

# 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

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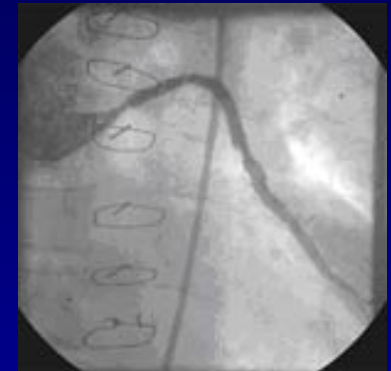
## Unlabeled/Unapproved Uses Disclosure

- ✦ Use of clopidogrel 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
- ✦ Patients at high risk of subsequent events



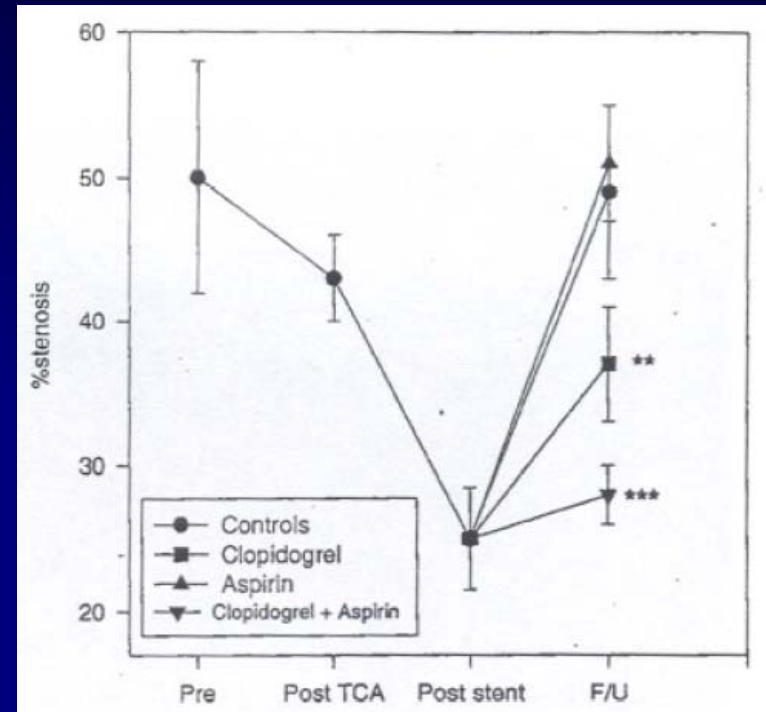
**Fitzgibbon GM et al. JACC 1996;28:616-26**

**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 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

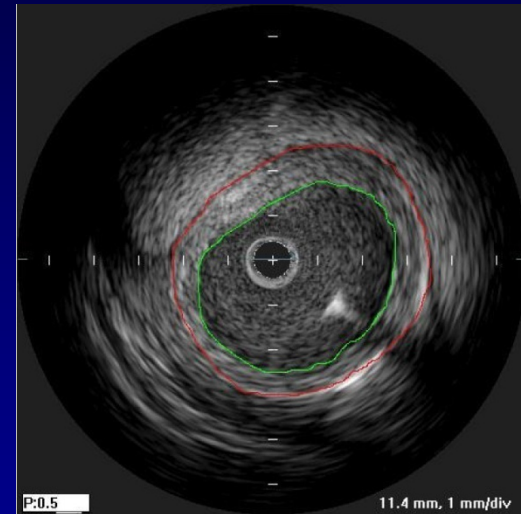
1 year duration

Coronary angiogram and intravascular ultrasound at 1 year



# Primary Outcome

- ✦ Vein graft intimal hyperplasia by intravascular ultrasound
- ✦ Intimal area measured circumferentially in the proximal 40 mm of a randomly selected vein graft
- ✦ 40 MHz imaging catheter
- ✦ Digitized study images were reviewed in a core laboratory



# Secondary Outcomes

- ✦ Vein graft patency
- ✦ Major adverse cardiovascular events
  - ✦ Cardiovascular death, myocardial infarction, stroke, readmission for coronary ischemia
- ✦ Bleeding events
  - ✦ Perioperative
  - ✦ Major
  - ✦ Minor



