Antithrombotic Therapy in Patients With Saphenous Vein and Internal Mammary Artery Bypass Grafts

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This chapter about prevention of coronary artery bypass occlusion is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004; 126: 179S–187S*). Among the key recommendations in this chapter are the following: For patients undergoing coronary artery bypass grafting (CABG), we recommend aspirin, 75 to 162 mg/d, starting 6 h after operation over preoperative aspirin (Grade 1A). In patients in whom postoperative bleeding prevents the administration of aspirin at 6 h after CABG, we recommend starting aspirin as soon as possible thereafter (Grade 1C). For patients undergoing CABG, we recommend against addition of dipyridamole to aspirin therapy (Grade 1A). For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po (Grade 1C+). In patients who undergo CABG for non–ST-segment elevation acute coronary syndrome (ACS), we recommend clopidogrel, 75 mg/d for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 1A). For patients who have received clopidogrel for ACS and are scheduled for CABG, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A). For patients undergoing CABG who have no other indication for vitamin K antagonists (VKAs), we suggest clinicians to not administer VKAs (Grade 2B). For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C). For all patients with coronary artery disease who undergo internal mammary artery (IMA) bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (Grade 1A). For all patients undergoing IMA bypass grafting without other indication for VKA, we suggest clinicians not use VKA (Grade 2C).

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Key words: antithrombotic; arterial bypass; graft; postoperative therapy

Abbreviations: ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CI = confidence interval; IMA = internal mammary artery; RCT = randomized controlled trial; VKA = vitamin K antagonist

One of the major complications of coronary artery bypass grafting (CABG) is graft closure, and this is largely related to platelet aggregation. Almost immediately after harvesting the saphenous vein, the endothelium is lost and the raw surface is vulnerable to platelet aggregation.[1] This may explain the need for early antithrombotic treatment. Several factors may affect graft patency: (1) Intraoperative factors may partially relate to endothelial damage.[2] For example, graft patency was reduced if operation time exceeded 5 h, bypass time exceeded 2 h, cross-clamp time exceeded 80 min, the temperature of the vein preservation solution exceeded 5°C, intermittent cross-clamping rather than continuous cross-clamping was used, or if there were two or more proximal anastomoses[2]; (2) The medium used for storage and rinsing of the vein grafts affects endothelial function and affects graft patency[3]; (3) Graft size: grafts $\geq$ 1.5 mm in diameter had a higher patency rate after 1 year than smaller grafts[4]; (4) Graft location: grafts inserted in regions of normal wall motion had higher patency rates than grafts with abnormal wall motion in the region of insertion; (5) Lipid levels: aggressive lowering of low-density lipoprotein cholesterol results in a reduced number of occluded grafts.[5]

Table 1 lists the question definition and eligibility criteria for the studies considered in this review. The first section describes the prevention of saphenous vein graft occlusion following CABG. Table 2 lists details of studies comparing the effects of antithrombotic therapy with placebo on graft patency in randomized controlled trials (RCTs) in CABG with vein grafts. The second section describes the prevention of internal mammary artery (IMA) bypass graft occlusion following CABG.

1.0 Prevention of Saphenous Vein Graft Occlusion following CABG

1.1 Treatment with antiplatelet agents

1.1.1 Aspirin

Metaanalysis: A systematic review[6] by the Antiplatelet Trialists' Collaboration of trials involving treatment with aspirin between 1966 and 1990 showed that treatment with antiplatelet agents, especially when initiated early, was associated with improved graft patency for an

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Table 1—*Question Definition and Eligibility Criteria for Antithrombotic Therapy in Patients With Saphenous Vein and IMA Bypass Grafts*

