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Dual antiplatelet therapy after coronary artery bypass grafting: Do we have a consensus?

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Abstract

Coronary artery bypass grafting (CABG) remains the gold standard treatment in patients with complex multivessel coronary artery disease (CAD). Reversed long saphenous vein is the most commonly used conduit despite the known early thrombotic failure and low long-term patency rate. Post-operative antiplatelet therapy is an established treatment to improve graft patency and also a secondary treatment of the underlying native CAD.

Aspirin has traditionally been the first line therapy; however, aspirin resistance especially in the early period after CABG, has been reported over the years and as a result, the use of dual antiplatelet therapy (DAPT) has become more common. However, there is limited evidence about the effect of DAPT and duration of use after CABG on graft patency, clinical outcomes (such as bleeding and myocardial infarction), and survival. The optimal dose of aspirin when given in DAPT is unclear and the duration of DAPT in association with quality of life is unknown.

Furthermore, a better understanding of the pathology of vein graft disease and how available drugs influence it, could lead to the development of customised therapy for cohorts of patients undergoing CABG with potential benefits to early and long term outcomes. Here we review the available evidence on the routine use of DAPT after CABG.

Coronary artery bypass grafting (CABG)

Ischaemic heart disease (IHD) is the main leading cause of death in the world, with 7.4 million deaths in 2012 [1,2]. Coronary artery bypass grafting (CABG) is the gold standard intervention in patients with complex multivessel disease [3]. In the UK, there are about 25,000 CABG operations performed annually [4] and the majority of these operations is carried out on patients over 70 years of age [5]. Demand for CABG is likely to increase considerably in the future as a result of rapidly ageing populations [6] and increased expectations of patients and surgeons to expand their indications for surgery.

During the early years of coronary surgery, saphenous vein grafts (SVGs) were the only conduits used [7]. Over the years different arterial conduits were introduced with variable degree of success [8-10]. Contemporary data on international use of grafts are available from the SYNTAX trial that included 1541 patients who underwent CABG at 85 sites in 18 countries between 2005 and 2007 [11]. The SYNTAX trial confirmed that the long saphenous vein (LSV) graft, is the most used conduit for multivessel revascularisation, despite its known low early and late patency rates.

The underlying mechanism behind vein graft disease is multifactorial and can include conduit trauma/graft thrombosis (within 1 month, early failure), activation of intimal hyperplasia associated with harvest and implantation into the arterial high-pressure system (1 to 12 months, intermediate failure), superimposed atherosclerosis (beyond 12 months, late failure) [12-15]. A prospective cohort study of 1,388 patients carried out between 1969 to 1994, in which patency was assessed using coronary angiograms, reported the rates of vein grafts occlusion of 10-25% in the first year, 1-2% each year in the first 5 years and 4-5% subsequently up to 10 years [16].

Intimal hyperplasia reduces the lumen of bypass grafts which leads to reduced flow and can ultimately result in graft occlusion. Intimal hyperplasia is defined as the abnormal migration and proliferation of smooth muscle cells with associated deposition of extracellular matrix in the intimal layer of the vein graft [17-20]. The pathophysiological triggers for intimal hyperplasia have been classified as injury, inflammation, and haemodynamic factors [21,22]. The "traumatized" endothelial surfaces of vein grafts are particularly sensitive to platelet and fibrin deposition, leading to early thrombosis or the subsequent development of neointimal hyperplasia and ultimately the establishment of atherosclerosis [23].

Prothrombotic genetic variations among CABG population that contribute to aspirin resistance (when aspirin is given as monotherapy) and increased risk of cardiovascular events may also lead to early vein grafts failure; however, the mechanism is not clearly understood. These genetic variations involve various genes including: (1) a polymorphism on the cyclooxygenase-1 (COX-1) gene affecting Ser529; (2) overexpression of COX-2 mRNA on platelets and endothelial cells; (3) polymorphism PLA1/A2 of the gene encoding glycoprotein IIIa (GPIIIa); and (4) the homozygous 807T (873A) polymorphism allied with increased density of platelet GP Ia/IIa collagen-receptor gene [24]. It has been reported that in Chinese population, allele frequencies

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of P2Y1 893T and 1622G were 3.5 and 30.6%, respectively and these candidate genes were chosen on the basis of their impact on platelet physiology and aspirin mode of action [25], hence it is an important factor to that may influence risk of early or late vein graft disease. Carriers of these genetic polymorphisms may be resistant to the antithrombotic effects of aspirin and should be considered for DAPT to lower the risk of vein grafts occlusion [24].

Aspirin monotherapy

Aspirin exerts antiplatelet effects by inhibiting the production of thromboxane, which under normal circumstances binds platelet molecules together to create a patch over damaged walls of blood vessels [26].

