

# Clopidogrel And Aspirin Versus Aspirin Alone After Coronary Bypass Surgery

## The Clopidogrel After Surgery For Coronary Artery Disease (CASCADE) Randomized Controlled Trial

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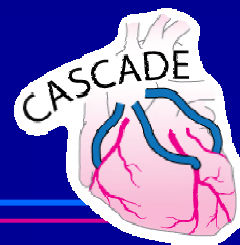
# Presenter Disclosure Information

## Financial Disclosures

- ✦ Michel Le May - Sanofi-Aventis Canada and Bristol Myers Squibb Canada, Research Grant
- ✦ Marc Ruel - Bristol-Myers Squibb Sanofi Canada Partnership, Research Grant
- ✦ Alexander Kulik – None
- ✦ Pierre Voisine – None
- ✦ Jean-Claude Tardif – None
- ✦ Robert De Laroche – None
- ✦ Sarika Naidoo - None
- ✦ George A. Wells – None
- ✦ Thierry G. Mesana – None

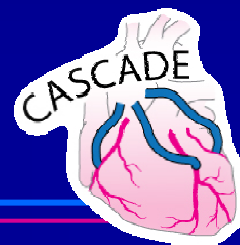
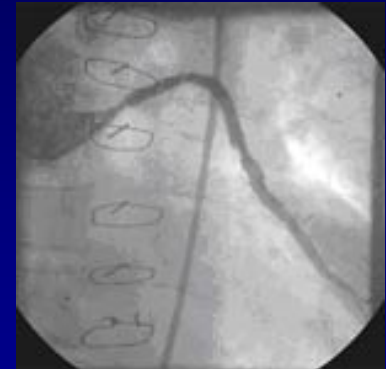
## Unlabeled/Unapproved Uses Disclosure

- ✦ Use of clopidogrel in patients after coronary artery bypass graft surgery is investigational



# Background

- ✦ CABG is an effective treatment of ischemic heart disease
- ✦ Long-term results compromised by vein graft disease
- ✦ Within 1 year
  - ✦ Up to 15% of vein grafts occluded
- ✦ By 10 years after surgery
  - ✦ Only 60% of grafts are patent
  - ✦ 50% of patent grafts are stenotic
- ✦ Patients at high risk of subsequent events



**Fitzgibbon GM et al. JACC 1996;28:616-26**

**Motwani JG et al. Circulation 1998;97:916-31**

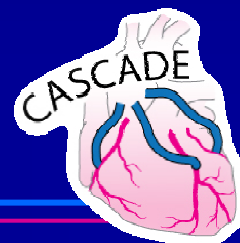
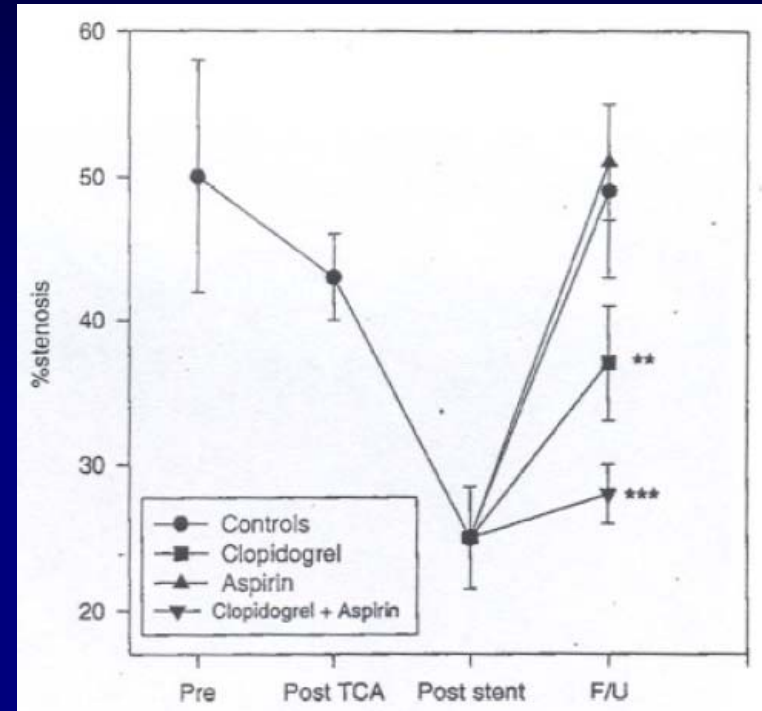
# Background