Section	Population	Intervention or Exposure	Outcomes	Methodology
1.1.1	Coronary artery bypass grafts; saphenous vein bypass grafts	Aspirin	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.2	Coronary artery bypass grafts; saphenous vein bypass grafts	Aspirin with dipyridamole	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.3	Coronary artery bypass grafts; saphenous vein bypass grafts	Dipyridamole	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.4	Coronary artery bypass grafts; saphenous vein bypass grafts	Indobufen	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.5	Coronary artery bypass grafts; saphenous vein bypass grafts	Ticlopidine	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.6	Coronary artery bypass grafts; saphenous vein bypass grafts	Clopidogrel	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.1.7	Coronary artery bypass grafts; saphenous vein bypass grafts	Sulfinpyrazone, triflusal	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
1.2	Coronary artery bypass grafts; saphenous vein bypass grafts	VKAs	Cardiovascular events, graft thrombosis, graft patency, or bleeding	RCTs
2.1	IMA bypass grafts	Aspirin, aspirin with dypiridamole	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs
2.2	IMA bypass grafts	VKAs	Cardiovascular events, death, graft thrombosis, graft patency, or bleeding	RCTs

average of 1 year after surgery. This metaanalysis[6] concluded that similar improvements in bypass graft patency could result from starting antiplatelet agents before operation or within 24 h thereafter. In addition, higher and hence more gastrotoxic doses of aspirin were no more effective than 75 to 325 mg/d (see chapter by Patrono et al in this Supplement).[6] The pooled odds reduction for graft closure was 44% in the five trials that compared low-dose aspirin (75 to 325 mg/d), and 50% in the nine trials that compared high-dose aspirin (500 to 1,500 mg/d) with placebo or control therapy, but this difference was not statistically significant.

Individual trials: Table 2 shows results of trials comparing aspirin with placebo. A 3-year follow-up study of 455 patients the study by Goldman et al[7] published in 1994 showed that continued use of aspirin, 325 mg/d, for 2 additional years after an initial year of therapy for the prevention of saphenous vein bypass graft occlusion showed no long-term benefit on graft patency compared to placebo at the end of the third year (62/365 = 17% vs 74/ 376 = 19.7%; p = 0.404). Among patients with patent saphenous vein bypass grafts 7 to 10 days after operation, the 3-year patency was more related to operative technique and underlying disease than to therapy with aspirin after the first year.[2] However, aspirin is indicated indefinitely in all patients with coronary heart disease (see chapter by Harrington et al in this Supplement).

Aspirin dosing: There were no significant differences in graft patency between high- and low-dose aspirin regimens.[6] In clinical practice, there is enthusiasm to use the lowest possible dose of aspirin. Unfortunately, when examining graft patency, there are no studies that directly compare low doses of aspirin, such as 50 to 100 mg/d, to the regimens of 325 mg/d.

Timing of aspirin administration: Indirect comparison of studies that started aspirin before vs after surgery administration of aspirin did not reveal differences in patency rates. One RCT published in 1991 compared the effects of preoperative aspirin, 325 mg/d (started the day before surgery), with aspirin begun 6 h after surgery.[8] Early aspirin was not more effective than aspirin after operation (started on the day of surgery) at improving early (7- to 10-day) graft patency, but it was associated with increased bleeding complications.

Recommendations

1.1.1.1. For all patients with coronary artery disease, we recommend aspirin, 75 to 162 mg/d, indefinitely (**Grade 1A**).

1.1.1.2. For patients undergoing CABG, we recommend aspirin, 75 to 325 mg/d, starting 6 h after operation over preoperative aspirin (**Grade 1A**).

1.1.1.3. In patients in whom bleeding prevents the administration of aspirin at 6 h after CABG, we recommend starting aspirin as soon as possible thereafter (**Grade 1C**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding cardiovascular complications and a relatively low value on avoiding bleeding complications.

1.1.2 Aspirin in combination with dipyridamole

Metaanalysis: The Antiplatelet Trialists' Collaboration overview[6] found no benefit of the combination of aspirin and dipyridamole over aspirin alone on graft patency. This section of the overview pooled data from nine RCTs conducted until 1990.