Aspirin is classified as class IA treatment (consistent Level I Studies or a systematic review SR or meta-analysis MA) recommendation post CABG based on the American College of Cardiology/American Heart Association guidelines [27]. It is now known that long term aspirin therapy in patients with coronary artery disease (CAD) reduces the risk of death, myocardial infarction and stroke [28] and prevents ischaemic complications [29]. A meta-analysis of placebo-controlled aspirin trials, including more than 125 000 patients in a variety of clinical settings, found a 3% absolute reduction ischemic events (cardiovascular death, MI or stroke) associated with aspirin therapy (RR 1⁄4 22%) [30].

There are many studies showing variability in the baseline response to aspirin using a variety of ex vivo, laboratory based, assays of platelet function including bleeding time [31], platelet aggregability [32], flow cytometric analyses of markers of platelet activation [33], classical platelet aggregometry [34,35] and point-of-care assays [36].

Most studies reported variable degrees of aspirin resistance, reaching as high as 90% in the early period after surgery but fading out by 6 months after surgery [37,38]. A randomised control trial (RCT) of 420 Chinese patients randomised to off pump coronary artery bypass grafting (OPCAB) vs. optimal medical therapy, reported high on-aspirin RPR (residual platelet activity) after OPCAB (OR = 4.5; 95% CI, 1.8-11.1); 15.7% on day 4, 4.6% on day 10 and 0% at 6th month post-surgery. It was suggested that this is associated with a transient effect related to genetic polymorphism in the gene (TBXA2R-924TT) [39].

It is well known that aspirin resistance is common, although reported prevalence varies widely from less than 1% to 61% in CABG cohorts [40,41] and it is an independent factor for vein graft occlusion within 6 months of surgery. It is unclear if aspirin resistance is a result of a transient surgery related effects (e.g. the use of cardiopulmonary bypass) or from mixed transient and/or permanent genetic polymorphisms. The frequency of prothrombotic genetic polymorphisms that lead to aspirin resistancein the CABG population and their effects on the mechanism leading to vein graft occlusion is unknown.

Furthermore, aspirin was reviewed by Dunning *et al.* [42] for the optimal dose when given as a monotherapy after CABG and the recommended dose is 325 mg [42]. Nevertheless the dose of aspirin in practice has been variable (ranges from 75 mg to 325 mg per day). However there is no standard recommendation for the dose of aspirin when given in DAPT and also there is no agreed duration of aspirin treatment after CABG.

Dual antiplatelet therapy (DAPT)

Although aspirin is the antiplatelet drug of choice after CABG, the second most commonly prescribed drug is clopidogrel (a thienopyridine). Clopidogrel works by irreversibly inhibiting a receptor called P2Y12, an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. Clopidogrel requires biotransformation into active metabolites and this step is dependent on genes encoding the cytochrome P40 system (specifically CYP2C19), which may suggest a degree of insensitivity or resistance, if it used as antiplatelet monotherapy following CABG [43,44]. The usual dose for clopidogrel is 75 mg daily. Other thienopyridines like prasugrel, ticlopidine (trade name Ticlid), and newer thienopyridine antiplatelet agents (such as Ticagrelor, a nucleoside analogue) are also available but they are 3-4 times more expensive than clopidogrel.

The evidence for DAPT use post CABG is limited to aspirin and clopidogrel. The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, recommended the use of clopidogrel after CABG only in case of aspirin intolerance, because there are no long-term RCTs comparing the efficacy of clopidogrel plus aspirin versus aspirin alone on graft patency in association with clinical outcome [45]. In a specific group of CABG patients, however, the 2013 NICE guidelines recommended continuing with DAPT for up to 12 months in a specific groups of CABG patients (those who had STEMI and received CABG) [46].

A recent meta-analysis compared the efficacy of aspirin alone versus aspirin and clopidogrel after CABG on the risk of graft occlusion, adverse cardiovascular events, and 30 day mortality, included five RCTs and six observational studies, with a total of 25,728 patients, of whom 18,558 patients were treated with aspirin alone and 6160 with a combination of aspirin and clopidogrel [47]. The five RCTs evaluated graft patency using coronary angiography or multi-slice computerized tomography. There was variation in the loading dose of aspirin administered in each study and the time of administration post-operatively (6-48h). Daily doses of aspirin were 81, 100 or 325 mg orally for a year. Clopidogrel was given at a standard dose of 75mg for a year. The result of this meta-analysis showed that DAPT after CABG reduced the risk of saphenous vein graft occlusion compared with aspirin alone (risk ratio (RR)=0.59, 95% CI 0.43–0.82) and there was no significant heterogeneity observed in the pooled group of studies (p=0.56). There was no effect of DAPT on arterial graft patency (give RR and 95% CI). In the same meta-analysis, data regarding major bleeding episodes was available from six studies including 18,090 patients. Major bleeding was defined as substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding which required transfusion of more than two units of blood. DAPT was associated with increased risk of bleeding (RR 1.17, 95% CI 1.00–1.37). Furthermore, DAPT therapy appeared to be most beneficial in patients undergoing OPCAB (two observational studies and one RCT [48-50] RR 0.29, 95% CI 0.11–0.72) [47].

