New antiplatelet agents and prosthetic heart valves

Sir,

Despite advances in prosthetic valve design, patients who undergo valve replacement are at risk of arterial thromboembolism and valve thrombosis. We present four cases where new antiplatelet agents have been used.

A 61-year-old man with aortic valve endocarditis underwent early mechanical valve replacement. He developed mitral regurgitation and an aortic-right-atrial fistula requiring surgical closure and mitral valve replacement. He had a persistent sternal wound infection with a sinus. After four operations, his sternum was finally reconstructed. He then presented with epistaxis secondary to high INR and an ischaemic right leg. He was diagnosed with *Candida* endocarditis, an aortic pseudoaneurysm and a large intrathoracic haematoma. He underwent an aortic root repair and femoral embolectomy. In view of post-operative haematoma and persistent pseudoaneurysm, he was not anticoagulated. He was maintained on aspirin 150 mg once daily and clopidogrel 75 mg once daily for 2 months. Warfarin was restarted subsequently and he is well 17 months later.

Aged 3 months, a boy underwent surgery for a VSD and truncus arteriosus with a composite homograft conduit in 1982. In 1996, he developed increasing tricuspid regurgitation and underwent a St Jude valve replacement. His target INR was 3.5–4.5. In 1997 he had erratic anticoagulation control; his warfarin was stopped for 4 days and he was admitted with prosthetic valve thrombosis and an INR of 2.0. He was treated with tissue plasminogen activator and unfractionated heparin, and made a good recovery. His target INR was increased to 4.0–4.5 and aspirin 150 mg daily added. He suffered a further prosthetic valve thrombosis in 2001, with an INR of 2.4, and was treated with tissue plasminogen activator. He was unable to tolerate dipyridamole and so was maintained on clopidogrel 75 mg daily, aspirin 150 mg daily and a target INR of 4.0–4.5. He is well 8 months later.

A 55-year-old lady who had a mitral valve replacement 4 months previously, presented with 3 weeks of breathlessness. Transthoracic echocardiography demonstrated a dilated left atrium, no paraprostatic mitral regurgitation, but a prolonged pressure half-time compared to that post-operation. Transoesophageal echocardiography showed an echogenic mass attached to the mitral valve replacement. Blood cultures were negative. A diagnosis of prosthetic valve thrombosis was made, and surgery was offered but declined. With an INR of 2.6, she received 50 mg of tissue plasminogen activator followed by a standard loading dose of 0.25 mg/kg of abciximab and 12 h infusion at 125 μg/kg/min. Repeat echocardiography at 24 h showed a 50% increase in the mitral valve area and marked symptomatic improvement. Aspirin 75 mg daily was added, and the target INR set at 3–4. Three weeks later, breathlessness returned and transoesophageal echocardiography showed a recurrent large mobile thrombus. Urgent valve replacement was undertaken, and histology revealed pannus formation with adherent organized thrombus.

A 78-year-old man presented with confusion and a subdural haematoma. Ten years earlier, he had had a Starr-Edwards mitral valve prosthesis inserted. His target INR was 2.5–3.5. Following neurosurgical opinion, conservative therapy was recommended; anticoagulation was discontinued and reversed with intravenous vitamin K. He was managed with clopidogrel 75 mg and aspirin 75 mg daily without warfarin for 3 weeks. His symptoms resolved, and repeat CT scanning demonstrated haematoma resolution. Warfarin was restarted, he was discharged and was well at 3 months.

Anticoagulation reduces the risk of thromboembolic events, but introduces the risk of severe or fatal bleeding, and may be contra-indicated in some patients. Antiplatelet agents are not as effective as warfarin, but do reduce thromboembolic risk when used with warfarin. The use of the new antiplatelet agents clopidogrel and abciximab in patients with prosthetic valves has not been described previously. These cases demonstrate their potential, but further studies are required to find their position in routine management.

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References

Reducing cholesterol and atherosclerosis: the importance of cellular adhesion molecules?

Sir,

We agree with the statement in the recent Editorial\(^1\) that even modest changes in LDL-cholesterol, using various lipid-lowering regimens, have significant effects on the incidence of clinical coronary events. We also agree that the improvement of cardiovascular end points is not fully explained by the reduction in LDL-cholesterol levels, and that statins may have other useful mechanisms of actions. Although it is mentioned that these include inflammatory responses and effects on plaque stability, there is no direct reference to the increasing evidence that suggests that statins have effects on the cellular adhesion molecule pathway. Cellular adhesion molecules may play an important role in the development of cardiovascular disease. However, the inconsistency of the results in some instances may be due to small sample sizes, differences in sample storage, selection, gender and/or ethnic group of participants.\(^2\)

In a recent study, we looked at large numbers of male and female individuals from different ethnic backgrounds taken from a population study.\(^3\) There were significant gender differences in all of the adhesion molecules measured apart from Vascular Cellular Adhesion Molecule-1 (sVCAM-1). Furthermore, people of first-generation Black African origin living in England have significantly lower levels of Intracellular Cell Adhesion Molecule-1 (sICAM-1), sVCAM-1 and sP-selectin, but not sE-selectin, than Whites living in the same area.\(^3\) Moreover, associations with known risk factors are adhesion-molecule-specific. These factors clearly need to be taken into account in future studies along with sample size and patient selection, and results from one population cannot be readily extrapolated to other groups.\(^2\)

The importance of serum lipids on the cellular adhesion molecule pathway is becoming increasingly apparent. Individuals with hypertriglyceridemia have higher levels of the sICAM-1 and sVCAM-1.\(^4\) HDL-cholesterol inhibits cytokine-induced expression of endothelial cell adhesion molecules. The oxidation of LDL can up-regulate the expression of adhesion molecules either directly, or indirectly, by amplifying the release of cytokines and oxidation of LDL enhances its uptake by monocytes.\(^5\)–\(^7\) Moreover, in our study there were strong associations between serum lipids and adhesion molecule levels.\(^3\)

Statins inhibit the synthesis of cholesterol, reduce cardiovascular morbidity and mortality and modulate several inflammatory mechanisms involved in the atherosclerotic processes.\(^7\) Atorvastatin treatment leads to a decrease in E-selectin levels\(^8\) and sP-Selectin, sICAM-1 and sE-Selectin levels are reduced following fluvastatin treatment.\(^9\) However, studies with pravastatin indicate that although it may not reduce adhesion molecule levels,\(^10\) it may be important in determining plaque stability rather than formation, as it increases the collagen content and decreases lipid content, inflammation, metalloproteinases and cell death in human carotid plaques.\(^11\) Thus different statins may have different actions.

Ethnic differences in serum lipid levels may influence the cellular adhesion pathways and provide a potential mechanism for the ethnic difference in CHD risk. Increased understanding of the underlying mechanisms and how their modification may vary in different individuals, particularly those of different ethnic origins, and how they may vary according to the drug used is therefore required to improve treatment regimens.

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References