- ✦ Saphenous vein graft disease is composed of 3 overlapping stages
  - ✦ Early thrombosis
  - ✦ Intimal hyperplasia
  - ✦ Atherosclerosis
- ✦ Intimal hyperplasia represents the foundation for graft atheroma
- ✦ Intimal hyperplasia is inhibited by clopidogrel, but not aspirin
  - ✦ Cell culture experiments
  - ✦ Animal models of thrombosis

Hermann A et al. *Thromb Res* 2002;105:173-5

Herbert JM et al. *Arterioscler Thromb* 1993;13:1171-9

Harker LA et al. *Circulation* 1998;98:2461-9



# CASCADE Trial

## Clopidogrel After Surgery For Coronary Artery Disease

Hypothesis: Clopidogrel plus aspirin will inhibit SVG intimal hyperplasia

Multicenter, double-blind, placebo-controlled trial

Patients undergoing primary multivessel CABG with at least 2 SVG's



**Aspirin 162 mg daily**

**Clopidogrel 75 mg daily**

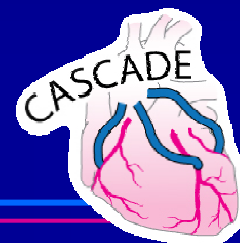
**Aspirin 162 mg daily**

**Placebo**

Starting on day of surgery when chest tube drainage  $\leq$  50 cc/hr for 2 hours

1 year duration

Coronary angiogram and intravascular ultrasound at 1 year



# Outcomes

## Primary outcome

- ◆ Vein graft intimal area by intravascular ultrasound

## Secondary outcomes

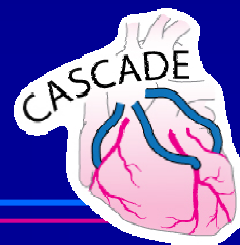
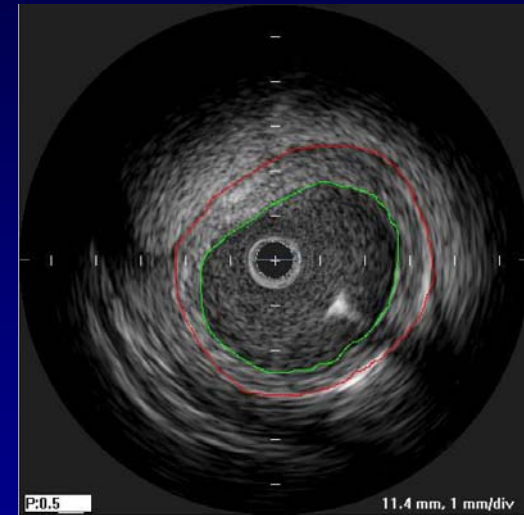
- ◆ Vein graft patency
- ◆ Major adverse cardiovascular events
- ◆ Bleeding