A second meta-analysis published in the same year [47] including the same five RCTs [47] reached similar conclusions; DAPT with aspirin and clopidogrel reduced the risk of vein graft occlusion compared with aspirin alone (RR=0.59, 95% CI 0.43–0.82). In contrast, arterial grafts did not benefit from this intensified therapeutic approach (OR 1.17, 95% CI 0.54-2.56). DAPT was associated with a 1.6% risk increase of major bleeding [51].

The influence of DAPT use after CABG on progression of native CAD was assessed recently in a secondary analysis of data from a RCT of 113 patients receiving aspirin plus clopidogrel or aspirin plus placebo for 1 year after CABG. 92 patients who underwent preoperative and 1-year postoperative angiograms had each of their coronary stenoses

graded serially by using 6 thresholds (grade 0 [0%-24%], grade 1 [25%-37%], grade 2 [38%-62%], grade 3 [63%-82%], grade 4 [83%-98%], and grade 5 [99%-100%]). At 1-year postoperatively, there were 103 evolving (94 worsened, 9 improved) and 22 new lesions. The right coronary artery territory and sites proximal to a graft were more commonly associated with worsening coronary artery disease ($P \leq 0.02$). There were no differences in clinical events between treatment groups, and the proportion of patients with evolving or new lesions was also similar (70% versus 74%, aspirin–clopidogrel versus aspirin–placebo, respectively; P=0.8). However, in evolving or new lesions, the mean grade change (1.1 ± 1.0 versus 1.6 ± 1.1, respectively; P=0.01) and the proportion of new occlusions were lower in the aspirin and clopidogrel group (7% versus 22%, respectively, P=0.02) [52].

Limitations of all the above-mentioned meta-analyses and secondary analysis [47,51,52] are that they included studies that they included highly heterogeneous studies comparing differing designs. Almost all studies included in the meta analyses looked at graft patency, but there are few or no data on clinical outcomes such as myocardial infarction, survival or quality of life. Furthermore, these studies do not provide any data regarding long-term major/minor bleeding risk and the data are insufficient to recommend an optimal dose of aspirin or the duration of DAPT therapy after CABG.

On contrary, a secondary analysis of the ROOBY trial (a multicentre RCT, on-pump *vs.* off-pump [53]), investigated the use and timing of clopidogrel post CABG on 12 months on graft patency (arterial and venous), assessed by angiography. Of a total of 2,203 patients undergoing CABG, 953 patients (43%) had DAPT with aspirin and clopidogrel. This study demonstrated that there was no difference in graft patency (86.5% *vs*. 85.3% respectively, p=0.43) [54].

Therefore, we can only extrapolate from the evidence available on patients with coronary artery disease undergoing PCI. In essence, CABG and PCI patients have the same underlying coronary pathomorphology, despite the fact that they are managed with deferent interventions. A recent meta-analysis of 10 RCTs (n=32 287) compared risks of short term (<12 months) or extended (>12 months) DAPT versus the standard of 12 months therapy, following PCI with drug eluting stents [55]. Short term DAPT use was associated with a significant reduction in major bleeding when compared with prolonged DAPT use (odds ratio 0.58 95% confidence interval 0.36 to 0.92). A shorter DAPT duration yields fewer bleeding events than a longer DAPT duration with comparable efficacy against ischemic complications. However, alonger DAPT duration yields a marked reduction of thrombotic complications at the price of increased bleeding rates [55]. The current recommendation is for 12 months duration of DAPT after drug eluting stent implementation as a compromise between ischaemic and bleeding risks [55]. However, although we can extrapolate from the PCI population with regards to the impact of DAPT on bleeding, we can't extrapolate with regards to the impact on ischaemic outcomes, since studies have shown that stent thrombosis has a greater effect on short-term and long-term mortality than graft occlusion [56]. Definitive trials are needed to determine the effect of DAPT on clinical outcomes and quality of life in the CABG population, and define the optimal thrombotic-bleeding risk balance in the CABG population.

Conclusion

Antiplatelet therapy plays a crucial role in the postoperative treatment of CABG patients. With evidence of single drug resistance and variable degree of biotransformation, there is a strong ground for the routine use of DAPT after CABG. Aspirin should remain the first line therapy with clopidogrel as second choice.

There are still significant gaps in our knowledge base regarding early graft thrombosis resulting from transient aspirin resistance, the effect of antiplatelet therapy on clinical outcomes such as bleeding, myocardial infarction and survival.The optimal dose of aspirin when given in DAPT is unclear and the duration of DAPT in association with quality of life is unknown.

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