (1974 to 2003, week 17)—using the following text and thesaurus terms in combination: clinical trial, research design, placebo, random, aspirin, anticoagulant, antithrombotic, platelet aggregation inhibitors, coronary artery bypass, vascular patency, graft occlusion, graft survival. This was performed in conjunction with methodological therapy filters specific to each database (full search details are available from EL). We also searched the Cochrane controlled trials register, the national research register, and trial sites on the internet for additional articles. The reference lists of all relevant studies were reviewed, and consultation was undertaken with senior colleagues and authors of previous trials.

#### Study selection

We included all randomised controlled trials that evaluated the efficacy of medium or low dose aspirin in preventing occlusion of vein grafts. No restrictions were placed on abstracts, conference proceedings, or language. 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 (to eliminate the effect of other concomitant therapy on vein graft patency) 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: if the same population appeared in other publications, 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. The studies in this meta-analysis 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 rate 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.

**Table 1** Participant characteristics of each trial

Trial and regimen	No randomised	Mean (SD) age (years)	Men (%)	Smokers (%)	Hypertensive (%)	Cholesterol (mmol/l)	Time to angiography (days)	Proportion not receiving angiography (%)
<b>Gavaghan<sup>42</sup>:</b>								
Aspirin 324 mg	127	56 (7)	87	65	45	7.1	363* (median)	8*
Placebo	110	56 (6)	84	67	39	7.0	363* (median)	8*
<b>Goldman<sup>41</sup>:</b>								
Aspirin 325 mg	104	59 (8)	100	NA	47	5.9	367* (median)	35*
Placebo	107	58 (8)	100	NA	53	5.7	367* (median)	35*
<b>Lorenz<sup>40</sup>:</b>								
Aspirin 100 mg	29†	55 (10)	83	NA	NA	6.9	131 (mean)	24
Placebo	31†	55 (6)	90	NA	NA	7.2	129 (mean)	23
<b>Sanz<sup>43</sup>:</b>								
Aspirin 150 mg	373	57 (8)	90	65	40	6.0	10 (mean)	17*
Placebo	371	56 (8)	89	68	38	6.0	11 (mean)	17*
<b>Hockings<sup>44</sup>:</b>								
Aspirin 100 mg	50	60 (9)	94	N/A	50	NA	180* (NA)	27*
Placebo	52	60 (9)	92	N/A	31	NA	180* (NA)	27*

NA=not available.  
 \*Value reported for entire study cohort.  
 †Number of patients reported at end of study.

**Statistical methods**

In the absence of randomised trials making head to head comparisons, an indirect comparison is possible using a common comparator.<sup>6-10</sup> We performed a meta-analysis combining trials of low dose aspirin versus placebo to obtain the estimated relative risk,  $RR_{LP}$ . A separate meta-analysis of trials comparing medium dose aspirin versus placebo yielded an estimated relative risk,  $RR_{MP}$ . We obtained the estimated difference in effect of low and medium dose aspirin,  $RR_{ML}$ , by combining the two estimated log relative risks as follows:

$$\log RR_{ML} = \log RR_{MP} - \log RR_{LP} \quad \text{var}(\log RR_{ML}) = \text{var}(\log RR_{MP}) + \text{var}(\log RR_{LP})$$

where var indicates the square of the standard error (variance). From these values we calculated a 95% confidence interval for  $\log RR_{ML}$ . All values were back transformed to give the estimate of  $RR_{ML}$  with a 95% confidence interval. This analysis can be seen as the simplest form of meta-regression<sup>11</sup> with a single binary trial factor or, equivalently, as an examination of the interaction between treatment effect and dose of aspirin.<sup>12</sup> We also performed the analysis using odds ratios instead of risk ratios, although we expected differences to be minor as the events are rare.

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>13</sup>

**Results**

**Trial flow and trial characteristics**

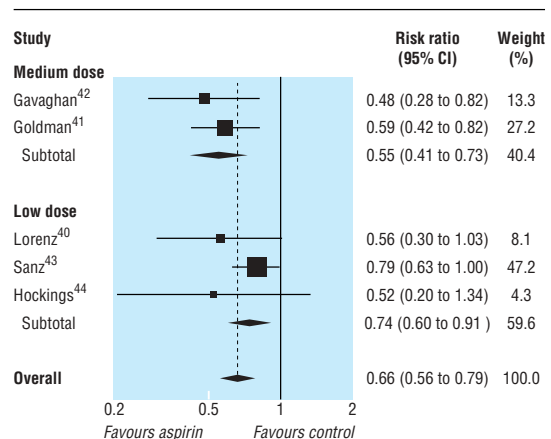
Of 32 publications identified for review, none were excluded for administering aspirin in doses of less than 50 mg, 14 were excluded for administering aspirin in dosages above 325 mg (ranging from 650 mg to 1200 mg a day),<sup>14-26</sup> seven trials did not have an aspirin only arm,<sup>27-33</sup> and two did not use placebo control.<sup>34, 35</sup> Four further publications were excluded because they were repeat publications with the same data.<sup>36-39</sup> We identified five published trials as eligible for overview and included them in the meta-analysis.<sup>40-44</sup> Three trials used low dose aspirin whereas two used medium dose regimens.