Individual trials: A later study by van der Meer et al[9]

Table 2—*Controlled Trials of Antithrombotic Therapy for Vein Graft Patency in Coronary Artery Bypass Surgery***

Treatment Drug/Daily Dose, mg	Onset, Postoperative d	Graft Patency, No. Patent of Grafts/Treated (%)	Graft Patency, No. Patent of Grafts/Control (%)	Study Duration, mo	p Value	Source
Aspirin						
100	1	36/40 (90)	36/53 (68)	4	0.012	Lorenz et al[15]
100	− 7	122/128 (95)	132/145 (91)	6	NS	Hockings et al[16]
150	1	639/745 (86)	615/750 (82)	1	0.058	Sanz et al[11]
325	− 1	291/340 (87)	267/345 (77)	12	< 0.05	Goldman et al[14]
325	− 1	347/371 (94)	327/384 (85)	< 2	< 0.01	Goldman et al[13]†
325	− 1	62/365 (17)	74/376 (19.7)	36	0.404	Goldman et al[7]†
324	0	112/119 (94)	88/100 (88)	12	0.01	Gavaghan et al[12]
975	− 1	313/339 (92)	327/384 (85)	< 2	< 0.05	Goldman et al[13]†
975	− 1	262/315 (83)	267/345 (77)	12	NS	Goldman et al[14]†
1,200	3–4	65/81 (80)	54/74 (72)	24	NS	McEnany et al[42]
975	3–5	87/111 (78)	76/95 (80)	12	NS	Sharma et al[22]
975	3–5	100/114 (88)	116/147 (79)	12	NS	Brown et al[24]
Aspirin plus dipyridamole						
150 + 225	1	646/742 (87)	615/750 (82)	1	0.017	Sanz et al[11]
1,300 + 100	1	69/75 (92)	72/93 (77)	3–6	< 0.02	Mayer et al[19]
990 + 225	− 1	87/95 (92)	88/118 (75)	6	< 0.01	Rajah et al[17]
975 + 225	− 1, − 2‡	330/359 (92)	327/384 (85)	< 2	< 0.05	Goldman et al[13]†
975 + 225	− 1, − 2	260/315 (83)	267/345 (77)	12	NS	Goldman et al[14]†
975 + 225	0, − 2§	425/478 (89)	364/486 (75)	12	< 0.05	Chesebro et al[20]
975 + 225	3	27/33 (82)	50/61 (82)	6	NS	Pantely et al[21]
975 + 225	3–5	119/138 (86)	116/147 (79)	12	NS	Brown et al[24]
975 + 225	3–5	74/89 (83)	76/95 (80)	12	NS	Sharma et al[22]
990 + 225	2–3	100/133 (75)	91/133 (68)	12	NS	Brooks et al[23]
1,000 + 225	0	24/37 (65)	8/38 (21)	12	< 0.001	Pirk et al[49]
Aspirin 325 or aspirin 975 or aspirin 975 plus dipyridamole 225	− 1, − 2	274/303 (90)‖	71/80 (89)	12	NS	Goldman et al[47]†
Dipyridamole						
400	− 2	316/413 (77)	305/421 (72)	12	NS	Ekstrom et al[25]
Ticlopidine						
500	2	185/220 (84)	153/207 (74)	12	0.01	Limet et al[30]
500¶	2	71/79 (90)	47/59 (80)	3	< 0.01	Chevigné et al[31]
Sulfinpyrazone						
800	− 2	296/328 (90)	327/384 (85)	< 2	NS	Goldman et al[13]†
800	− 2	248/303 (82)	267/345 (77)	12	NS	Goldman et al[13]†
800	1	204/212 (96)	199/219 (91)	< 1	< 0.025	Baur et al[39]
Oral anticoagulant						
	3–4	55/65 (85)	54/74 (72)	24	NS	McEnany et al[42]
	3	29/37 (78)	50/61 (82)	6	NS	Pantely et al[21]
	7	227/251 (90)	199/238 (85)	2	< 0.015	Gohlke et al[41]

*NS = not significant.
†Include data from one trial.
‡Dipyridamole was started 2 days before operation; aspirin was started 12 h before operation.
§Dipyridamole was started 2 days before operation; aspirin was started on the day of operation.
‖All grafts were to left anterior descending coronary artery only in this subset analysis.
¶Studied by scintigraphy or coronary angiography.

