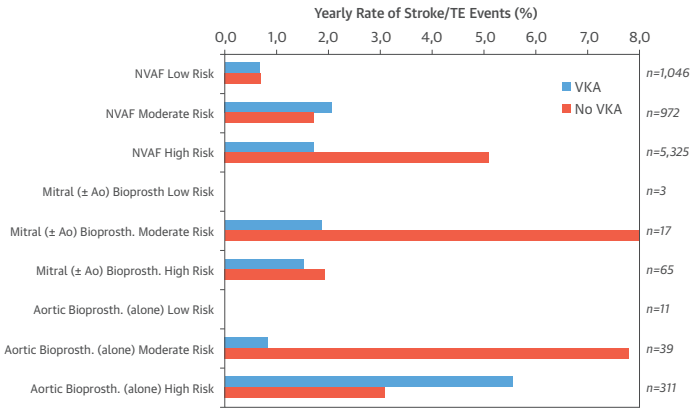
FIGURE 1 Yearly Rate of Thromboembolic Events in AF Patients



Low risk: CHA_2DS_2-VASc 0 in males, 1 in females; moderate: 1 in males, 2 in females; high: >1 in males, >2 in females. Ao = aortic; AF = atrial fibrillation; NVAF = nonvalvular atrial fibrillation; VKA = vitamin K antagonist.

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Effects of P-Selectin Antagonist Inclacumab in Patients Undergoing Coronary Artery Bypass Graft Surgery

SELECT-CABG Trial

Despite unprecedented advances over the last few decades, saphenous vein graft (SVG) failure remains a major concern following coronary artery bypass graft (CABG) surgery (1), and since contemporary treatment options are limited in these patients, there is an unmet need for novel therapeutic concepts. Early evidence to support the adhesion molecule P-selectin as a potential therapeutic target was provided by different animal models of vascular inflammation (2,3), as well as phase I clinical studies (4). The recent SELECT-ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Segment Elevation Myocardial Infarction) trial then demonstrated the efficacy of inclacumab, a human monoclonal antibody directed against P-selectin, in reducing myocardial damage following percutaneous coronary intervention in patients presenting with acute coronary syndromes (5). The SELECT-CABG (Effects of P-Selectin Antagonist Inclacumab in Patients Undergoing Coronary Artery Bypass Graft Surgery) trial was therefore designed to assess the effects of inclacumab on SVG disease assessed by quantitative coronary angiography 1 year after CABG surgery.

Between December 2010 and May 2012, this prospective, randomized, multicenter, double-blind, placebo-controlled trial enrolled patients undergoing CABG surgery (with the use of ≥1 SVG) at 38 centers in Canada and the United States. Of 394 patients

TABLE 1 Patient Characteristics, Angiographic Efficacy Measures, and Clinical Outcomes

Per-Protocol Population	Placebo (n = 144)	Inclacumab (n = 148)	All (n = 292)
Patient characteristics			
Age, yrs	62.8 ± 8.2	62.1 ± 9.2	62.4 ± 8.7
Male	129 (89.6)	132 (89.2)	261 (89.4)
Primary efficacy measure at 1 year			
Patients with diameter stenosis >50% of at least 1 SVG	38 (26.4)	33 (22.3)	71 (24.3)
Adjusted odds ratio (95% confidence interval)		0.80 (0.47–1.38)	
p value		0.43	
Secondary efficacy measures at 1 year			
SVG with diameter stenosis >50%	49 (15.5)	47 (14.0)	96 (14.7)
Adjusted odds ratio (95% confidence interval)		0.89 (0.53–1.49)	
p value		0.65	
Patients with diameter stenosis >75% of at least 1 SVG	34 (23.6)	31 (20.9)	65 (22.3)
Adjusted odds ratio (95% confidence interval)		0.86 (0.49–1.50)	
p value		0.59	
SVG with diameter stenosis >75%	43 (13.6)	43 (12.8)	86 (13.2)
Adjusted odds ratio (95% confidence interval)		0.93 (0.54–1.60)	
p value		0.79	
Minimal lumen diameter in SVG, adjusted mean, mm	2.24	2.10	
95% confidence interval	1.92–2.56	1.78–2.41	
p value		0.32	
Major adverse cardiovascular events at 1 year	20 (13.9)	21 (14.2)	41 (14.0)
Adjusted odds ratio (95% confidence interval)		1.05 (0.54–2.04)	
p value		0.88	
All-cause and cardiovascular death	0 (0)	0 (0)	0 (0)
Nonfatal myocardial infarction	4 (2.8)	5 (3.4)	9 (3.1)
Stroke	1 (0.7)	2 (1.4)	3 (1.0)
At least 1 revascularization procedure	15 (10.4)	12 (8.1)	27 (9.2)
Hospitalization for heart failure	2 (1.4)	4 (2.7)	6 (2.1)
Hospitalization for acute coronary syndrome >24 h	0 (0)	1 (0.7)	1 (0.3)

