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SPECIAL ARTICLE
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Intra-operative and post-operative management of conduits for coronary artery bypass grafting: a clinical consensus statement of the European Society of Cardiology Working Group on Cardiovascular Surgery and the European Association for Cardio-Thoracic Surgery Coronary Task Force

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Abstract

The structural and functional integrity of conduits used for coronary artery bypass grafting is critical for graft patency. Disruption of endothelial integrity and endothelial dysfunction are incurred during conduit harvesting subsequent to mechanical or thermal injury and during conduit storage prior to grafting, leading to acute thrombosis and early graft failure. Late graft failure, in particular that of vein grafts, is precipitated by progressive atherogenesis. Intra-operative management includes appropriate selection of conduit-specific harvesting techniques and storage solutions. Arterial grafts are prone to vasospasm subsequent to surgical manipulation, and application of intra-operative vasodilatory protocols is critical. Post-operative management includes continuation of oral vasodilator therapy and selection of antithrombotic and lipid-lowering agents to attenuate atherosclerotic disease progression in conduits. In this review, the scientific evidence underlying the key aspects of intra- and post-operative management of conduits for coronary artery bypass grafting is examined. Clinical consensus statements for best clinical practice are provided, and areas requiring further research are highlighted.

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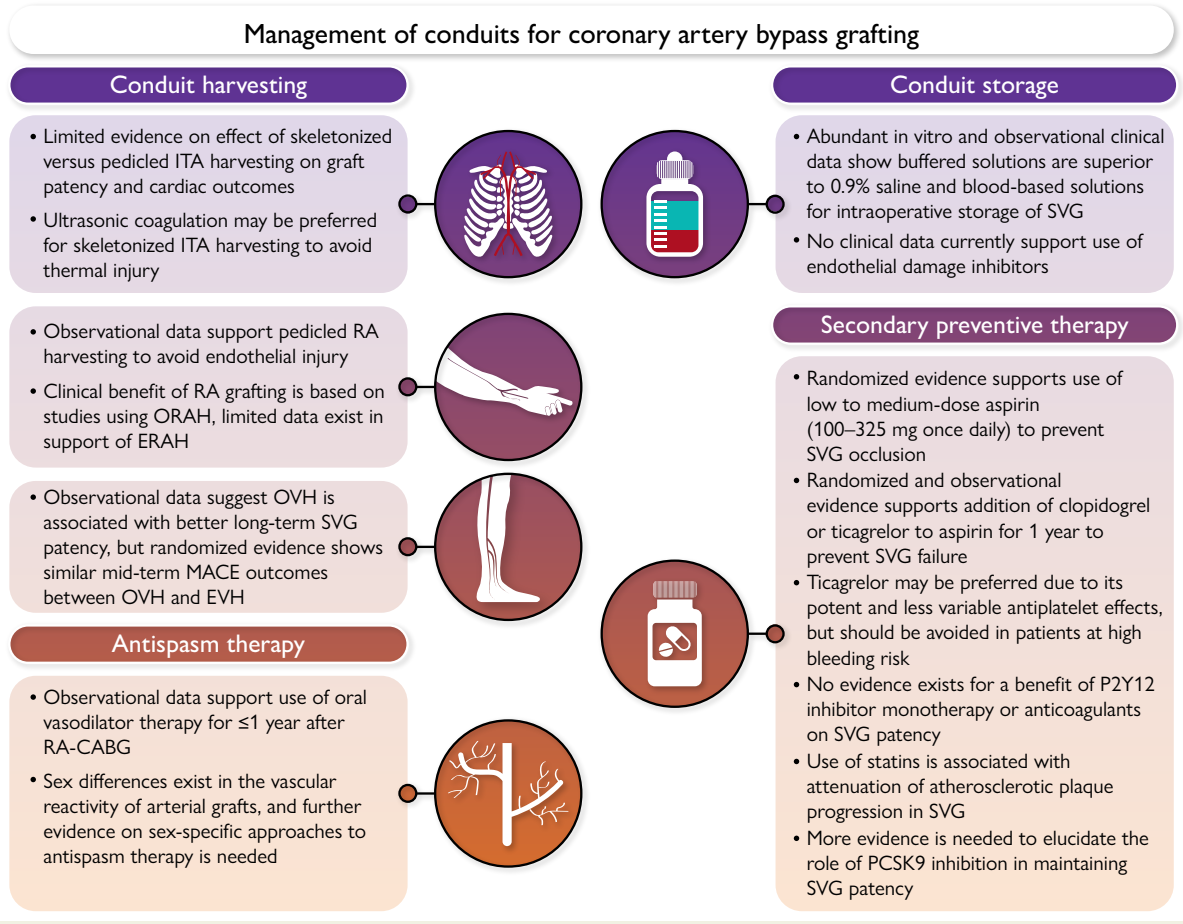
Graphical Abstract



Intra-operative and post-operative management of conduits for coronary artery bypass grafting. CABG, coronary artery bypass grafting; ERAH, endoscopic radial artery harvesting; EVH, endoscopic vein harvesting; ITA, internal thoracic artery; MACE, major adverse cardiac events; ORAH, open radial artery harvesting; OVH, open vein harvesting; PCSK9, proprotein convertase subtilisin/kexin type 9; RA, radial artery; SVG, saphenous vein graft.

Keywords Coronary artery bypass grafting • Internal thoracic artery • Radial artery • Saphenous vein • Harvesting technique • Vasospasm • Graft failure

Introduction

Graft patency is the mechanism for the sustained clinical benefits of coronary artery bypass grafting (CABG). Continued patency of bypass grafts protects against spontaneous myocardial infarction (MI) and reduces the need for repeat revascularization.[1] In the largest individual participant data pooled analysis on graft failure to date [seven randomized clinical trials (RCTs) involving 4413 patients and 13 163 grafts], graft failure was strongly associated with non-fatal cardiac events, as well as mortality after CABG.[2] Graft failure is a multifactorial process that involves acute thrombosis, intimal hyperplasia, inflammation, spasm, and atherosclerosis.[3] Conduit harvesting techniques, intra-operative storage prior to reimplantation into the coronary circulation, and targeted pharmacotherapy therefore represent the key determinants to preserve the structural and functional integrity and, ultimately, the efficacy of CABG conduits. In this clinical consensus statement by the European Society of Cardiology (ESC) Working Group on Cardiovascular Surgery and the European Association for Cardio-Thoracic Surgery Coronary Task Force, we review the scientific evidence and provide best practice statements for the intra- and post-operative management of CABG conduits. We also highlight gaps in knowledge and future research directions.