assessed 1-year angiographic vein-graft patency after CABG surgery in 948 patients assigned to aspirin, aspirin plus dipyridamole, or oral anticoagulants in a blinded RCT. Dipyridamole, 5 mg/kg per 24 h IV for 28 h, followed by 200 mg bid, and oral anticoagulants (desired prothrombin time range 2.8 to 4.8 international normalized ratio) were started before surgery, and aspirin, 50 mg/d, was started after surgery. The authors assessed clinical outcome as incidence of myocardial infarction, thrombosis, major bleeding, or death. Occlusion rate of distal anastomoses was 11% in the aspirin-plus-dipyridamole group vs 15% in the aspirin group (relative risk, 0.76; 95% confidence interval [CI], 0.54 to 1.05) and 13% in the oral anticoagulants group. Clinical events occurred in 20.3% of patients receiving aspirin plus dipyridamole compared with 13.9% of the aspirin group (relative risk, 1.46; 95% CI, 1.02 to 2.08) and 16.9% of the oral anticoagulants group. The data provided no convincing evidence that addition of dipyridamole to 50 mg/d of aspirin improves aortocoronary vein graft patency, and

there was evidence for increased overall clinical event rate.

Agnew et al[10] randomized 100 patients to aspirin, 100 mg/d, or aspirin, 100 mg/d, and dipyridamole, 300 mg/d, before undergoing CABG. Patients received treatment at least 36 h before operation and were followed up for 1 year. Angiography at 9 weeks and 1 year showed vein graft patency rates of 93% and 87% for subjects treated with aspirin alone; and 90% and 89% in those who received aspirin plus dipyridamole, respectively. There was similar progression of coronary lesions in both groups. The study did not establish superiority of one regimen over another in terms of graft patency or progress of lesions in native vessels. Patients reportedly tolerated low-dose aspirin better than combination therapy.

One trial[11] compared placebo, aspirin at 150 mg/d alone, and aspirin at 150 mg/d plus dipyridamole at 225 mg/d, all begun the day after surgery in patients who received dipyridamole, 400 mg/d, until the day of surgery. Aspirin plus dipyridamole showed improved graft patency vs placebo, whereas aspirin alone showed only a trend toward a benefit.[11] However, there was no significant difference comparing aspirin alone with aspirin plus dipyridamole.[11]

Indirect comparisons of the effects of aspirin plus dipyridamole with aspirin alone, begun no later than 1 day following surgery, showed no benefit with the addition of dipyridamole.[11–19] Dipyridamole in combination with high doses of aspirin, 975 to 1,300 mg/d, started 2 days before operation to 1 day after operation was not consistently more beneficial than aspirin alone.[13,14,17–20] Dipyridamole in combination with high doses of aspirin, 975 to 990 mg/d, started 2 to 5 days after operation was no more effective than aspirin alone and often no different from placebo.[21–24]

Recommendation

1.1.2. For patients undergoing CABG, we recommend **against** addition of dipyridamole to aspirin therapy (**Grade 1A**).

1.1.3 Dipyridamole as single agent

Only one trial[25] compared dipyridamole alone (100 mg/d po for 2 days preoperatively, 5 mg/kg body weight/24 h IV preoperatively, and 100 mg/d po for 1 year postoperatively) to placebo in 360 patients undergoing CABG. A total of 48 patients receiving dipyridamole and 57 patients receiving placebo were withdrawn from the study, and in the remaining patients there was no greater graft patency in the dipyridamole group compared with placebo when all grafts were evaluated. The Étude de la Perméabilité des Pontages Aorto-coronaires was a randomized, blinded RCT[26] that compared the patency of coronary bypass grafts in two groups of coronary patients after surgery: one group treated with an oral vitamin K antagonists (VKAs) and placebo (n = 196), and one group treated with VKAs and dipyridamole (n = 182). Two independent observers evaluated graft patency at coronary angiography performed 6 months after surgery. There was no benefit of dipyridamole over placebo in patients receiving oral VKAs. Because of the sparse evidence, we are not making a recommendation regarding use of dipyridamole, as a single agent, in patients with CABG.

