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The percutaneous treatment of Ischaemic heart disease: Risks, complications and perioperative considerations

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Abstract
Ischaemic heart disease (IHD) is a pathological condition caused by stenosis of the coronary arteries. The condition leads in insufficient oxygen and nutrient delivery to the heart muscle (myocardium). Cardiologists and scientists are endeavoring to translate experimental knowledge into effective, innovative treatments for IHD. The prevention of 'stent thrombosis' is at the forefront of clinical research and is one area of interest currently undergoing rapid growth in Australia and internationally. This paper will attempt to elucidate the pathology and aetiology of IHD. Furthermore, an examination of the use of balloon angioplasty (PCI) to treat IHD will be made. The introduction of bare metal stents (BMS) and drug-eluting stents (DES) ushered in a period of excitement for interventional cardiologists around the world. The pros and cons of BMS and DES use, as well as the risks associated with discontinuation of antiplatelet therapy, have not been fully elucidated. Through the critical evaluation of a range of diverse scientific literature, it is hoped that an overview of the current status of this important area of medicine is achieved.

Keywords: ischaemic heart disease (IHD), bare metal stents (BMS), drug-eluting stents (DES)

Introduction

The Pathophysiology of Ischaemic Heart Disease

The heart is an aerobic organ (i.e. the myocardium depends almost completely on aerobic metabolism) and relies on the oxidation of substrates for the generation of energy [1]. As a result, the heart requires a continuous supply of oxygen. Coronary blood flow is closely coupled to oxygen carrying capacity [2]. The oxygen content of coronary venous blood is low, permitting little additional oxygen extraction, and oxygen reserves in the heart are generally considered to be low [2, 3]. Changes in myocardial oxygen balance lead to rapid alterations in coronary vascular resistance. For example, occlusion of a coronary artery for less than one second leads to an increase in coronary blood flow above baseline immediately following release of the occlusion [2]. This response is called coronary reactive hyperaemia, and it ensures that the myocardium is adequately perfused during perturbations to flow, such as occur during contraction of the ventricle and peak systolic pressure. The coupling of cardiac metabolism with coronary vascular resistance is associated with known mediators, including adenosine, nitric oxide (NO), prostaglandins, and carbon dioxide [3]. However, dysfunction of vasodilators and chemoreceptor ligands, as well as thrombosis, plaque formation and other 'occlusive events', all lead to varying degrees of IHD [3-5].

Ischaemic heart disease is characterised by oxygen deprivation (hypoxia or anoxia) and a concomitant reduction in the clearance of metabolites from the myocardium. Pathologically, IHD is defined as an imbalance between myocardial oxygen supply and demand [1-3]. Ischaemic heart disease may manifest clinically as anginal pain, and pathologically as ST-segment deviation on an electrocardiogram (ECG), a reduced uptake of radioisotopes including thallium 201 or technetium 99 in myocardial perfusion images, and regional (local) or global (general) impairment of ventricular function [4-6]. Myocardial ischaemia can occur as a result of increased myocardial oxygen demand, reduced myocardial oxygen supply, or a combination of both.

Classically, in the presence of coronary artery obstruction, an increase in myocardial oxygen requirements caused by exercise, stress or tachycardia (rapid heart rate) leads to an episode of transitory imbalance (demand ischaemia); this condition is responsible for most episodes of chronic stable angina (CSA) [5]. In other cases, however, the imbalance is caused by acute reduction of oxygen supply resulting from increased coronary vascular tone (pathologic or idiopathic coronary vasospasm) or by a discernible reduction in coronary flow as a result of platelet aggregation, atherosclerosis or thrombosis. Obstruction to flow is called supply ischaemia; this condition is responsible for myocardial infarction (MI) and most episodes of unstable angina (UA) [4]. Often, however, ischaemic symptoms result from both an increase in oxygen demand and a reduction in supply, that is, a metabolic supply vs. demand mismatch.

The impairment of endothelial function that occurs in atherosclerosis also plays an important role in the subsequent development of IHD [6]. When associated with coronary artery stenosis, the loss of endothelium-dependent vasodilation leads to myocardial ischaemia [4]. Although "plaque fissuring" or rupture with platelet aggregation and thrombus formation is characteristic of UA and MI, constriction of the coronary vasculature is mediated by the response of atheromatous vessels to products of platelet aggregation and thrombosis, especially serotonin and histamine, which are released from aggregating platelets in conditions of sheer stress. Patients with IHD and complex plaques/lesions thus have augmented release of serotonin and other inflammatory mediators into the coronary circulation resulting in constriction [5]. Furthermore,

patients with recent UA or MI show evidence of endothelial vasodilator dysfunction in the infarct-affected artery that is more evident than in vessels with stable stenoses [4].