Values are mean ± SD or n (%), unless otherwise indicated.
SVG = saphenous vein graft.

screened, 384 were randomized between 4 h and 6 weeks before CABG surgery to receive inclacumab (20 mg/kg; F. Hoffmann-La Roche, Basel, Switzerland) or placebo administered at 4-week intervals during a treatment period of 32 weeks. Quantitative coronary angiography was performed utilizing the Cardiovascular Measurement System (Medis Medical Imaging Systems, Leiden, the Netherlands). Plasma soluble P-selectin was measured utilizing an enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, Minnesota). The institutional review boards approved the protocols, and all patients provided written informed consent. Endpoints were compared using a logistic regression model or analysis of variance adjusting for on-pump versus off-pump CABG surgery and endoscopic versus open saphenous vein harvesting. The proportion of vessels with different stenosis cutoff values was analyzed using generalized estimating equation models. For plasma soluble P-selectin levels, differences between groups were described through placebo-adjusted geometric mean percent change and compared utilizing repeated-measures analysis of covariance.

Patient characteristics are summarized in Table 1. Baseline plasma soluble P-selectin levels (geometric means) were 29.2 ng/ml (23.7 to 33.7 ng/ml) and 32.4 ng/ml (27.5 to 41.7 ng/ml) in the placebo and inclacumab groups. Inclacumab resulted in a placebo-adjusted geometric mean percent change of -23.4% ($p = 0.006$) at 48 h after CABG surgery. In the 292 patients of the per-protocol population, 26.4% and 22.3% of patients in the placebo and inclacumab groups had ≥1 SVG with a diameter stenosis >50%, the primary efficacy measure (adjusted odds ratio [OR]: 0.80; 95% confidence interval [CI]: 0.47 to 1.38; $p = 0.43$) (Table 1). In the 311 patients of the intention-to-treat population who received ≥1 SVG and at least 1 study drug

infusion and underwent angiography at 1 year follow-up, corresponding rates were 28.7% and 21.4%, respectively (adjusted OR: 0.67; 95% CI: 0.40 to 1.13; p = 0.14). Differences between placebo and inclacumab groups for all pre-specified secondary efficacy measures were not statistically significant (Table 1). 13.9% and 14.2% of patients in the placebo and inclacumab groups had ≥1 reported major adverse cardiovascular event (p = 0.88) (Table 1). There were no apparent inclacumab-induced effects on bleeding events.

Post hoc analyses showed an interaction between the plasma soluble P-selectin level at baseline and the treatment arm on the primary efficacy measure (p = 0.053). In patients with baseline P-selectin levels above the median, the primary efficacy measure tended to be reduced in the inclacumab (12.8%) as compared to the placebo group (27.8%; adjusted OR: 0.37; 95% CI: 0.12 to 1.15; p = 0.085), while this trend was not observed in patients with baseline levels below the median (27.0% in the inclacumab vs. 19.1% in the placebo group; adjusted OR: 1.69; 95% CI: 0.60 to 4.77; p = 0.33).

This SELECT-CABG study showed that the specific anti-P-selectin antibody inclacumab did not exert significant favorable effects on SVG disease progression. Given these results, it is possible that the P-selectin pathway plays an overall less important role in the pathogenesis of venous graft failure than previously hypothesized. However, a post hoc analysis suggested that the pre-existing level of activation of the P-selectin pathway may determine the response to inclacumab, a finding that needs to be evaluated prospectively.

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Drug-Coated Balloon Treatment as Default Strategy for DES-ISR

We read with interest the publication of RIBS IV (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs Everolimus-eluting Stent) trial by Alfonso et al. (1), questioning the role of drug-coated balloons (DCB) in the treatment of drug-eluting stent restenosis (DES-ISR).

The use of DCB and bioresorbable scaffolds not only reduces vessel occlusion but serves to promote vascular healing by leaving no permanent implant within the vessels. To obtain the full benefit of such treatment, optimal lesion preparation is crucial (2). When starting a DCB program, a learning curve is inevitable, addressing factors like handling the device, geographical mismatch, and knowledge of