Mechanisms and consequences of impaired endothelial function

The long-term patency of vein or arterial grafts is highly dependent on the anatomical integrity of the graft *in situ* and the anatomical and haemodynamic characteristics of the target vessel, but also the biology of the graft. The integrity and the biological 'health' of the endothelial layer of the graft are critical factors that determine its early patency given that trauma to the graft during harvesting and storage may lead to disruption of the endothelial layer exposing the subendothelial collagen to the circulating platelets, leading to acute graft thrombosis and failure early after CABG.[3] This mechanism, together with technical

anastomotic issues, lead to slow blood flow through the graft and largely explain the early thrombosis and graft failure observed in ~11% of saphenous vein grafts (SVGs) within the first few weeks post-surgery.[4,5] Beyond these mechanical factors, endothelial dysfunction [related to reduced endothelial nitric oxide (NO) bioavailability] leads to redox dysregulation in the graft wall and triggers pro-inflammatory and pro-thrombotic mechanisms that may result in graft occlusion.[3,6] Indeed, endothelial dysfunction related to clinical risk factors, such as smoking, diabetes or insulin resistance, obesity, and hypercholesterolaemia, is driven by activation of pro-oxidant enzymatic systems in the endothelial cell, such as nicotinamide adenine dinucleotide phosphate oxidases, which generate free radicals like superoxide (O_2-), damaging endothelial cell structures.[7–9] The same redox dysregulation results in oxidative degradation of endothelial NO synthase (eNOS) co-factor tetrahydrobiopterin, which then induces eNOS uncoupling in the graft's endothelial cell, further increasing superoxide generation and endothelial dysfunction.[8,10] On the other hand, late (>1 year) graft failure is often associated with intimal hyperplasia as part of atherogenesis. Clinical risk factors and the graft biology (e.g. redox dysregulation and endothelial dysfunction)[11] lead to proliferation and migration of smooth muscle cells and may also trigger the classic mechanisms of plaque formation, plaque rupture, and late graft failure. Size mismatch, particularly when larger SVGs are grafted to small coronary targets, may predispose to non-laminar flow patterns, which may lead to intimal hyperplasia or graft occlusion.[12] Grafts are also prone to spasm, driven by the imbalance between vasoconstrictors (e.g. thromboxane A2 and endothelin) and vasodilators [e.g. NO, endothelial derived relaxation factor, and prostacyclin (PGI2)] subsequent to endothelial dysfunction. Finally, evidence suggests that maintaining perivascular adipose tissue around the graft [internal thoracic artery (ITA) or SVG] could have a beneficial effect on graft patency,[13,14] given that perivascular adipose tissue secretes a range of vasodilatory agents [e.g. adiponectin and hydrogen sulfide (H_2S)] that could improve endothelial function and the graft's overall redox state.[15,16] An overview of the role of endothelial dysfunction and vascular redox dysregulation in graft failure is shown in *Figure 1*.

Conduit harvesting

Skeletonized vs. pedicled harvesting of arterial grafts

The ITA can be harvested as a pedicled graft (including perivascular fat, veins, and the endothoracic fascia) or as a skeletonized graft (without surrounding tissue). The skeletonized method is technically more challenging, but results in a longer and more versatile conduit that facilitates sequential and composite grafting, and has been shown to improve conduit flow (*Figure 2*).[17–19] Skeletonizing the ITA reduces sternal devascularization[25] and has been associated with lower risk of deep sternal wound infection in non-randomized studies and meta-analyses.[20,21,26] This benefit is especially pronounced in diabetic patients and when harvesting bilateral ITAs.[20,27] Patients with deep sternal wound infection have an increased risk of adverse short- and long-term clinical outcomes, including an increased mortality risk.[28,29] However, recent reports have suggested that the skeletonized technique may result in lower patency rates and worse long-term clinical outcomes than the pedicled technique, probably as a result of mechanical trauma to the ITA during harvesting.[21–23] Limited evidence suggests that semi-skeletonized harvesting[30] may be associated with better results when compared with pedicled harvesting with respect to graft length and flow without increasing operative time, although there are insufficient data to compare the incidence of sternal wound complications or long-term clinical outcomes.[31]

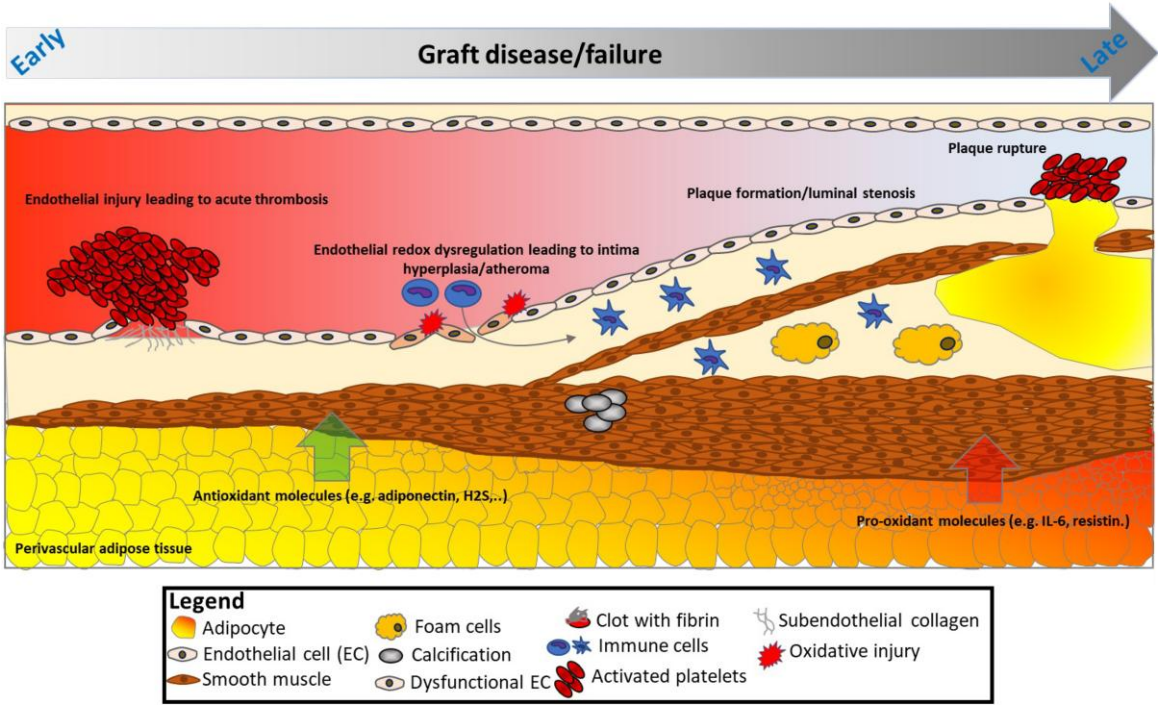


Figure 1 Graft failure: from early endothelial injury to late atherosclerotic plaque formation and rupture

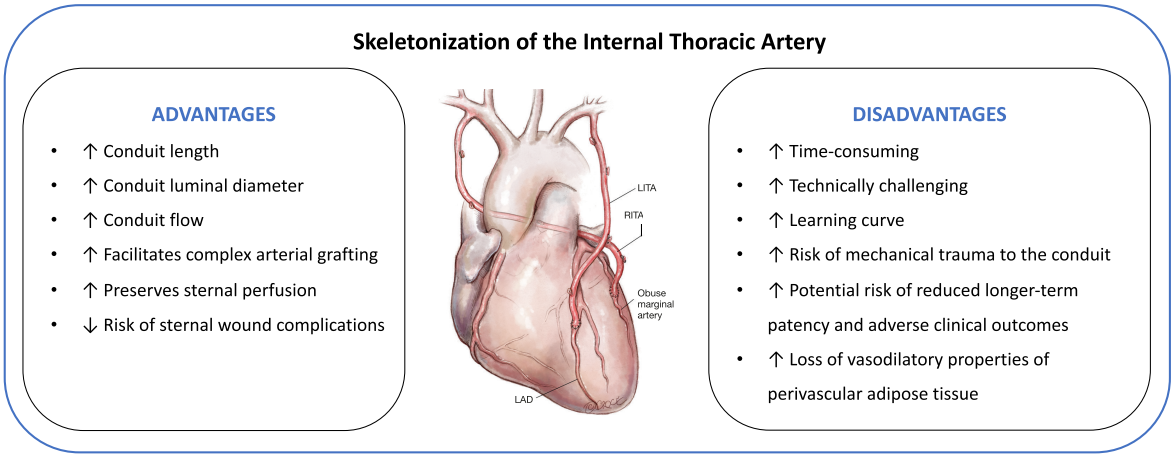


Figure 2 Advantages and disadvantages of the skeletonization technique for internal thoracic artery harvesting. The supporting evidence is based on data from meta-analyses of non-randomized studies and small randomized clinical trials and non-randomized studies.[19–23] LAD, left anterior descending artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery. Image reproduced with permission from Taggart DP *et al.*[24]