Balancing the Risks and Benefits of Stents in the Treatment of Ischaemic Heart Disease

'Stenting' or PCI is an interventional approach used in the treatment of IHD to reopen blocked or narrowed coronary arteries. In the procedure, a guidewire is threaded through a blood vessel (usually the femoral artery) until it reaches the heart; from here, the guidewire may be placed in the lumen of the artery of interest. After the guidewire has been satisfactorily positioned, a balloon is inflated to open up the vessel. A stent is then placed which ensures that the vessel remains patent. Stents are small, wire-mesh tubes that help prevent restenosis (secondary blockage). The two basic kinds of stents are the BMS and the DES [5]. BMS are, as the name suggests, made of metal. BMS act as simple scaffolding to maintain the patency of blood vessels after PCI. In the process of healing, when tissue grows around the stent, fibrous tissue in the arterial lining increases the risk that the artery will undergo restenosis; this condition requires repeat treatment known as revascularisation [7].

Indeed, DES were developed to address this problem [8]. Many DES are coated with Sirolimus (an antimitotic agent or immune suppressant) or similar medication that is slowly eluted to inhibit the proliferation of fibrous tissue and smooth muscle migration in the arterial lining [9, 10]. However, patients who have a DES still need to take aspirin (an anti-inflammatory agent that acts as a cyclic oxygenase inhibitor) and clopidogrel (an ADP receptor antagonist) or other suitable thienopyridine, for example ticlopidine, for at least 12 months to prevent thrombosis [9]. Both aspirin and the thienopyridines are antiplatelet drugs that reduce the chance of thrombus formation within the stent. This treatment is essential because thrombosis can result in MI or death [6].

The use of DES can significantly reduce the rate of restenoses and target vessel revascularisations (TVR) compared with BMS [9]. Stent thrombosis is a complication that occurs less frequently than restenosis, but it is associated with greater morbidity and mortality [11, 12]. Data indicates that the occurrence of late stent thromboses caused by delayed endothelialisation or hypersensitivity reactions may be more likely with the use of DES [13]. Late stent thrombosis is defined as onset between seven and 18 months after stent implantation [14]. Recent advances in surface modification of biodegradable-polymer drug-eluding stents (BP-DES) have been shown to enhance biocompatibility, and thus address the risk of thrombosis associated with first-generation DES [27, 28]. Data to date shows BP-DES to be effective and safe for use in clinical practice [29, 30], although there is no significant evidence to say that BP-DES reduces the incidence of major adverse cardiovascular events including thrombosis and MI when compared with first generation DES [30].