1.1.4 Indobufen

Indobufen is a reversible platelet cyclooxygenase inhibitor that allows platelet function to recover promptly after discontinuation. In three randomized trials,[27–29] graft patency after indobufen was compared to aspirin combined with dipyridamole. Efficacy was comparable,[27–29] although indobufen was associated with fewer adverse events or better tolerance.[28,29] In one of the investigations,[29] both the indobufen arm of the study and the aspirin-plus-dipyridamole arm showed low patency rates. Indirect comparison to aspirin alone suggests similar patency rates for indobufen. Since there is a lack of direct comparison with aspirin and because indobufen has no proven effects on long-term patency, we do not make a recommendation for the use of indobufen.

1.1.5 Ticlopidine

Ticlopidine, 500 mg/d, starting 2 days after operation was effective in maintaining graft patency in two RCTs.[30,31] However, ticlopidine is associated with serious adverse effects including fatal thrombocytopenic purpura or neutropenia.[32,33] Because of the uncertain balance of benefits and risks and because other antiplatelet agents are available, we do not make a recommendation regarding ticlopidine.

1.1.6 Clopidogrel

Clopidogrel is a newer antiplatelet agent (see chapter by Patrono et al in this Supplement).[34] It has been compared to aspirin in subgroup analyses of large RCTs (see chapters by Harrington et al in this Supplement).[35]

Individual trials: Investigators compared clopidogrel to aspirin in a subgroup analysis of the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial.[36] In subgroup analyses, these investigators[37] sought to determine whether antiplatelet therapy with clopidogrel would be more effective than aspirin in patients who underwent coronary artery bypass surgery. They determined the event rates for all-cause mortality, vascular death, myocardial infarction, stroke, and rehospitalization for the 1,480 patients with a history of cardiac surgery randomized to either clopidogrel or aspirin. The annual event rates were 22.3% in the 705 patients randomized to aspirin and 15.9% in the 775 patients randomized to clopidogrel ($p = 0.001$). They observed a relative risk reduction in each of the individual end points examined, including a 42.8% relative risk reduction in vascular death in patients receiving clopidogrel vs aspirin ($p = 0.030$).

The Clopidogrel in Unstable Angina To Prevent Recurrent Events trial[38] randomized 12,562 patients with non–ST-segment elevation acute coronary syndrome (ACS) to receive clopidogrel (300 mg immediately followed by 75 mg qd) or placebo in addition to aspirin, 75 to 325 mg/d, for 3 to 12 months. The first primary outcome was a

composite of death from cardiovascular causes, nonfatal MI, or stroke, and the second primary outcome was death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia. The benefits of clopidogrel were consistent across a broad range of patient subsets including those with revascularization procedures following randomization (n = 4,577). Moreover, the benefit of clopidogrel tended to be higher in patients who had undergone a revascularization procedure prior to enrollment in the study (relative risk of the first primary outcome, 0.56; 95% CI, 0.43 to 0.72). The study did not report results of the primary end point separately for the 2,072 patients (16.5%) who underwent CABG after randomization or the 2,568 patients (21.2%) who underwent percutaneous transluminal coronary angioplasty. There was no difference in overall bleeding risk between patients with CABG receiving clopidogrel or placebo (1.3% vs 1.1%; relative risk, 1.26; 95% CI, 0.93 to 1.71). However, in most patients scheduled for CABG surgery, investigators discontinued the study medication before the procedure (median time before the procedure, 5 days). In the 910 patients in whom the study medication was discontinued > 5 days before the procedure (5 days being the duration of the effect of clopidogrel), there was no apparent excess of major bleeding within 7 days after surgery (4.4% of the patients in the clopidogrel group vs 5.3% of those in the placebo group). In the 912 patients who stopped taking the medications within 5 days before CABG surgery, the rate of major bleeding was 9.6% in the clopidogrel group and 6.3% in the placebo group (relative risk, 1.53; $p = 0.06$). Overall, the risk of minor bleeding was significantly higher in clopidogrel-treated patients (5.1% vs 2.4%; $p = 0.001$).