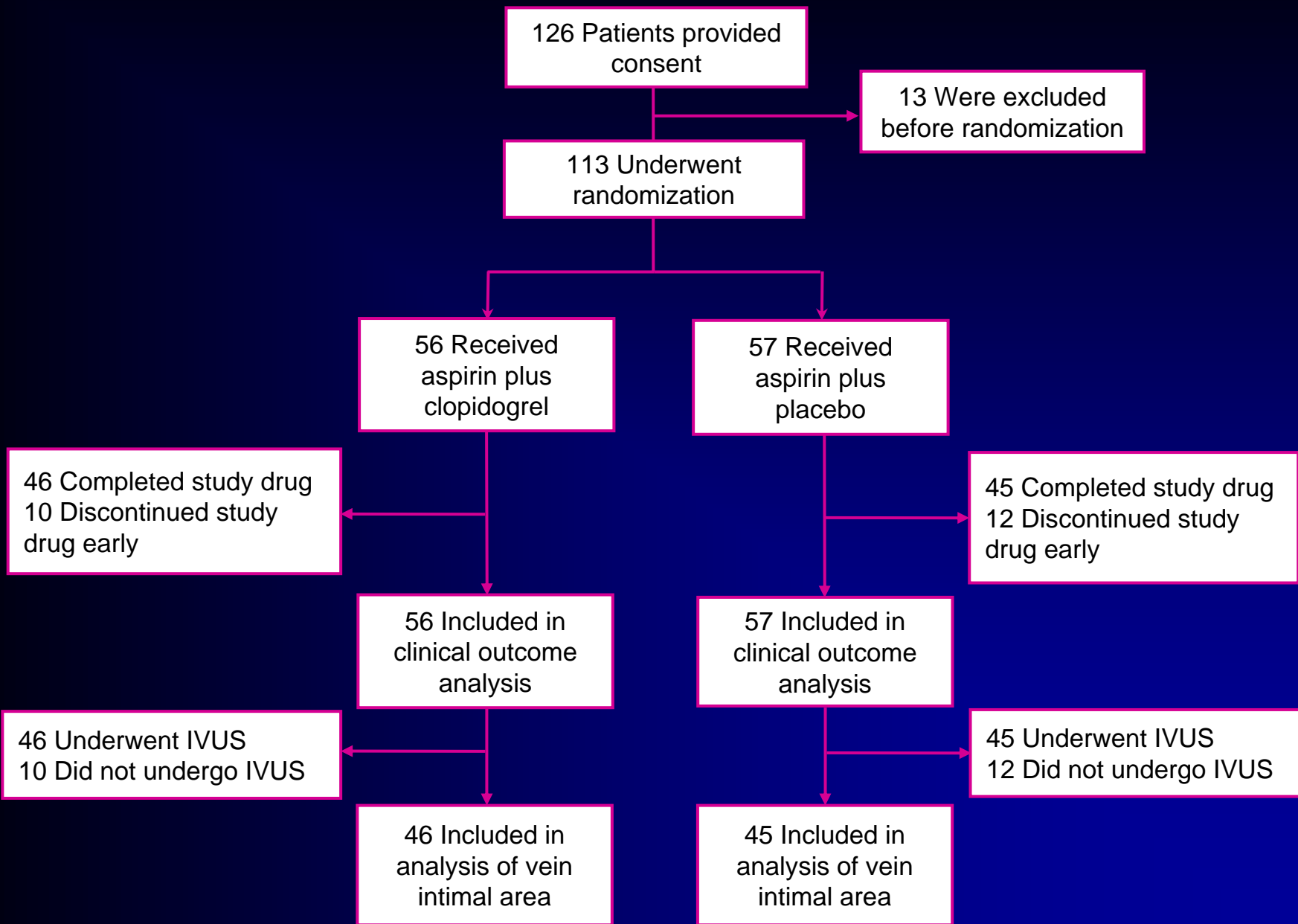
## Sample size

- ◆ Intimal area of normal SVG at 1 year  
 $5.26 \pm 1.38 \text{ mm}^2$

**Hozumi T et al. Heart 1996;76:317-20**

- ◆ 20% clinically relevant reduction with clopidogrel
- ◆  $\alpha$  level 0.05, power 0.90, drop out up to 35%
- ◆ Total 100 patients required





# Table 1

	Aspirin-Clopidogrel (N=56)	Aspirin-Placebo (N=57)
Age (years)	64.9 ± 7.5	68.1 ± 7.4 *
Male (%)	51 (91.1%)	50 (87.7%)
Diabetes (%)	14 (25.0%)	19 (33.3%)
Smoker (%)	6 (10.7%)	9 (15.8%)
Recent MI (%)	10 (17.9%)	11 (19.3%)
Cross-clamp time (min)	66.2 ± 22.4	62.9 ± 17.7
Cardiopulmonary bypass time (min)	91.5 ± 28.1	88.7 ± 20.9
Off-pump CABG (%)	3 (5.4%)	1 (1.8%)
Number of bypasses	3.6 ± 0.8	3.4 ± 0.6
Left internal mammary graft (%)	56 (100%)	56 (98.2%)
ICU length of stay (days)	1.6 ± 1.2	1.3 ± 0.7
Hospital length of stay (days)	9.2 ± 6.8	8.1 ± 4.5
Postoperative statin (%)	51 (91.1%)	52 (91.2%)
Postoperative beta-blocker (%)	53 (94.6%)	52 (91.2%)