Two trials were multicentred<sup>41, 43</sup> and the three others were single institution studies.<sup>40, 42, 44</sup> Method of recruitment was explic-

itly stated in two trials.<sup>41, 43</sup> Exclusion criteria included upper age limit<sup>42, 43</sup> and previous or concomitant surgery.<sup>41-44</sup> Two trials reported standardisation of surgical procedure.<sup>40, 42</sup> All trials were blinded and included a placebo control arm. Three trials reported formal randomisation by research coordinating centres or pharmacy.<sup>41-43</sup> In all five trials postoperative aspirin was given within the first 24 hours. Two trials reported independent angiographic analysis of vein graft patency,<sup>40, 41</sup> and one trial reported further assessment of reliability of angiographic analysis.<sup>41</sup> Table 1 summarises the baseline participant characteristics within each study arm and between the medium and low arms.

**Meta-analysis**

Table 2 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) (figure). However, this analysis is per vein and thus includes patients more than once, so that the results are overprecise. The results for event rates in patients were broadly similar (table 2, figure) but with a relative risk ratio of 0.81 (0.57 to 1.16; P=0.25). When we used odds ratios rather than relative risk the results were similar.



Relative risk of each aspirin regimen compared with placebo for graft occlusion (see table 2 for complete data)

**Table 2** Results of trials of aspirin treatment after coronary surgery

Trial and regimen	No of distal anastomosis	No of occlusions	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>42</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>41</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>40</sup> :								
Aspirin 100 mg	57	11	0.19	0.56	29	6†	0.27	0.44
Placebo	81	28	0.35	(0.30 to 1.03)	31	15‡	0.63	(0.21 to 0.92)
Sanz <sup>43</sup> :								
Aspirin 150 mg	745	106	0.14	0.79	373	101	0.27	0.82
Placebo	750	135	0.18	(0.63 to 1.00)	371	122	0.33	(0.66 to 1.03)
Hockings <sup>44</sup> :								
Aspirin 100 mg	128	6	0.05	0.52	50	5	0.10	0.58
Placebo	145	13	0.09	(0.20 to 1.34)	52	9	0.17	(0.21 to 1.61)

\*Not all patients randomised underwent angiography.

†6/22 events reported.

‡15/24 events reported.

## Discussion

No one likes prescribing any drug in a higher dose than is absolutely necessary to get the job done. 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>45</sup> However, limited evidence provided by five placebo controlled trials that randomised 1356 patients showed that medium rather than low dose regimens were more effective in reducing vein graft occlusion (risk ratio of 0.74; 0.52 to 1.06) and event rates in patients (0.81; 0.57 to 1.16). 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, of course, is by head to head comparison in a prospective randomised trial. Unfortunately, this has never been done. We therefore performed indirect comparison meta-analysis with placebo as an intermediary. This statistical technique does not replace randomised trials of direct comparison but is used to estimate treatment effect when direct comparative studies have not been performed<sup>5-7</sup> or to strengthen the power of comparisons where few direct studies are available.<sup>8</sup>

The validity of indirect comparison meta-analysis 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.<sup>43</sup> Although graft occlusion this early is often attributed to surgical technique,<sup>46</sup> a beneficial effect of aspirin compared with placebo on graft patency was already evident in this early time frame.

Although the indirect meta-analysis approach leads to greater uncertainty, it is clear that current evidence is inadequate to allow a definitive answer. Previous meta-analyses have shown that vascular graft patency is better with low to medium dose aspirin than with high dose regimes, but the possibility of differ-

ing effects between the low and medium dose groups was not examined.<sup>4 5</sup>

## Clinical implications

The financial implications of converting from low to medium dose therapy are marginal. Twenty 75 mg tablets 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>47</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>48</sup> thus supporting the safety of early postoperative aspirin administration. That is not to say that aspirin administration is without complications. 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>49 50</sup>

Although it may be tempting to believe that low dose aspirin can attain a better safety profile while retaining therapeutic efficacy for graft patency, evidence to support either is limited. To take the argument further, 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>51</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

How does aspirin improve graft patency? 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>48</sup> Although low dose aspirin is sufficient to inhibit production of platelet thromboxane in patients with atherosclerosis,<sup>52</sup> aggregometry after coronary bypass surgery showed that low dose aspirin (100 mg) did not inhibit early postoperative platelet

### 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

aggregation.<sup>53</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 at aspirin at higher doses. Later phases of intimal hyperplasia and vein graft atherosclerosis are not influenced by aspirin therapy,<sup>54</sup> and this is reflected by the attenuation of the beneficial effects on vein graft patency after the first year.<sup>38</sup>

If the antiplatelet action of aspirin is important for graft patency, further work is required to establish the optimum dosage for greatest biological effect and for it to be supported by trials with an emphasis on clinical outcome.

### 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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