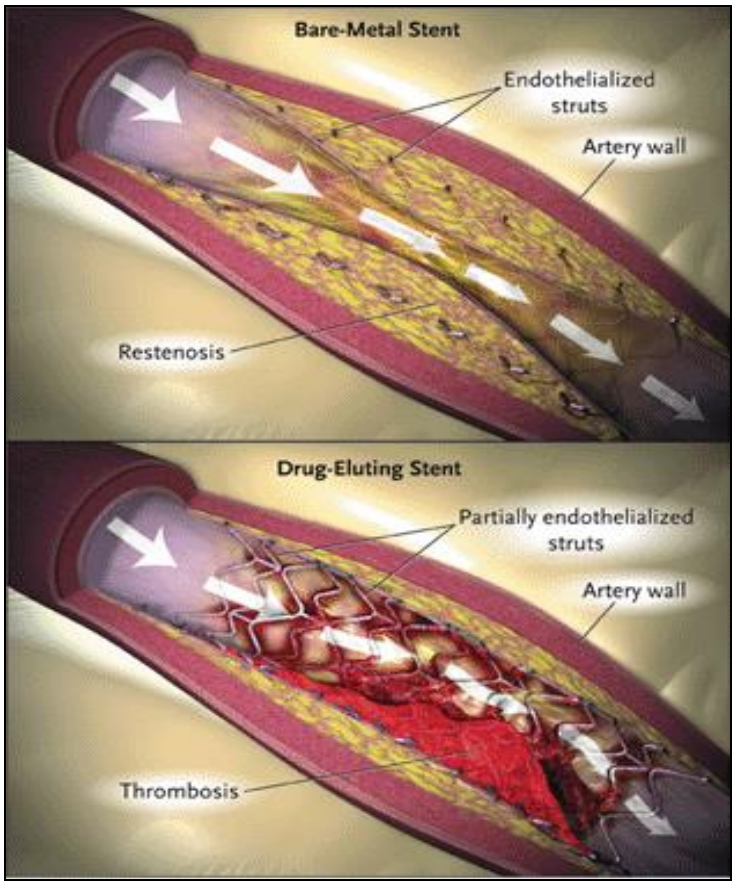

Fig 2: Potential complications of coronary stenting: restenosis in a traditional BMS and late thrombosis in a DES. Arrows indicate blood flow [14].

Concerns have been raised in multiple trials conducted over a period of many years with regards to the increased morbidity

and mortality in certain subgroups of patients treated with PCI, when compared with Coronary Artery Bypass Graft (CABG) surgery [15-18]. Diabetes, in particular, has been shown to be a predictor of adverse events following PCI or CABG. Given the high rate of diabetes in patients IHD, this is not insignificant. Until recently, this data was comparing traditional BMS with CABG [19]. The SYNTAX trial [20] examined the impact of diabetes on 5-year outcomes after PCI with drug eluding stents and CABG. The conclusion was that PCI resulted in higher rates of cardiac death and revascularisation procedures at 5-years, and although is a treatment option for patients with less complex lesions or fewer co-morbidities, CABG should be the revascularization option of choice for higher-risk patients. This conclusion is also supported by the CARDia trial [21].

Discontinuation of Antiplatelet Therapy after DES Implantation

The BASKET-LATE (Basel Stent Kosten Effektivitäts Trial) trial showed for the first time in a prospective randomised study that the incidence of cardiac death or MI after discontinuation of clopidogrel was higher among subjects with DES implantation than among those with BMS implantation [22, 23]. Late clinical events occurred during the entire follow-up period after withdrawal of clopidogrel (after 15-362 days). Compared with BMS-treated subjects, there was a persistent increase in the cumulative event rate over the entire observation period following DES implantation [22]. Contemporary studies have focused on the pathophysiological basis of late stent thrombosis after DES implantation [24, 25]. Indeed, DES-treated subjects had less endothelialisation and a more frequent occurrence of thrombi than BMS-treated subjects three to six months after PCI [24]; this finding is supported by other published data [14, 26].

Delayed endothelialisation after DES implantation has been shown to lead to late stent thrombosis and related MI or death [13, 31]. A consecutive series of 746 patients with 1,133 stented lesions, surviving 6 months without major events, were followed for one year after the discontinuation of clopidogrel [22]. Patients were assigned randomly 2:1 to DES versus BMS in the BASKET-LATE trial. The primary focus of this study was cardiac death and MI. It was found that rates of 18-month cardiac death or MI were not different between DES and BMS patients [22]. However, after the discontinuation of clopidogrel (between months seven and 18), these events occurred in 4.9% of cases after DES implantation versus 1.3% after BMS implantation. Furthermore, TVR remained lower after DES, resulting in similar rates of all clinical events for this time period (DES 9.3%; BMS 7.9%).

Moreover, late stent thrombosis and related death or MI was twice as frequent after DES versus BMS (2.6% versus 1.3%). The study concluded that after the discontinuation of clopidogrel, the benefit of DES in reducing TVR is maintained but has to be balanced against an increase in late cardiac death or MI, events associated with late stent thrombosis [22, 32]. The increased risk of haemorrhage and the high cost of prolonged dual-antiplatelet therapy are also important considerations in the treatment of IHD patients after PCI [33]. Efforts are being made to implement new treatment regimens in the area of antiplatelet therapy (34), with developments in stent technology, such as BP-DES, as well as modifications in the dose and action of stent antimitotic medications.

