Background

Coronary artery bypass graft surgery (CABG) is the most durable approach for the treatment of ischemic heart disease [1], with >400,000 procedures performed annually in the United States alone [2]. Despite the increasing application of arterial conduits during CABG, the saphenous vein remains the most common conduit, employed for more than 70% of grafts [3]. However, saphenous vein graft (SVG) disease presents an important clinical problem. Even with aggressive medical therapy [4-11], up to 15% of vein grafts occlude in the first year after bypass surgery. Between 1 and 6 years, the graft attrition rate is 1% to 2% per year, and between 6 and 10 years it rises to 4% per year. By 10 years after surgery, only 60% of grafts are patent and only 50% of patent vein grafts are free of significant stenosis. In addition, native coronary artery disease progresses in 5% of patients annually [12-15]. Reflecting the graft and native vessel attrition, this population is at high risk for subsequent ischemic events, including death, myocardial infarction (MI) and stroke [14]. Further revascularization, either reoperation or percutaneous coronary intervention, is required in 4% of patients by 5 years, 19% of patients by 10 years and 31% of patients by 12 years after the initial bypass surgery [3,16].

The process of SVG disease is composed of three mechanistically interlinked stages: thrombosis, intimal hyperplasia, and atherosclerosis [13,14,16-18]. Early graft thrombosis can occur at the time of surgery secondary to focal endothelial disruption [19,20]. Grafts that survive this early period develop a progressive thickening of the media that begins within days after implantation. This process, termed intimal hyperplasia, is a consequence of smooth muscle cell proliferation and extracellular matrix protein synthesis [21,22]. Platelets play a fundamental role in the process of smooth muscle cell proliferation and intimal hyperplasia [23,24]. Intimal hyperplasia is present in all grafts 1 month after implantation [25] and forms a template for the development of superimposed atherosclerotic changes [17,18]. With the passage of a sufficient period of time, the thrombotic occlusion of vein grafts is almost inevitable due to progressive atherosclerosis [17].

Despite its established benefit in patients with coronary artery disease, aspirin therapy has numerous limitations. It is a relatively weak antiplatelet agent and has no effect on thrombin, which is believed to play a major role in acute coronary syndrome [26]. Even with aspirin therapy for secondary prevention, a large number of recurrent events occur [27]. A significant proportion of patients undergoing CABG may be aspirin resistant, defined as undetectable platelet inhibition after one week of therapy [28,29]. Depending on the population studied and the specific definition of aspirin resistance, anywhere from 10–40% of patients appear to have an inadequate antiplatelet response to aspirin [28,30]. Such patients appear to be at increased risk for the development of vascular events. In theory, these aspirin-resistant patients may derive particular benefit from additional antiplatelet therapy [31].

Clopidogrel is a thienopyridine antiplatelet agent that inhibits ADP-dependent platelet activation and aggregation [32]. Sevenfold more potent than ticlopidine, clopidogrel is free of its adverse side effects such as neutropenia, diarrhea and rash [33]. Unlike aspirin [24,34], clopidogrel has been shown to inhibit the process of platelet-mediated intimal proliferation and smooth muscle hyperplasia in laboratory experiments. In a cell culture model, clopidogrel significantly inhibited platelet adhesion to immobilized fibrinogen and also inhibited platelet-dependent mitogenic signaling and DNA synthesis in cultured coronary artery smooth muscle cells [35]. Similarly, in animal thrombosis models, clopidogrel but not aspirin significantly inhibited platelet-mediated intimal proliferation and smooth muscle hyperplasia [33,36]. Furthermore, the combination of clopidogrel with aspirin led to potent synergistic antithrombotic effects and a decrease in myointimal proliferation compared to either therapy alone [24,36,37].

Several large clinical trials have demonstrated that clopidogrel reduces ischemic events and mortality in patients with coronary and vascular disease [38-41]. In the CAPRIE (Clopidogrel versus Aspirin in Patients with Ischemic Events) trial, clopidogrel (75 mg/day) was demonstrated to be significantly more effective than aspirin (325 mg/day) in preventing vascular thrombotic events (ischemic stroke, MI or vascular death) in patients with clinical evidence of atherosclerotic disease (clopidogrel 9.78% vs. aspirin 10.64%, relative risk reduction [RRR] 8.7%, $p = 0.045$) [38]. In patients presenting with acute coronary syndromes, the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) study demonstrated that the combination of clopidogrel and aspirin was more effective at reducing the primary outcome (cardiovascular death, nonfatal MI or stroke) compared to aspirin alone (clopidogrel and aspirin 9.3% vs. aspirin alone 11.4%, RRR 20%, $p < 0.001$) [40]. Subgroup analysis from these trials suggested that patients that underwent surgical revascularization also benefited from clopidogrel [39,42,43]. However, no trial to date has prospectively evaluated the combined effects of clopidogrel plus aspirin on saphenous vein graft disease after CABG.

There currently exists a clinical equipoise regarding the optimal antiplatelet therapy for patients who have undergone coronary artery bypass surgery. While some