Recommendations

1.1.6.1. For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po (**Grade 1C+**).

1.1.6.2. In patients who undergo CABG for non–ST-segment elevation ACS, we recommend clopidogrel, 75 mg/d, for 9 to 12 months following the procedure in addition to treatment with aspirin (**Grade 1A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding myocardial infarction and a relatively low value on avoiding bleeding complications.

1.1.6.3. For patients who have received clopidogrel for ACS and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

1.1.7 Other antiplatelet agents

Sulfinpyrazone, 800 mg/d, compared to aspirin or placebo, starting from 2 days before operation to 1 day after, was not consistently effective in maintaining graft patency at 2 weeks up to 1 year after CABG.[13,14,39] Triflusal is a platelet inhibitor structurally related to aspirin. It is a weaker inhibitor of cyclooxygenase than aspirin, but a stronger inhibitor of cyclic adenosine monophosphate phosphodiesterase.[40] When started 1 day preoperatively, therapy with triflusal, 900 mg/d, plus dipyridamole, 225 mg/d, resulted in fewer distal anastomotic occlusions compared to aspirin, 150 mg/d, plus dipyridamole, 225 mg/d.[40] Because of the limited evidence about efficacy of sulfinpyrazone and triflusal, we do not make a recommendation regarding these antiplatelet agents.

1.2 Treatment with oral anticoagulants

1.2.1 VKAs

Individual trials: Three randomized trials[21,41,42] compared oral anticoagulants with placebo for long-term graft patency; in each case, anticoagulants were started 3 to 7 days after operation. One study[42] investigated long-term patency of vein grafts after follow-up of up to 24 to 48 months. From an initial group of 216 patients, vein graft patency was determined in only 111 patients (220 grafts) during the follow-up period, and discontinuation of therapy was high (55 patients were not reevaluated). There was a trend toward better cumulative graft patency in patients receiving warfarin, but the results did not achieve statistical significance. Improved results with warfarin were most marked among patients who were restudied within 24 months of CABG operation, in most instances because of the development of recurrent angina pectoris.

One study[41] showed increased graft patency with VKAs. This study enrolled 89 patients with 251 saphenous vein grafts who were treated with phenoprocoumon (prothrombin time 1.5 to 2.0 times the control) beginning on the seventh postoperative day. The control group was similar in terms of clinical characteristics with 84 patients receiving 238 grafts. Eight weeks following surgery, graft patency (90.4% vs 84.6%) and numbers of patients with all grafts patent (81% vs 67%) were significantly greater in the anticoagulation group. Patients with a graft flow of < 90 mL/min at the time of surgery benefited from anticoagulation. No graft with a flow > 90 mL/min was occluded.

Pantely et al[21] randomly assigned 50 patients to one of four groups to determine the effects of antiplatelet or anticoagulant therapy on graft patency: 24 patients served as controls; 13 patients received aspirin, 325 mg tid, and dipyridamole, 75 mg tid; and 13 patients received closely regulated warfarin therapy begun on the third postoperative day. Six months after surgery, all patients underwent coronary angiography to assess graft patency. There were no statistically significant differences between groups in various clinical, hemodynamic, and angiographic findings. Vein graft patency was 50 of 61 grafts (82%) in control patients and 29 of 37 grafts (78%) with warfarin ($p < 0.5$). All patients had at least one patent graft. There was no benefit from treatment with either aspirin plus dipyridamole or VKAs.

In other studies, VKAs begun from 14 days prior to operation to 2 days after operation (sometimes with heparin) yielded a graft patency comparable to low-dose aspirin (50 mg or 100 mg) or low-dose aspirin in combination with dipyridamole.[9,43–45] Fewer bleeding complications occurred with aspirin plus dipyridamole than with

oral anticoagulants.[43] Warfarin has also been compared to dipyridamole alone (both started 2 or 3 days after surgery).[46] Graft patency after 1 year or 2 years was comparable for the two regimens (96% for dipyridamole and 89% for warfarin).[46]

Recommendations

1.2.1. For patients undergoing CABG who have no other indication for VKA, we suggest clinicians **not** administer VKAs (**Grade 2B**).