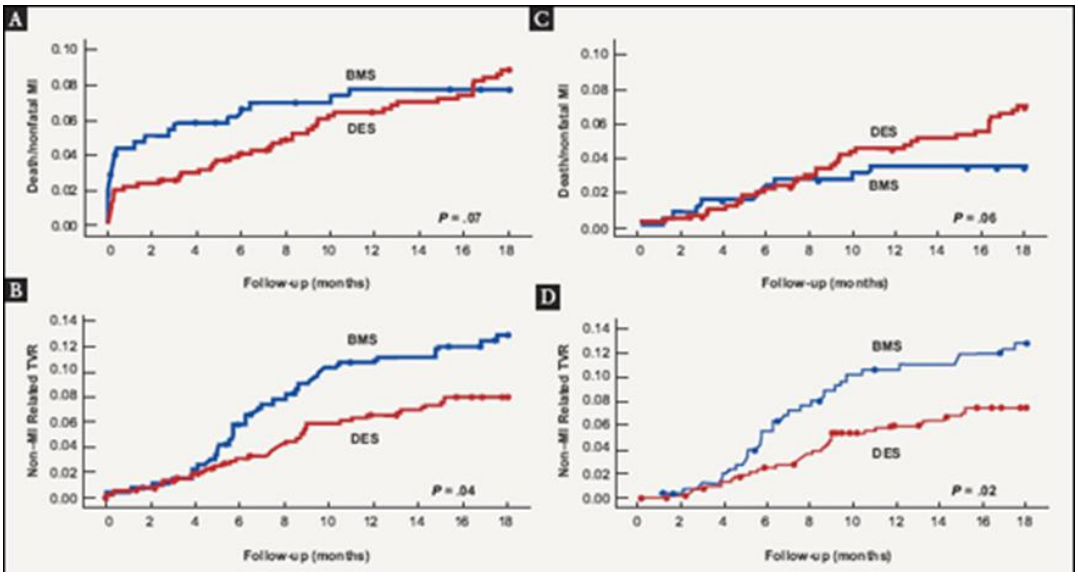

Fig 2: Cardiac death/myocardial infarction (MI) and restenosis-related target vessel revascularizations (TVR) after drug-eluting (DES) versus bare-metal stent (BMS) implantation. Comparison of the occurrence of cardiac death/nonfatal myocardial infarction (MI) (A and C) and the need for "restenosis-related" target vessel revascularization (TVR; B and D) after DES (red) versus BMS (blue) implantation. Note that in this graph, the initial 30-day events that are not related to drug-eluting properties of the stents are included (A and B; period 0 to 18 months) or disregarded (C and D; period 1 to 18 months). (Reprinted from Pfisterer M, Brunner-La Rocca HP, Buser PT, *et al.*, for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol.* 2006; 48[12]:2584-2591 with permission from American College of Cardiology Foundation). (Pfisterer *et al*. 2006).

The inhibition of the $P2Y_{12}$ pathway by clopidogrel is associated with a marked reduction in platelet activity. Recent

reports have shown that $P2Y_{12}$ inhibition has anti-inflammatory effects as well [35, 36]. The dual effects of clopidogrel and aspirin are associated with a marked reduction in platelet activity; this is the main mechanism through which dual antiplatelet therapy exerts its clinical benefits [22, 37]. These positive outcomes may also be attributed in part to the fact that many patients have very high platelet reactivity despite being treated with aspirin; these patients, the so-called "low responders", have a higher risk of ischaemic events [23]. Studies also indicate that clopidogrel has anti-inflammatory properties [35, 36, 38]. By nullifying platelet reactivity and inflammation, both of which contribute to atherothrombotic disease, clopidogrel decreases the incidence of sudden cardiac death and non-fatal MI. Even with DAPT, high inter-individual variability in the clinical response to clopidogrel means that certain groups do not achieve an appropriate level of anti-platelet activity [39]. Population models based on recent data are being developed with the aim optimising clopidogrel dosing on an individual basis [40].

A number of plausible explanations for the platelet hyperactivity rebound phenomenon associated with cessation of clopidogrel have also arisen from recent studies [25], including a weakened response to aspirin after cessation of clopidogrel due to a loss of antiplatelet synergism with aspirin [41], platelet sensitization to ADP from long-term clopidogrel use resulting in increased platelet activity [42, 43], an increase in biomarkers of inflammation resulting in a pro-inflammatory state and increased local vascular inflammation [25], or a combination of all of the above factors. Studies are now looking at the optimal method of clopidogrel discontinuation. There is some evidence that tapering clopidogrel results in significantly lower platelet aggregation at two weeks post cessation, when compared with abrupt discontinuation [44], although no significant difference in cardiovascular complications or bleeding at 90-days [45].