While skeletonization of the radial artery (RA) theoretically attenuates potential sympathetic responses and vasoconstriction due to denervation,[32] it does not result in significant added conduit length and is more frequently associated with endothelial damage.[33] When using non-skeletonized RA grafts, incising the RA fascia after harvesting for the entire length of the RA to allow for maximal dilatation and to protect against local constrictive fibrous bands may combine the advantages of both techniques.[32,34] Limited skeletonization for 2–3 cm at the distal and proximal ends of the RA allows maximal dilatation at the anastomotic points and protects against accidental incorporation of any fibrous bands that may distort the anastomosis.[34]

The gastroepiploic artery (GEA) is mainly used to revascularize the distal branches of the right coronary artery and has shown excellent early and long-term patency rates when harvested as a pedicle including omental tissue.[35] As reported for other arterial grafts, skeletonization of the GEA results in larger diameter conduits and may prevent spasm due to arterial denervation and facilitate visual inspection and sequential anastomosis.[36] In observational studies, graft patency of skeletonized GEA conduits up to 4 years after surgery was either similar or superior to that of pedicled GEA conduits.[37]

Electrocautery vs. harmonic scalpel harvesting

Conventional electrocautery enables easy and rapid harvest of the ITA. However, the heat that is transmitted to the artery can injure the endothelium leading to segmental vasospasm.[38,39] Yoshida *et al.*[40] using scanning electron microscopy found nearly complete loss of endothelium on the flow surface of the ITA in the branch orifice area following monopolar cauterization vs. partial loss with bipolar cauterization. Bipolar electrocautery enables precise control of current and avoids random spraying of heat in contrast to monopolar electrocautery.[41]

The harmonic scalpel is an alternative to electrocautery and may be preferred when harvesting the ITA using a skeletonized technique. Ultrasonic coagulation generates lower temperature compared with electrocautery, which reduces thermal-related injuries and tissue charring[42] as well as vasospasm.[43] Isomura *et al.*[43] found that the tissue temperature is <80°C when ultrasonic coagulation is used, while it is >300°C when electrocautery is used. In addition to generating less heat, ultrasonic coagulation produces less surgical smoke and requires fewer surgical clips. Urso *et al.*[44] in a randomized comparison of electrocautery vs. harmonic scalpel harvesting found that the intra-operative mean graft flow was similar with both techniques. Kieser *et al.*[45] in the largest observational series of harmonic ITA skeletonization found no significant differences in the risk of reoperation for bleeding [0.80, 95% confidence interval (CI) −3.20–4.80], ITA damage (0.25, 95% CI −1.10–1.60), sternal wound complications (−0.40, 95% CI −2.80–2.00), or peri-operative MI (0.70, 95% CI −2.60–4.00) compared with electrocautery.

In observational analyses of RA harvesting, harmonic scalpel induced less spasm and intimal injury compared with electrocautery[46,47] and was associated with larger conduit luminal diameter. Nonetheless, no differences in intra-operative graft flow or post-operative graft patency were found.[47]

Open vs. endoscopic harvesting techniques

The effectiveness of the endoscopic technique for SVG harvesting [endoscopic vein harvesting (EVH)] in reducing the incidence of harvesting site complications and post-operative pain, as well as increasing patient satisfaction and mobility relative to the open technique [open vein harvesting (OVH)], is well established[48] and supports the use of EVH as standard of care in patients who are at risk of leg wound complications (*Figure 3*). A pooled analysis of 29 studies (11 919 patients) showed that the odds of wound complications (including abscess, necrosis, dehiscence, drainage, seroma, oedema, and haematoma) were significantly reduced by 71% with EVH compared with OVH [odds ratio (OR) 0.29, 95% CI 0.22–0.37, $P < .00001$].[48] However, patency data for EVH compared with OVH are mixed. Whereas two small RCTs with angiographic follow-up of 3 and 6 months, respectively, did not find a difference in the rate of SVG failure between EVH and OVH,[49,50] observational evidence with longer angiographic follow-up, in particular the non-randomized *post hoc* analyses of the Project of Ex-vivo Vein

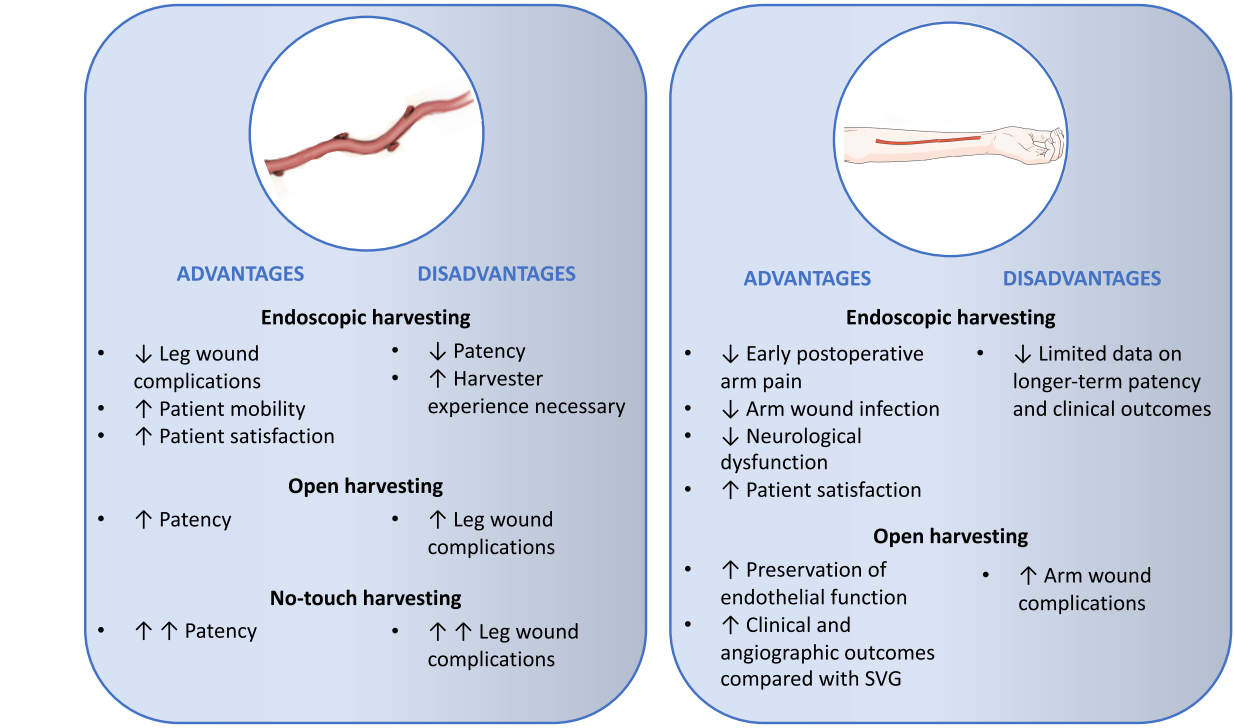


Figure 3 Advantages and disadvantages of harvesting techniques for the saphenous vein (left) and radial artery (right). SVG, saphenous vein graft. Parts of the figure were drawn using Servier Medical Art (smart.servier.com) licensed under a Creative Commons Attribution 4.0 International Licence (https://creativecommons.org/licenses/by/4.0/)