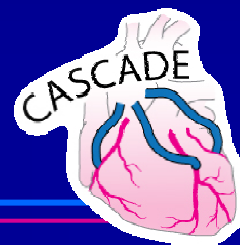
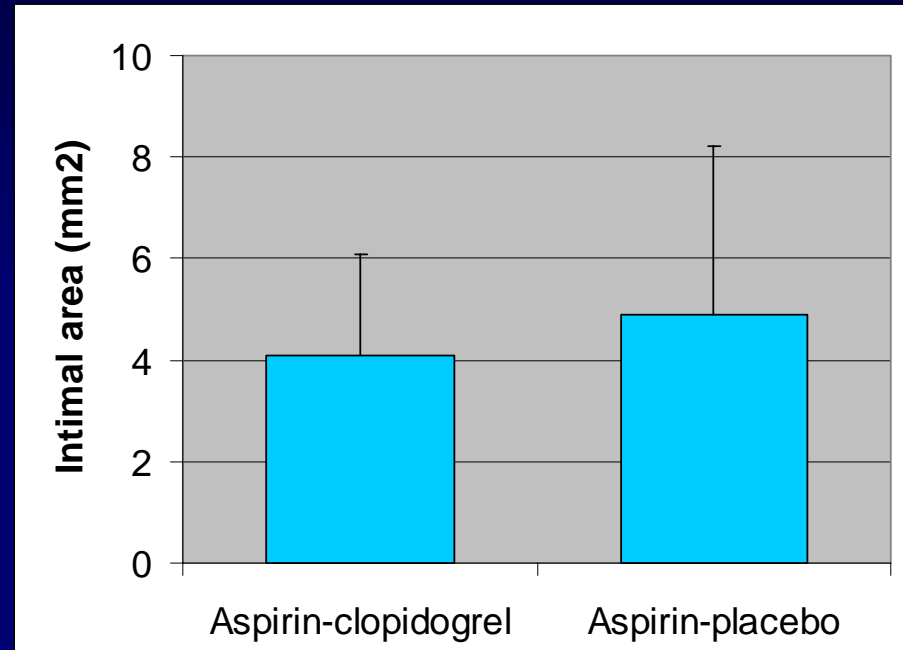
# Primary Outcome

IVUS performed for 90 patients

Vein graft intimal area at 1 year

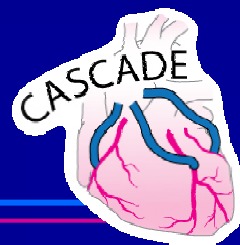
- ◆ Aspirin-clopidogrel  
4.1 ± 2.0 mm<sup>2</sup>
- ◆ Aspirin-placebo  
4.9 ± 3.3 mm<sup>2</sup>      P=0.21

14.8% reduction in intimal area  
(95% CI -38.1%, 8.5%)