1.2.2. For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (**Grade 2C**).

Bleeding complications of antithrombotic therapy in CABG: Evidence on bleeding complications during CABG with vein grafts is limited because only few selected trials[12,13,15,16,42] report this data. Therefore, there is a high risk of reporting bias for blood loss associated with antithrombotic therapy. For example, Lorenz et al[15] reported that there was no blood loss in aspirin-treated (100 mg started one day postoperatively, n = 29) and placebo-treated (n = 32) patients. Hockings and colleagues[16] described blood loss of 1,193 mL in aspirin-treated patients (100 mg started 7days preoperatively), compared to 989 mL in the placebo group (n = 52, $p > 0.05$). In the RCT by Gavaghan and coworkers[12] blood loss in the aspirin group (325 mg started on the day of CABG, n = 127) was similar compared to the placebo group (n = 708; 732 mL vs 708 mL, $p > 0.05$). Goldman et al[13] reported higher blood loss in the aspirin-treated group (started one day preoperatively) compared to the placebo group. In that RCT, 154 patients receiving 325 mg of aspirin had 965 mL of blood loss, and 155 patients receiving 975 mg had 1,175 mL of blood loss, compared to 805 mL in the 153 patients randomized to placebo ($p < 0.02$ for both comparisons). VKA-treated patients were more likely to cause major and minor bleeding in 68 patients receiving a VKA started on days 3 or 4 postoperatively (4.4% major bleeding and 10.3% minor bleeding), compared to no reported bleeding in the placebo group ($p < 0.01$).[42]

2.0 Prevention of Internal Mammary Bypass Graft Occlusion Following CABG

No study included only patients with IMA bypass grafts, and the data for prevention of IMA bypass graft occlusion following CABG is restricted to subgroup analysis of studies investigating bypass grafting with both venous and arterial grafts.

2.1 Aspirin With and Without Dipyridamole

Individual trials: The VA Cooperative study[7] evaluated the efficacy of aspirin in long-term patency of internal mammary grafts. After receiving 325 mg/d of aspirin for 3 years, IMA graft occlusion rate was 10.3% (8 of 78 patients) vs 7.9% for those treated with placebo (7 of 89 patients, $p = 0.60$). There was also no effect on IMA graft patency when investigators compared aspirin initiated 12 h before with aspirin administered 6 h after surgery.[47]

An RCT[19] evaluated the effect of high-dose aspirin, 1,300 mg/d, plus dipyridamole, 100 mg/d, starting on the first postoperative day, on IMA patency rates at 3 to 6 months in 18 patients with IMA grafts to the left anterior descending artery. At follow-up, overall patency was 98% (44 of 45 IMA grafts remained patent) with no differences between placebo and treatment groups.

Van der Meer and colleagues[48] compared the efficacy and safety of aspirin, aspirin plus dipyridamole, and oral anticoagulant agents on IMA graft occlusion. The investigators assessed graft patency at 1 year in 494 patients who received both IMA and vein grafts. These patients were a subgroup of a prospective, randomized vein graft patency study[48] in 948 patients assigned to treatment with aspirin, aspirin plus dipyridamole, or VKAs. The design was blinded for both aspirin groups, but open-label for VKA treatment. Patients received dipyridamole (5 mg/kg body weight per 24 h IV, followed by 200 mg bid) or VKA (target international normalized ratio, 2.8 to 4.8) before operation, or low-dose aspirin (50 mg/d) after operation. The combined clinical outcomes were myocardial infarction, thrombosis, major bleeding, or death. Occlusion rates of distal anastomoses were 4.6% in the aspirin-plus-dipyridamole group and 6.8% in the oral anticoagulant group, vs 5.3% in the aspirin group ($p > 0.05$). Rates of the combined outcomes were 23.3% and 13.3% in the aspirin-plus-dipyridamole group and the aspirin group, respectively, and 17.1% in the VKA group. Thus, IMA graft patency at 1 year was not improved with oral anticoagulant agents over aspirin plus dipyridamole or low-dose aspirin alone.