Graft Engineering via Transfection (PREVENT)-IV[51] and Randomized On/Off Bypass (ROOBY)[52] trials, has suggested that EVH is associated with reduced long-term SVG patency.[53] A meta-analysis of 11 studies (18 131 patients) reported lower SVG failure rates with OVH at a mean follow-up of 2.6 years (OVH 17.7% vs. EVH 24.9%, OR 0.61, 95% CI 0.43–0.87, $P = .01$).[54] A meta-analysis that included only studies with angiographic follow-up > 1 year (5 studies, 5235 patients) also reported lower SVG patency with EVH (OR 0.80, 95% CI 0.70–0.91).[55] The Randomized Endovein Graft Prospective (REGROUP) trial[56] did not find a significant difference between OVH and EVH in the risk of the composite of death, MI, or repeat revascularization at a median follow-up of 2.78 years [15.5% vs. 13.9%, hazard ratio (HR) 1.12, 95% CI 0.83–1.51, $P = .47$] that was confirmed at median follow-up of 4.7 years (OVH 23.5% vs. EVH 21.9%, HR 0.92, 95% CI 0.72–1.18, $P = .52$).[57] Importantly, the REGROUP trial did not include angiographic follow-up and specified minimum harvester experience for both techniques, which has been shown to affect SVG quality.[58] In a comparison of OVH vs. EVH performed by experienced (>30/month, >900 total cases) vs. less experienced (<3/month, <100 total cases) harvesters, the incidence of SVG endothelial injury was significantly lower when grafts were procured by experienced harvesters and when using OVH.[58]

The effectiveness of the endoscopic RA harvesting (ERAH) technique compared with open RA harvesting (ORAH) in reducing the incidence of arm wound complications, including infection,[48] haematoma,[48] and incisional pain,[59] is consistent with the benefits of endoscopic harvesting of the SVG (*Figure 3*). However, similarly, there are concerns that ERAH may adversely affect RA patency and cardiac outcomes due to potential mechanical injury to the endothelium. This consideration is particularly important for a predominantly muscular and highly spastic conduit such as the RA. Whereas older studies have reported no difference between ORAH and ERAH,[60,61] a more contemporary organ bath study showed that ORAH was associated with better preservation of endothelial function compared with ERAH.[62] Meta-analyses of observational studies and small RCTs, individually limited by expertise bias, short follow-up, and low statistical power, reported that ERAH was associated with similar 30-day and longer-term mortality and graft patency rates compared with ORAH.[63,64] No adequately powered RCT exists evaluating a strategy of ORAH vs. ERAH on cardiac outcomes. The vast majority of the evidence in support of the efficacy and safety of RA grafting is based on studies that used ORAH. Open radial artery harvesting should therefore currently be considered standard of care.

High-pressure distension

During preparation, the SVG is frequently distended using a handheld syringe to overcome graft spasm and check for leaks. Manual distension leads to intraluminal pressures in excess of 600 mmHg[65] that results in endothelial and medial damage[66] that has been associated with reduced patency rates.[67] Galea *et al.*[68] found that apoptosis was increased in SVGs after distension with 350 mmHg for 2 min. Levels of eNOS remained unchanged in SVGs distended with 100 and 200 mmHg but were significantly lower in SVGs distended with 300 mmHg.[69] Stigler *et al.*[70] showed that distension pressures above 50 mmHg were associated with incrementally increased endothelial cell loss and neointimal proliferation. At 50, 100, and 300 mmHg pressures, endothelial loss levels assessed by CD31 immunostaining were 29%, 54%, and 91%,

respectively. Although only limited data exist, a pressure-controlling syringe may be helpful in preventing excess graft dilatation and subsequent endothelial damage.

No-touch SVG

Mechanism of benefit

Ahmed *et al.*[71] performed multiple studies assessing changes associated with no-touch (NT) compared with conventional (CON) SVG harvesting using discarded segments of human SVGs from the operating room. On light microscopy, endothelial cushions were present in the NT-SVGs while the endothelial surface was flattened with loss of endothelial integrity in the CON-SVGs. In addition, after dilatation, the total wall thickness was typically greater after NT than CON-SVG harvesting.[72] On transmission electron microscopy, the medial smooth muscle cells had a normal appearance in the NT-SVGs but were non-uniform in the CON-SVGs.[71] Others have documented the appearance of markers of smooth muscle cell activation, potential precursors of intimal hyperplasia, in the CON compared with the NT-SVGs.[73] Furthermore, the adventitial layer consisting of connective tissue, fat, vasa vasorum, and perivascular nerves is preserved in the NT-SVGs, while it is removed with CON-SVG harvesting. Studies with and without retention of the surrounding tissue showed partial reduction of distension-induced endothelial injury in the NT-SVGs.[72] The basis for this protective effect may include partial buttressing of the SVG which then limits conduit overdistension. Other possible mechanisms are preservation of eNOS activity, which is highly expressed in the adventitia tissue,[72] and certain adipose specific markers such as leptin and adiponectin which are expressed in the perivascular fat.[74] More recent studies have shown that the phenotype of peri-saphenous and peri-ITA fat has similarities with the perivascular fat of atherosclerosis-prone vessels such coronary arteries or the aorta.[75] Finally, some data suggest that the vasa vasorum of NT-SVGs remain patent unlike with CON-SVGs.[76]

Angiographic and clinical outcomes

A recently published network meta-analysis of 18 graft patency RCTs (6543 patients and 8272 grafts) concluded that graft occlusion was substantially reduced [risk ratio (RR) 0.56; 95% CI, 0.44–0.70] at a mean follow-up time of 3.5 years compared with the CON-SVG and that the NT-SVG and RA were ranked as the best conduits.[77] Tian *et al.*[78] in an RCT that included 2655 patients showed that SVG occlusion on computed tomography angiography (CTA) was significantly reduced for NT-SVG grafts compared with CON-SVG both at 3 months (2.8% vs. 4.8%, OR 0.57, 95% CI 0.41–0.80, $P < .001$) and at 12 months (3.7% vs. 6.5%, OR 0.56, 95% CI 0.41–0.76, $P < .001$). The SWEDEGRAFT registry-based RCT (NCT03501303) compares NT-SVG vs. CON-SVG in 900 patients with a primary endpoint of graft failure on protocol-specified CTA imaging or death at 2 years.[79] To date, there is no convincing evidence for better cardiac outcomes when using the NT-SVG compared with the CON-SVG.[53]No-touch saphenous vein graft harvesting is however associated with a significantly higher risk of leg wound complications (*Figure 3*).[53] Tian *et al.*[78] reported that the NT technique was associated with higher rates of leg wound surgical interventions at 3 months (10.3% vs. 4.3%; OR, 2.55; 95% CI, 1.85–3.52; $P < .001$). Minimally invasive NT-SVG harvesting techniques have recently been described,[80,81] including one approach whereby the NT-SVG is harvested endoscopically with the perivascular tissue intact,[82] thus combining the advantage of endoscopic harvesting with respect to harvest site complications and the improved patency of NT-SVG.