# 1 Year Graft Patency

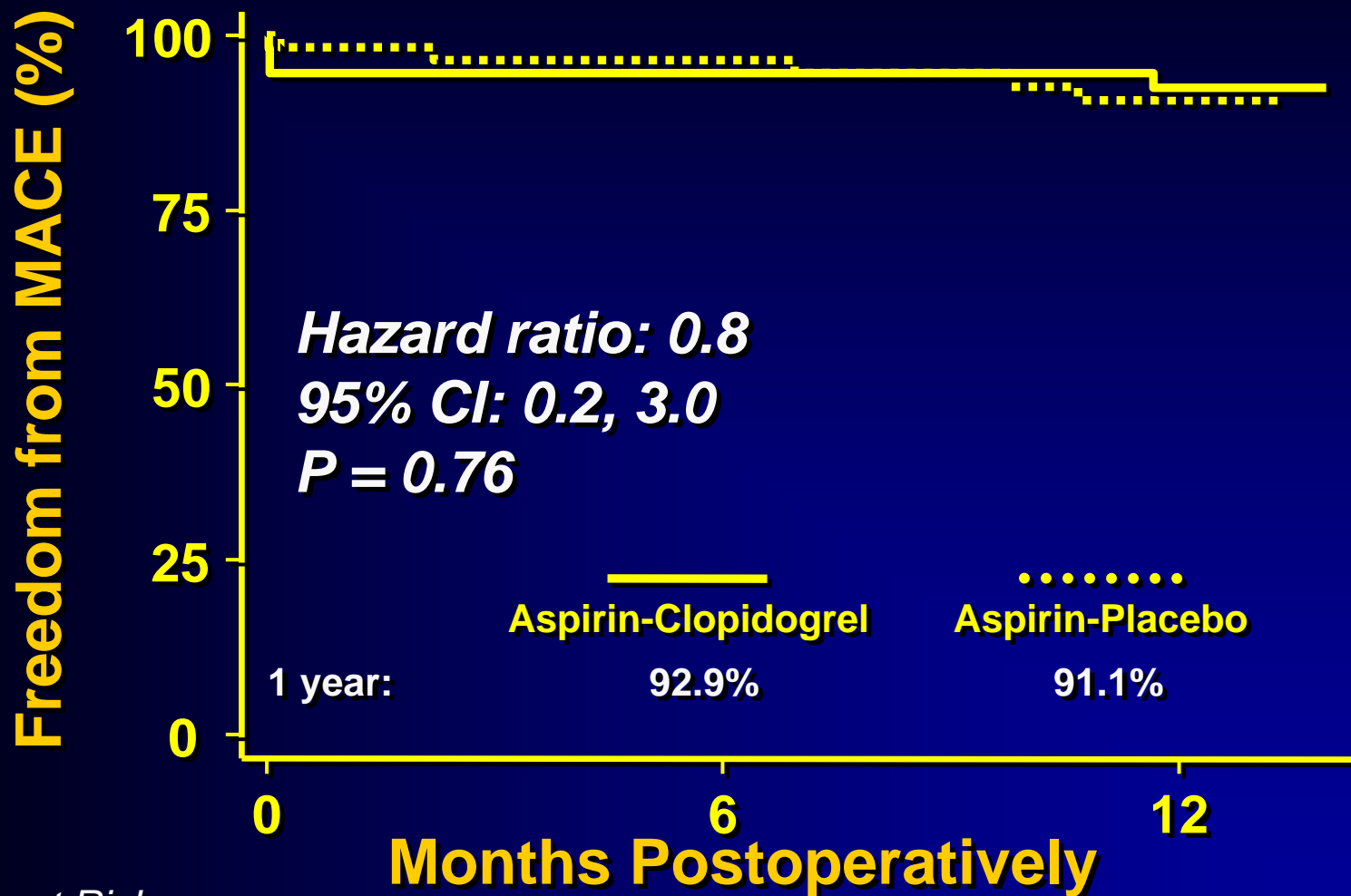
	Aspirin- Clopidogrel (N=56)	Aspirin- Placebo (N=57)	P Value
Overall patency (%)	95.2%	95.5%	1.00
ITA patency (%)	96.6%	100%	0.50
SVG patency (%)	94.3%	93.2%	0.78



# Major Adverse Cardiovascular Events

	Aspirin- Clopidogrel (N=56)	Aspirin- Placebo (N=57)	P Value
<b>Overall death (%)</b>	<b>0 (0%)</b>	<b>1 (1.8%)</b>	<b>1.00</b>
<b>Cardiovascular mortality (%)</b>	<b>0 (0%)</b>	<b>1 (1.8%)</b>	<b>1.00</b>
<b>Myocardial infarction (%)</b>	<b>4 (7.1%)</b>	<b>1 (1.8%)</b>	<b>0.21</b>
<b>Stroke (%)</b>	<b>0 (0%)</b>	<b>2 (3.5%)</b>	<b>0.50</b>
<b>Hospitalization for coronary ischemia (%)</b>	<b>1 (1.8%)</b>	<b>3 (5.3%)</b>	<b>0.62</b>
<b>Need for coronary intervention (%)</b>	<b>1 (1.8%)</b>	<b>2 (3.5%)</b>	<b>1.00</b>
<b>Any MACE (%)</b>	<b>4 (7.1%)</b>	<b>5 (8.8%)</b>	<b>1.00</b>