Mayer et al[19] performed an RCT in patients with left IMA to the left anterior descending coronary artery. Saphenous vein grafts were used for the left anterior descending coronary artery if the IMA was inadequate and for all other vessels. Patients (n = 174) received either 1,300 mg of aspirin and 100 mg of dipyridamole (po each day) or no drug. Patients returned 3 to 6 months after operation for repeat angiography. Of the 45 IMA grafts in both groups, only 1 IMA graft was occluded and there was no significant difference between the two groups.

Recommendation

2.1.1. For all patients with coronary artery disease who undergo IMA bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (**Grade 1A**).

Remarks: This recommendation reflects that aspirin is indicated in all patients with coronary artery disease, irrespective of its effects on graft patency (see chapter by Harrington et al in this Supplement).[35]

2.2 VKAs

Individual trials: In the study by van der Meer and colleagues,[48] graft patency at 1 year was not different between patients assigned to aspirin plus dipyridamole, low-dose aspirin alone, or oral anticoagulant agents.

Recommendation

2.2. For all patients undergoing IMA bypass grafting who have no other indication for VKAs, we suggest physicians **not** use VKAs (**Grade 2C**).

3.0 Methodologic Considerations for Studies in Patients Undergoing CABG

Data from trials of antithrombotic therapy in CABG are confounded by methodologic limitations. For example, most trials report data on graft patency rather than on important clinical outcomes, such as hospitalizations, recurrent angina, requirements for repeat interventions, myocardial infarction, and death.[14–17,19–22,25,31,39,41] In addition, in most studies[7,11–17,19,21,22,24,30,31,39,41,42] investigators treated the number of patent vessels as independent within patients; for example, a patient with four patent vessels contributed four events to the analysis. Such analysis may violate statistical assumptions of independence and bears the risk of important bias. Future studies should include patient important outcomes and adjust in their analysis for multiple outcomes within patients when appropriate.

Summary of Recommendations

1.0 Prevention of Saphenous Vein Graft Occlusion Following CABG

1.1 Treatment with antiplatelet agents

1.1.1.1. For all patients with coronary artery disease, we recommend aspirin, 75 to 162 mg/d, indefinitely (**Grade 1A**).

1.1.1.2. For patients undergoing CABG, we recommend aspirin, 75 to 162 mg/d, starting 6 h after operation over preoperative aspirin (**Grade 1A**).

1.1.1.3. In patients in whom bleeding prevents the administration of aspirin at 6 h after CABG, we recommend starting aspirin as soon as possible thereafter (**Grade 1C**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding cardiovascular complications and a relatively low value on avoiding bleeding complications.

1.1.2. For patients undergoing CABG, we recommend **against** the addition of dipyridamole to aspirin therapy (**Grade 1A**).

1.1.6.1. For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po (**Grade 1C+**).

1.1.6.2. In patients who undergo CABG for non–ST-segment elevation ACS, we recommend clopidogrel, 75 mg/d, for 9 to 12 months following the procedure in addition to treatment with aspirin (**Grade 1A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding myocardial infarction and a relatively low value on avoiding bleeding complications.

1.1.6.3. For patients who have received clopidogrel for ACS and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

1.2 Treatment with oral anticoagulants

1.2.1. For patients undergoing CABG who have no other indication for VKAs, we suggest clinicians **not** administer VKAs (**Grade 2B**).

1.2.2. For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKAs in addition to aspirin (**Grade 2C**).

2.0 Prevention of Internal Mammary Bypass Graft Occlusion Following CABG

2.1 Aspirin with and without dipyridamole

2.1.1. For all patients with coronary artery disease who undergo IMA bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (**Grade 1A**).

Remarks: This recommendation reflects that aspirin is indicated in all patients with coronary artery disease, irrespective of its effects on graft patency (see chapter by Harrington et al in this Supplement).

2.2 Vitamin K antagonists

2.2. For all patients undergoing IMA bypass grafting who have no other indication for VKAs, we suggest clinicians **not** use VKAs (**Grade 2C**).

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