Best practice clinical consensus statements: conduit harvesting	Strength of evidence
• Use the skeletonized technique to harvest the ITA in patients at high risk of sternal wound complications, particularly when harvesting bilateral ITAs	Meta-analyses of non-randomized studies and small RCTs[20,21,26]
• Use an endoscopic SVG harvesting technique in patients at risk of leg wound complications, considering harvester experience	Single large RCT,[56] meta-analyses of non-randomized studies and small RCTs[48]
• Use an open, preferably no-touch, SVG harvesting technique in patients at low risk of leg wound complications	Large RCT,[78] meta-analyses of non-randomized studies and RCTs[54,55]
• Avoid high-pressure distension of SVGs, using a pressure-controlling syringe when possible	Multiple *in vitro* studies[65,70]

Conduit storage

The evidence on the effect of conduit storage solutions is mixed, and data are derived mainly from *in vitro* studies (*Figure 4*). Traditionally, heparinized 0.9% saline or autologous whole blood (AWB) has been used in clinical practice.[83] However, at a pH of 5.5, saline is acidic and has been shown to cause endothelial damage when used as an *ex vivo* storage solution.[84,85] Unlike circulating blood which is under arterial and venous pressure, extracorporeal blood is under atmospheric pressure, which results in loss of partial pressure of CO_2 and causes the pH of blood to rapidly become alkaline. Loss of endothelial and smooth muscle cell viability has been shown to occur even after short-term exposure to slightly alkaline solutions at a pH of 8.0.[86] Whereas some studies have shown less endothelial injury, inflammatory changes, and tissue necrosis with the use of AWB compared with saline,[84] other studies did not find a difference between the two solutions.[87] In functional tests, AWB was superior to saline with regard to contraction and relaxation rates, likely due to improved preservation of vascular contractile and endothelial function.[88–91]

Buffered solutions (such as University of Wisconsin preservation solution, histidine-tryptophan-ketoglutarate, TiProtec, and He solutions) provide better ionic balance and physiological pH, and *in vitro* studies have shown improved preservation of endothelial structural integrity and function compared with both AWB and saline.[92] A *post hoc* analysis of the PREVENT-IV trial showed that use of buffered solutions was associated with lower rates of SVG failure and possibly better clinical outcomes.[93] There is evidence to suggest that AWB may increase the susceptibility of the RA to spasm[94] and a buffered asanguineous solution may be preferred for intra-operative storage of the RA.[32,34]

An endothelial damage inhibitor (EDI) is a buffered solution with antioxidative, radical-scavenging, and eNOS-supporting properties that were developed based on the GALA formulation (reduced glutathione, L-ascorbic acid, and L-arginine).[95] In a small RCT using multidetector CTA, lower mean SVG wall thickness at 12 months was found

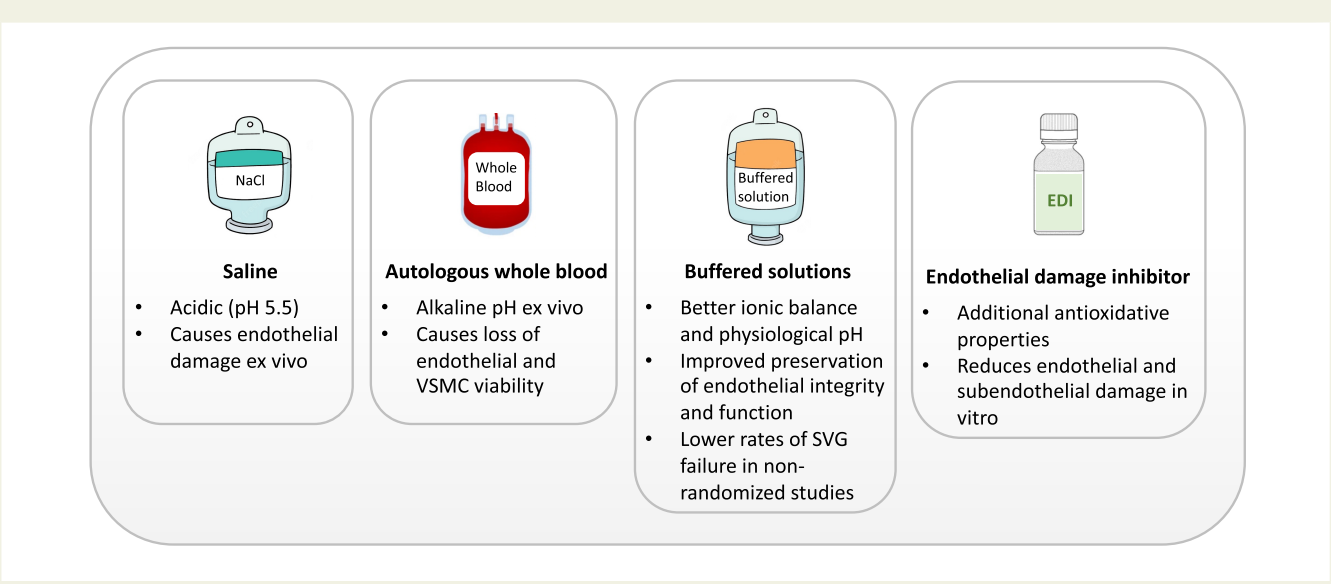


Figure 4 Comparison of solutions for intra-operative conduit storage. SVG, saphenous vein graft

for SVGs treated with EDI compared with saline.[96] Recent *ex vivo* studies using EDI on SVGs[97,98] as well as RA grafts[99] have suggested significant reduction of endothelial and subendothelial damage and reduced levels of reactive oxygen species that correlated with a reduction of hypoxic damage (eNOS and caveolin-1) and significant increase of oxidation-reduction potential when compared with standard buffered solutions[98,99] and saline or AWB.[97] No comparative studies of EDI vs. other buffered storage solutions have been performed with regard to graft patency or clinical outcomes. Use of EDI increases the cost of the CABG procedure.[100]

The temperature of the storage solution is probably important in endothelial protection, but evidence is limited. Bush *et al.*[67] reported that the best protection is achieved at room temperature and 37°C, whereas temperature at 4°C causes separation at the basal membrane and spherical changes in cells.

Best practice clinical consensus statements: conduit storage	Strength of evidence
• Avoid the use of 0.9% saline for intra-operative graft storage	Multiple *in vitro* studies[89]
• Use buffered solutions for storage of SVGs	Large non-randomized study[93]
• Asanguineous solutions for storage of the RA may be preferred to reduce susceptibility to spasm	In vitro study and expert opinion[32,94]

Prevention and treatment of arterial graft spasm

Pathophysiology of arterial graft spasm

The mechanisms of vasospasm in arterial CABG grafts have been described by He and Taggart.[101] Vasospasm may be precipitated by vasoconstrictor substances (spasmogens), which in arterial grafts include endothelium-derived contracting factors (e.g. endothelin-1), prostaglandins (e.g. thromboxane A2), alpha-adrenoceptor agonists (e.g. norepinephrine), and platelet-derived substances (e.g. serotonin), among others.[101] Arterial grafts such as the ITA and RA are predominantly alpha-adrenoceptor vessels with a high constriction responsiveness to norepinephrine. In comparison with the ITA, the RA has higher receptor-mediated contractility to endothelin, angiotensin II, vasopressin, serotonin, and thromboxane A2. Vasospasm in arterial grafts may also be related to endothelial dysfunction.[101] The intact endothelium prevents spasm of the graft by releasing endothelium-derived relaxing factors (e.g. NO and PGI2) which balance vasoconstriction and relaxation in arterial grafts. Whereas the ITA has better endothelial function and releases more NO and other vasorelaxing factors, the RA and GEA have less eNOS expression and require more active pharmacologic interventions.[101] The diameter of the ITA is inversely correlated with its tendency for spasm, suggesting that the distal end of the ITA should not be harvested.[102] Aspirin exhibits vasoconstrictive properties and inhibits arachidonic acid-dependent vasodilator pathways even at low doses (75–300 mg).[103]

Sex-related differences in arterial graft physiology

Radial artery size and flow are smaller in women,[104,105] whereas ITA segments have been noted to be comparable in size between women and men,[106] and both are more likely to be related to body size rather than sex.