# Major Adverse Cardiovascular Events



Patients at Risk:

Aspirin-Clopidogrel	56	55	52
Aspirin-Placebo	57	54	50

# Bleeding

- Postoperative chest tube drainage after study drug administration

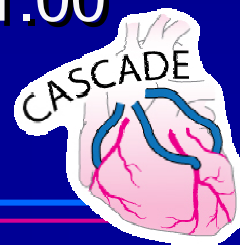
Aspirin-clopidogrel	451 ± 301 mL	
Aspirin-placebo	324 ± 247 mL	P=0.02

- Major bleeding

Aspirin-clopidogrel	2 patients (3.6%)	
Aspirin-placebo	0 patients (0%)	P=0.24

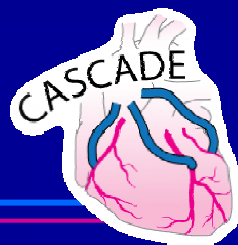
- Minor bleeding

Aspirin-clopidogrel	3 patients (5.4%)	
Aspirin-placebo	3 patients (5.3%)	P=1.00



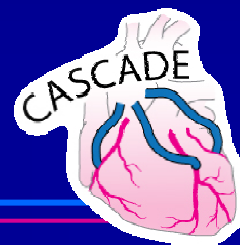
# Discussion

- ✦ The addition of clopidogrel to aspirin led to no significant benefit in terms of reducing vein graft intimal hyperplasia
- ✦ Vein graft patency rates did not differ between the two groups
- ✦ The incidence of major adverse cardiovascular events were similar
- ✦ Our results do not support the use of dual antiplatelet therapy for the prevention of vein graft disease after CABG



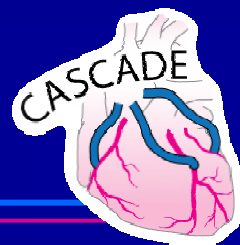
# Potential Limitations

- ✦ Powered for the vein graft intimal hyperplasia
  - ✦ Marker of vein graft disease
  - ✦ Surrogate for angiographic or clinical outcomes
- ✦ Not powered for vein graft patency
- ✦ Angiography rate of 81%
  - ✦ Compares favorably with RAPS and PREVENT IV
    - Desai ND et al. *NEJM* 2004;351:2302-9
    - Alexander JH et al. *JAMA* 2005;294:2446-54
- ✦ Extent of platelet inhibition not assessed
- ✦ No bolus of clopidogrel
- ✦ Long-term vein graft patency unknown



# Conclusions

- ✦ Treatment with aspirin and clopidogrel for 1 year did not significantly reduce the process of vein graft intimal hyperplasia or improve graft patency in patients undergoing primary multivessel CABG





# Acknowledgments

## ✦ Research grants

- ✦ Physicians' Services Incorporated Foundation
- ✦ Boston Scientific Inc.
- ✦ Bristol-Myers Squibb Sanofi Canada Partnership

## ✦ Research Nurses

- ✦ S. Naidoo, RN
- ✦ M. Poirier, RN

## ✦ Intravascular ultrasound

- ✦ Dr. R. de Larocheliere
- ✦ Dr. M. Le May
- ✦ Dr. J.C. Tardif

## ✦ Surgeons

- ✦ Dr. P.J. Bédard
- ✦ Dr. E. Charbonneau
- ✦ Dr. W.G. Goldstein
- ✦ Dr. P.J. Hendry
- ✦ Dr. B.K. Lam
- ✦ Dr. R.G. Masters
- ✦ Dr. P. Mattieu
- ✦ Dr. T.G. Mesana
- ✦ Dr. M. Ruel
- ✦ Dr. P. Voisine

## ✦ Data analysis

- ✦ Dr. G.A. Wells
- ✦ K. Williams, MS