Recent meta-analyses have found that there is evidence that extension of dual antiplatelet therapy (DAPT) after PCI may increase the risk of bleeding without reducing ischaemic events or improving mortality [46-51]. There was no significant difference in outcomes between ≤6 months of DAPT and ≥12 months of DAPT in patients with coronary artery disease and DES implantation. There was some suggestion that extended DAPT ≥12 months should be considered for patients with very high ischaemic risk, and/or low bleeding risk [46]. The standard duration of DAPT has been 12 months following an index event, after which patients would withdraw clopidogrel and maintain aspirin indefinitely [52]. However, more recent data has shown an increase in bleeding events despite no reduction in overall mortality with prolonged DAPT [53], and the latest guidelines recommend a six month duration of DAPT for those at high bleeding risk and 12 months for those at high ischaemic risk, with re-evaluation at both of these points to consider a longer duration of DAPT [53].

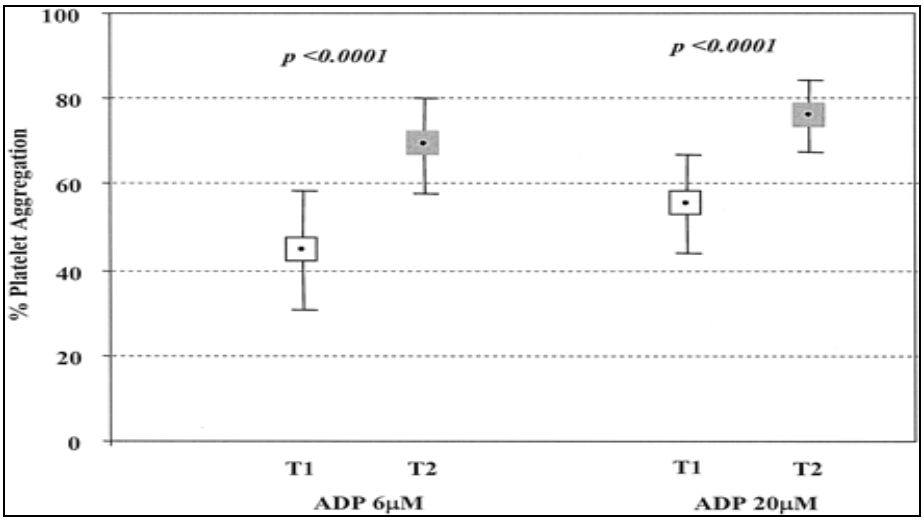

Fig 3: Platelet aggregation in six and 20 µmol/l ADP-stimulated platelets before (T1: patients on aspirin and clopidogrel) and 1 month after (T2: patients only on aspirin) clopidogrel withdrawal. Data are expressed as percentage of maximal platelet aggregation (means ± SD) [22].

The increased risk of ischaemic events and stent thrombosis should be weighed against the reduced risk of bleeding events when considering discontinuation of anti-platelet therapy prior to cardiac and non-cardiac surgery in individual patients (53). Studies have shown that patients on antiplatelet therapy undergoing various surgical procedures may not be at significantly increased risk of bleeding when compared with no antiplatelet, or interrupted antiplatelet therapy (54-57). Antiplatelet therapy is not considered to be an absolute contraindication to early surgery in the acute orthopaedic setting (57, 58). Current recommendations are that if the agents are to be discontinued, clopidogrel should be suspended for five days prior to surgery.

Conclusion

The prompt reperfusion of ischaemic myocardium following coronary artery occlusion is one of the bastions of clinical cardiology for the treatment of coronary artery disease. Ischaemic heart disease is characterised by oxygen deprivation and a reduction in the clearance of metabolites from the myocardium, i.e. an imbalance between myocardial oxygen supply and demand. For patients undergoing PCI, current recommendations are to base the duration of DAPT on risk of bleeding versus risk of thrombosis. Studies suggest that DES

implantation has a tendency towards late thrombosis a year or more after implantation. In spite of this, the use of DES can significantly reduce the rate of restenoses and TVR compared with BMS. While this complication is infrequent, it is associated with high morbidity and mortality. In the short term, up to 18 months' duration, cardiac death or MI rates do not differ significantly between DES and BMS patients. However, among patients who receive a DES in the setting of an acute myocardial infarct, clopidogrel is often prematurely discontinued, which markedly increases subsequent mortality. Ongoing improvements with BP-DES show promise to reduce the complication of late thrombosis associated with clopidogrel withdrawal in DES. Nevertheless, more research needs to be undertaken to examine the efficacy of new treatment regimens in the area of antiplatelet therapy. The prevention of late stent thrombosis should focus on further developments in stent technology, including the application of bioabsorbable stents and more effective stent medications.

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