Internal thoracic artery endothelial cells in post-menopausal women show impaired expression of messenger RNA for eNOS and reduced eNOS protein levels compared with men,[107] suggesting NO-mediated endothelial dysfunction. This is consistent with the findings of lower levels of vasodilators (including NO) and higher levels of vasoconstrictors in the circulating blood of women vs. men.[108] It is unclear if these differences contribute to function or the propensity for graft spasm in either sex. Sex differences in vascular reactivity, plasma levels of mediators of microvascular tone, and pharmacologic responses have been described and postulated to be related to higher levels of NO or eNOS in younger women due to higher levels of oestrogen.[108]

The presence of oestrogen is postulated to delay cellular senescence by a NO-dependent mechanism, and menopause would thus lead to less NO bioavailability and impaired endothelial metabolism.[107]

Endothelial cyclooxygenase pathway–mediated ITA hypersensitivity to serotonin and to alpha[1]-adrenergic stimuli in women may be a biological mechanism contributing to post-operative ITA graft spasm in women,[109] and excessive ITA graft constriction in women administered catecholamines.[110] *Table 1* summarizes the sex differences in vascular reactivity responses of *ex vivo* ITA segments to mediators of vascular tone.

Vasodilatory protocols

Intra-operative protocols

Papaverine is the most widely used agent for vasodilation of the ITA. Papaverine can either be injected into endothoracic fascia before harvesting or topically applied after harvesting and the ITA covered with a papaverine-soaked gauze.[114] Several studies have shown the beneficial effect on ITA graft flow after periarterial or intraluminal administration of papaverine.[115] Intraluminal papaverine administration may increase vasodilation over topical administration, but it is associated with the risk of intimal injury.[116,117] Sodium nitroprusside has also been shown to be a potent vasodilator when used topically on the ITA, but is less frequently used.[118]

Several RA bath options have been described.[32,119] The most commonly used topical vasodilating agents for the RA in clinical practice are calcium channel blockers (CCBs) and nitrates. In particular, the combined use of verapamil and nitroglycerine is favoured and is more effective at RA vasospasm prevention than when each agent is used individually. A verapamil/nitroglycerine solution better preserves RA endothelial function than does papaverine.[120] For an RA bath including papaverine, a buffered solution such as Ringer's lactate, or heparinized blood at 37° may be used.[34] The phosphodiesterase inhibitor milrinone has a potent vasodilatory effect on the RA and may be used topically in heparinized arterial blood.[32,34]

Post-operative protocols

Patients with RA grafts commonly receive oral antispasm therapy post-operatively, and the CCBs amlodipine and diltiazem are used most frequently[121] (*Table 2*). However, the evidence on the effect of CCB on the RA is inconsistent. A small RCT that assigned 100 patients to either receive or not receive diltiazem for 1 year starting in the early post-operative period showed no difference in clinical or angiographic outcomes at 1 year.[132] Similarly, a *post hoc* analysis of the Radial Artery Patency Study found that among 440 patients with RA grafts, the incidence of string sign (the highest degree of RA spasm) was not associated with patients' compliance with the prescribed post-operative CCB therapy.[133] In a *post hoc* analysis of the RADIAL database that included 732 patients with RA grafts, CCB therapy was associated with a significantly lower risk of major adverse cardiac events (MACE) (HR, 0.52; 95% CI, 0.31–0.89; $P = .02$) and RA occlusion (HR, 0.20; 95% CI, 0.08–0.49; $P < .001$).[134] Calcium channel blocker therapy for 1 year was associated with a greater reduction in the risk of MACE ($P < .001$) and RA occlusion ($P = .006$) than a shorter duration of CCB therapy. A benefit of a longer duration of CCB therapy was not demonstrated ($P = .08$), although the numbers of patients on prolonged CCB therapy was small. After implantation in the coronary circulation, RA grafts undergo remodelling of the vessel wall with a progressive reduction in the muscular component of the media and thus a reduction in the propensity for spasm.[135] This process is completed 1 year post-operatively,[135] suggesting that in clinical practice, the duration of CCB therapy may be limited to the first post-operative year.

It is unclear whether there is a difference in the antispasm efficacy on the RA between amlodipine and diltiazem. In the *post hoc* analysis of RADIAL, use of amlodipine (HR, 0.30; 95% CI, 0.12–0.74; $P = .009$) and diltiazem (HR, 0.20; 95% CI, 0.07–0.51; $P < .001$) was associated with a similar protective effect on the risk of RA occlusion when compared with non-use of CCBs.[134]

It should be noted that chronic CCB use has side effects including headache, tachycardia, flushing, and peripheral oedema. In addition, use of CCB therapy due to its hypotensive effect may preclude the use of secondary preventive medications such as beta-blockers or renin–angiotensin–aldosterone system inhibitors.

An RCT that compared a strategy of 24 h i.v. infusion of nitroglycerine with diltiazem, followed by 6-month treatment with a daily oral dose of isosorbide mononitrate or diltiazem, found no differences in clinical outcomes.[136] Tachyphylaxis may render oral nitrates less effective for continued prevention of RA graft vasospasm, and no evidence exists evaluating their post-operative use with regard to graft patency.

Best practice clinical consensus statements: antispasm prophylaxis	Strength of evidence
• Consider oral calcium channel blockers (amlodipine or diltiazem) for 1 year post-operatively after RA grafting	Non-randomized study[134]

Secondary prevention of graft failure

The mechanism of graft failure is distinctly different between arterial grafts and SVGs. Acute thrombosis and late atherosclerosis are observed predominantly in SVGs, and pharmacological therapy is thus mainly aimed at preventing SVG failure (*Table 2*). The role of pharmacological therapies in optimizing the late patency of arterial grafts is not well characterized.

Antithrombotic therapy

Aspirin

The routine use of aspirin is based on decades-old RCTs demonstrating the benefit of aspirin compared with placebo to prevent SVG occlusion.[122–124] Goldman *et al.*[122] in the largest RCT with angiographic follow-up including 772 patients (Veterans Administration Cooperative Study) found that aspirin significantly decreased SVG occlusion vs. placebo early and at 1 year after CABG (15.8% vs. 22.6%, $P = .029$).[137] A meta-analysis of 17 RCTs that included 1443 patients showed that a low (100 mg) to medium (325 mg) daily aspirin dose initiated within 6 h post-CABG is most effective, without an increase in post-operative bleeding.[124,138] Randomized clinical trials of delayed (≥24 h post-operatively) initiation of aspirin did not find a benefit on SVG patency.[138,139] Low-dose aspirin (75–100 mg daily) appears sufficient as maintenance therapy as it exceeds the minimal effective dose required for platelet thromboxane A2 suppression and overcomes interindividual variability in drug response.[140] More than once-daily dosing may be considered in the immediate post-operative phase after

Table 1 **Summary of published internal thoracic artery and saphenous vein segment vascular reactivity testing in women and men**

Author, year	Conduit evaluated	Vascular reactivity results	Patient age	Endothelium dependent	Cyclooxygenase dependent	NO dependent
Dignan, 1992[106]	IMA segments	• Serotonin (women greater strength contraction) • Norepinephrine (women weaker contraction) • Nitroprusside (women equal relaxation)	50–76 years			
Akar, 2007[111]	IMA segments	• Noradrenaline (no difference) • Vasodilatory effects of levosimendan (K_{ATP} channel opener) greater in men vs. women • Levosimendan vasodilatory effect in men inhibited by blockade of K_{ATP} and K_{Ca} channels in men but not women	Men 44–73 years Women 46–73 years			
Muir, 2010[112]	IMA and SV segments	• Acetylcholine (endothelium dependent) relaxation greater in men vs. women • Nitroprusside (endothelium independent) no difference	Men 29–82 years Women 44–79 years; all post-menopausal			
Mannacio, 2012[107]	IMA segments	• Acetylcholine (women lower maximal relaxation response vs. men)	Men 62 ± 4 years Women 62 ± 4 years; all post-menopausal			
Lamin, 2018[109]	IMA segments	• Serotonin (women increased sensitivity vs. men) • Thromboxane A_2 (no difference) • Nitroprusside (no difference)	Men 66.8 ± 10.4 SD Women 66.6 ± 12.2 SD	Yes—serotonin response	Yes—serotonin response	No—serotonin response
Riedel, 2019[113]	IMA segments	• Norepinephrine (constriction less in women vs. men) • Isoprenaline (women more relaxation vs. men)	Men and Women 48–55 years	Yes—norepinephrine, isoprenaline		Yes—norepinephrine, isoprenaline
Jaghoori, 2020[110]	IMA and SV segments	• Phenylephrine (IMA and SV hypersensitive in women vs. men) • Endothelin-1 (no difference)	Men 67.7 ± 10.5 SD Women 69 ± 10.1 SD; all post-menopausal	Yes—phenylephrine	Yes—phenylephrine	No—phenylephrine

K_{ATP}, adenosine triphosphate-sensitive potassium channel; K_{Ca}, calcium-activated potassium channel; ITA, internal thoracic artery; SV, saphenous vein; NO, nitric oxide.

Table 2 **Therapeutic strategies for preventing arterial graft spasm and graft atherogenesis after coronary artery bypass grafting**

Agent	Mechanisms of action	Time of initiation after CABG and treatment duration	Main study findings	Strength of evidence
Vasospasm prevention				
Amlodipin, diltiazem	Calcium channel antagonist	Treatment duration 1 year	↓ incidence of RA occlusion	Observational[32]
Inhibition of platelet aggregation				
Aspirin	Cyclooxygenase inhibition	Within 24 h (ideally with 6 h) after CABG and continued indefinitely	↓ incidence of SVG occlusion	Multiple RCTs and MAs of RCTs[122–124]
Clopidogrel	Irreversible P2Y12 receptor inhibitor	Variable timing of post-operative initiation; treatment duration 3–12 months	↓ incidence of SVG failure or occlusion Conflicting findings with regard to incidence of major bleeding	Several study-level MA of small RCTs and observational studies[125–127]
Ticagrelor	Reversible P2Y12 receptor inhibitor Pleiotropic effects including attenuation of ischaemia–reperfusion injury, inflammation, and atherosclerosis[128]	Within 48 h after CABG and continued for 1 year	↓ incidence of SVG failure ↑ incidence of BARC types 2, 3, 5 bleeding, no difference in incidence of BARC types 3 and 5 bleeding compared with aspirin alone	Single RCT of 500 patients,[129] study-level MA of RCTs,[125] IPD-MA of RCTs[130]
LDL-C-lowering				
Statins	HMG-CoA reductase inhibition Pleiotropic effect on inflammation	Continued peri-operative treatment to LDL-C target level	↓ progression of graft atherosclerosis	One large RCT[131]

BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; HMG-CoA, hydroxy-methylglutaryl coenzyme A; MA, meta-analysis; RA, radial artery; RCT, randomized clinical trial; SVG, saphenous vein graft.

on-pump CABG. Use of cardiopulmonary bypass promotes post-operative platelet turnover leading to increased synthesis of thromboxane and may reduce early post-operative aspirin efficacy. However, more frequent aspirin dosing must be balanced with an increased risk of bleeding. Based on an association between aspirin dosing and outcomes in a *post hoc* analysis of the Platelet Inhibition and Patient Outcomes Study, low-dose aspirin should be used in patients treated with ticagrelor.[141]

Current clinical practice is to continue antiplatelet therapy life-long after CABG, but evidence in support of a clinical benefit is limited. There is in fact little evidence to support a clinical benefit, as opposed to a graft patency benefit, from aspirin use after CABG.[142,143] Most studies showed no effect on mortality, or even a trend to excess mortality,[124,144] but they were underpowered for small to moderate differences in clinical outcomes and, in particular, in mortality.[125,137,145] However, a pooled analysis of 7 contemporary RCTs with systematic graft imaging (4413 patients, 13 163 grafts) showed that graft failure is strongly associated with adverse cardiac events (adjusted OR 3.98, 95% CI 3.54–4.47, $P < .001$) and mortality after CABG (adjusted OR 2.79, 95% CI 2.01–3.89, $P < .001$),[2] indirectly supporting a potential clinical benefit of aspirin. On the other hand, 1 trial randomized 213 patients 1 year after CABG to continue aspirin 325 mg/day or switch to placebo for the following 2 years and found no difference in the rate of graft occlusion, MI, or death (although the trial was not formally powered and the described power limitations apply).[145]

Dual antiplatelet therapy

Evidence from RCTs and observational studies supports a strategy of dual antiplatelet therapy (DAPT) after CABG to reduce SVG failure. An early meta-analysis of 11 studies (5 RCTs, 6 observational studies) and 25 728 patients showed that aspirin + clopidogrel compared with aspirin was associated with a significantly lower risk of SVG occlusion (RR 0.59, 95% CI 0.43–0.82, $P = .02$), but also with a higher risk of major bleeding events (RR 1.17, 95% CI 1.00–1.37, $P = .05$).[126] A sub-analysis that included 2 RCT (560 patients) showed that aspirin + clopidogrel was associated with a lower risk of SVG occlusion after off-pump CABG. Dual antiplatelet therapy compared with aspirin was associated with a lower risk of 30-day/in-hospital mortality (RR 0.38, 95% CI 0.26–0.57, $P < .001$); there was no difference between the treatment strategies in the risk of angina or MI (RR 0.60, 95% CI 0.31–1.14, $P = .12$).[126] Another meta-analysis of 5 RCTs and 958 patients that compared aspirin + clopidogrel with aspirin also showed an association between aspirin and the risk of SVG occlusion (OR 1.70, 95% CI 1.20–2.40) but not arterial graft occlusion (OR 1.17, 95% CI 0.54–2.56).[146] A network meta-analysis that included 20 RCTs (4803 patients) investigating 9 different antithrombotic strategies showed that the use of either aspirin + ticagrelor (2 RCTs, OR 0.50, 95% CI 0.31–0.79) or aspirin + clopidogrel (7 RCTs, OR 0.60, 95% CI 0.42–0.86) was associated with a lower risk of SVG failure compared with aspirin alone, without significant differences in major bleeding, MI, and death.[125] However, the analyses were likely underpowered to detect small to moderate differences in clinical outcomes. All these study-level meta-analyses were limited by heterogeneity with regard to type and duration of P2Y12 inhibitor treatment, duration of follow-up, and definitions of SVG failure and bleeding.

In an individual patient data meta-analysis of 4 RCTs (1316 patients) that used rigorous re-adjudication of outcomes, aspirin + ticagrelor was associated with a significantly lower incidence of SVG failure compared with aspirin (11.2% vs. 20%; OR 0.51, 95% CI 0.35–0.74; $P < .001$).[130] This finding was consistent for patients undergoing on- or off-pump CABG ($P_{int} = .15$) and for SVG and arterial grafts (including ITA and RA grafts, $P_{int} = .93$). However, patients receiving aspirin + ticagrelor had a significantly increased risk of clinically important bleeding events [Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 bleeding: 22.1% vs. 8.7%, OR 2.98, 95% CI 1.99–4.47; $P < .001$]. Of note, the median treatment duration with aspirin + ticagrelor was 1 year. The specific impact of DAPT on arterial graft patency, particularly in relation to different arterial graft types, has not yet been studied in detail.

These findings highlight the importance of a DAPT strategy after CABG that reduces bleeding risk while retaining its efficacy in reducing SVG failure. Platelet-driven thrombosis is the predominant mechanism of early SVG failure and typically occurs during the first month after surgery,[147] providing a biological rationale for intensified antiplatelet therapy in the first month after CABG. The 1-month DAPT with ticagrelor in coronary artery bypass graft patients (ODIN) trial (NCT05997693) is an investigator-initiated prospective, randomized, international, multicentre trial that is designed to compare the effect of treatment with ticagrelor in addition to low-dose aspirin for 1 month vs. aspirin alone on the 1-year incidence of ischaemic events and graft failure among patients with chronic coronary syndromes undergoing CABG.[148] ODIN will also inform whether short-term DAPT provides a net clinical benefit in this patient population. The Ticagrelor-based De-escalation of Dual Antiplatelet Therapy after Coronary Artery Bypass Grafting (TOP-CABG) trial (NCT05380063) will investigate whether de-escalation of DAPT (ticagrelor + aspirin) to aspirin monotherapy after 3 months is non-inferior to DAPT for 12 months in reducing SVG occlusion and superior in reducing bleeding events.

No randomized head-to-head comparison of ticagrelor vs. clopidogrel (on a background of aspirin) for SVG patency exists. Ticagrelor has a rapid onset and offset of action and provides faster, more powerful, and predictable platelet inhibition than clopidogrel.[149] Clopidogrel has a variable interindividual response, with approximately one-third of patients having inadequate platelet inhibitory effects. Importantly, such patients who continue to have high platelet reactivity despite use of clopidogrel are at increased risk of thrombotic events.[150] Clopidogrel may be preferred when ticagrelor is not available, not tolerated or contraindicated, and in patients at high bleeding risk.

P2Y12 inhibitor monotherapy and anticoagulant therapy

Current evidence does not support P2Y12 inhibitor monotherapy as an alternative to aspirin after CABG.[129,151,152] When pooling individual patient data from the two RCTs investigating the effect of ticagrelor monotherapy, ticagrelor was not associated with a significant difference in the risk of SVG failure compared with aspirin, although the point estimate favoured ticagrelor monotherapy (OR 0.86, 95% CI 0.58–1.27).[130] In a substudy of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, the factor Xa inhibitor rivaroxaban either alone or in combination with aspirin did not reduce the 1-year incidence of graft failure compared with aspirin alone (rivaroxaban vs. aspirin: 7.8% vs. 8.0%; OR: 0.95, 95% CI: 0.67–1.33; $P = .75$; rivaroxaban + aspirin vs. aspirin: 9.1% vs. 8.0%; OR: 1.13, 95% CI 0.82–1.57; $P = .45$).[153]

Lipid-lowering therapy

In patients with clinical atherosclerotic cardiovascular disease (ASCVD), including those with a history of CABG, high-intensity statin

therapy is guidelines recommended with the aim of achieving a ≥50% reduction in LDL cholesterol (LDL-C) to reduce the risk of cardiovascular events.[154] The magnitude of the benefit of high-intensity statins is similar among women and men,[155,156] although high-intensity statins remain underused in women. Elevated LDL-C levels are associated with atherosclerotic plaque progression in SVGs.[157] In addition to lowering LDL-C, statins are also known to have pleiotropic effects, improving endothelial function, NO levels, and antioxidant function, as well as inhibiting inflammatory response, vasoconstriction, thrombosis, and platelet aggregation.[158] Several studies have examined the effect of statins on graft patency.[131,159,160] The Post Coronary Artery Bypass Graft (Post CABG) trial showed that aggressive (target LDL-C < 85 mg/dL) compared with moderate (target LDL-C < 140 mg/dL) lowering of LDL-C using lovastatin decreased obstructive changes in CABG grafts by 31% at >4 years of follow-up.[131] In a non-randomized *post hoc* comparison of participants on statin therapy in the Clopidogrel after Surgery for Coronary Artery Disease trial, 12-month graft patency as assessed by coronary angiography was higher in those with LDL-C levels < 100 mg/dL than in those with LDL-C levels > 100 mg/dL (96.5% vs. 83.3%, $P = .03$).[161] The ACTIVE trial, comparing a strategy of 10 mg (moderate-intensity) vs. 80 mg (high-intensity) atorvastatin, did not find a difference in the incidence of SVG occlusion at 1 year; however, the trial was limited by small sample size and high rate of protocol violations, with approximately one-third of patients in each arm discontinuing the assigned treatment over the course of the study.[160]

More recently, circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) has been shown to induce macrophage activation and vein graft lesion development via LDL receptor-independent mechanisms,[162] representing a potential target for pharmacologic intervention. A small cross-sectional study from China (231 patients) showed a significant association between circulating PCSK9 levels and the presence of SVG disease at >1 year after CABG.[163] The Effect of Evolocumab on Saphenous Vein Graft Patency Following Coronary Artery Bypass Surgery (NEWTON-CABG) trial (NCT03900026) will examine the effect of the PCSK9 inhibitor evolocumab vs. placebo in addition to statin therapy for 24 months on SVG disease (defined as significant stenosis ≥ 50% or total occlusion) on protocol-specified CTA or earlier clinically indicated coronary angiography.

Best practice clinical consensus statements: secondary prevention of graft failure	Strength of evidence
• Initiate aspirin (100–325 mg once daily) within 6 h post-operatively to reduce the risk of SVG occlusion	Meta-analysis of RCTs[124]
• Consider clopidogrel or ticagrelor in addition to aspirin in the first post-operative year in patients who are not at high bleeding risk to reduce the risk of SVG failure, irrespective of the use of cardiopulmonary bypass	Study-level and individual participant data meta-analyses of RCTs[125,130]
• Use high-intensity or maximally tolerated statin therapy to reduce LDL-C and the risk of SVG disease progression	Large RCT[131]

Future research directions

Several gaps in our knowledge remain with respect to intra-operative and post-operative management of conduits, and further research is urgently needed to address these.

- Randomized studies are needed comparing skeletonized and pedicled ITA harvesting to determine how these techniques affect ITA graft patency and post-operative cardiac outcomes.
- Further studies are needed to evaluate the effect of ERAH on cardiovascular and patient-reported outcomes, given that the majority of randomized trials demonstrating superiority of the RA over the SVG have used ORAH.
- Further research is needed to investigate potential relative clinical benefits of available storage solutions and address cost-effectiveness.
- The role of oestrogen in arterial graft physiology remains unclear. Outcomes following CABG are worse in women (pre- and post-menopausal) compared with men and have been noted to be significantly worse in younger women.[164] Clarification of pathways that are influenced by the levels of oestrogen will be important for future therapeutics. Sex-specific management of arterial conduits should be a focus of future research.
- Randomized studies are needed to evaluate the efficacy of continued oral antispasm therapy in patients with RA grafts.
- Low-grade systemic inflammation is a more powerful determinant of recurrent cardiovascular events and death than LDL-C in patients with stable ASCVD.[165] The clinical benefit of targeted inflammation inhibition has been shown in particular for low-dose colchicine.[166] Given the pro-inflammatory mechanisms implicated in graft failure subsequent to endothelial injury, further studies are needed to determine whether patients after CABG would benefit from the addition of these pharmacotherapies to reduce the risk of graft failure.

Summary

Preserving the structural and functional integrity of the conduit during graft harvesting and storage, prevention and treatment of vasospasm, and attenuating atherogenesis are integral to graft patency and the clinical benefits of CABG. The best practice clinical consensus statements outlined in this document provide a comprehensive, evidence-based approach to the intra-operative and post-operative management of conduits for CABG surgery. These strategies can serve as a valuable resource for multidisciplinary heart teams, facilitating more informed and effective treatment planning tailored to individual patient needs and local practices.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

This document is submitted following review and approval by the ESC Scientific Documents Committee (SDoC). The declarations of interests review is handled by the respective oversight body according to the section 6.3.3 'DOI review' of the ESC Scientific Documents policy.

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