# Sample Size

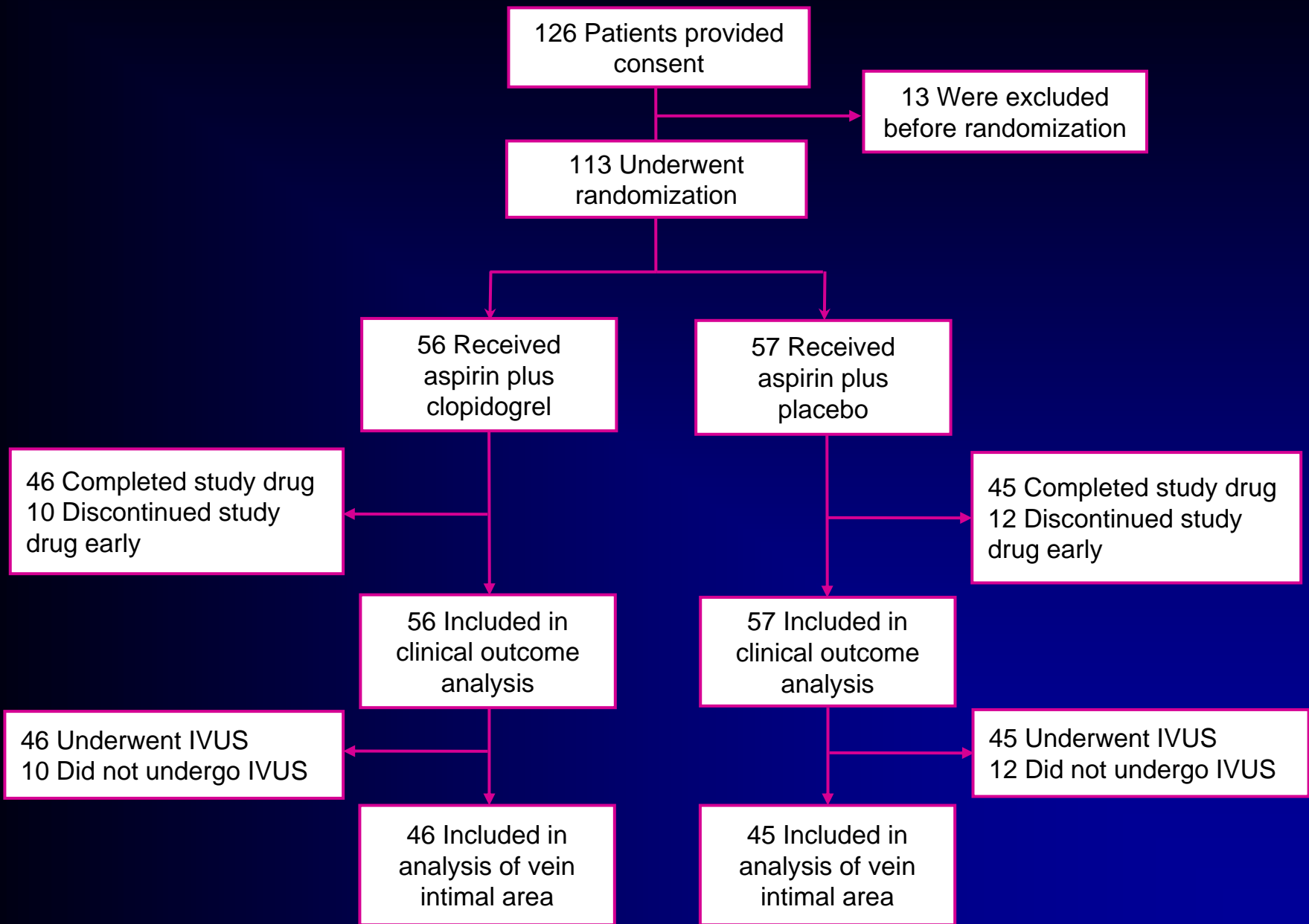
- ✦ Intimal area of normal SVG at 1 year  
 $5.26 \pm 1.38 \text{ mm}^2$

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

- ✦ 20% clinically relevant reduction with clopidogrel
- ✦  $\alpha$  level 0.05 and 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



# Primary Outcome

Vein graft intimal hyperplasia assessed by IVUS in 90 patients

Vein graft intimal area at 1 year

◆ Aspirin-clopidogrel

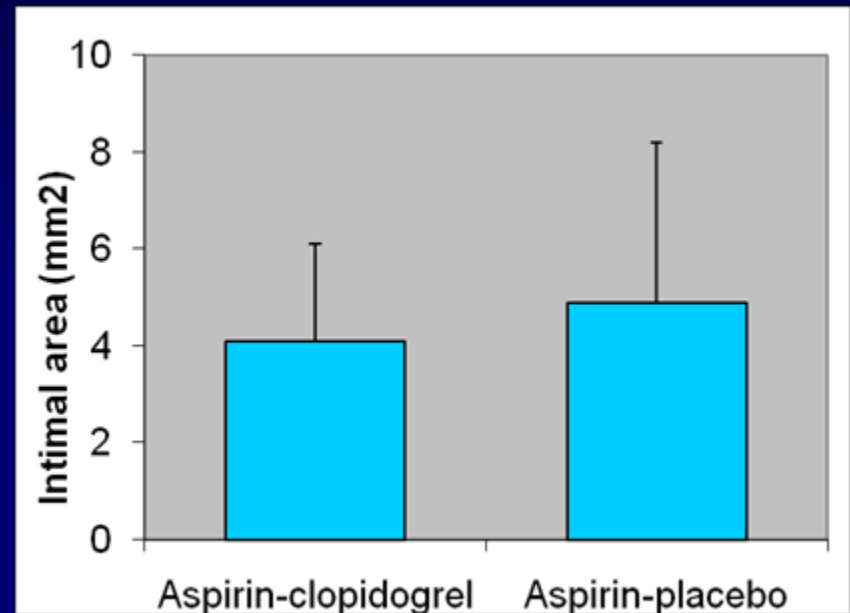
$4.1 \pm 2.0 \text{ mm}^2$

◆ Aspirin-placebo

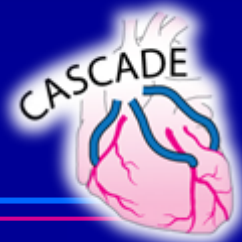
$4.9 \pm 3.3 \text{ mm}^2$

P=0.21

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



# Secondary Outcomes



# 1 Year Graft Patency

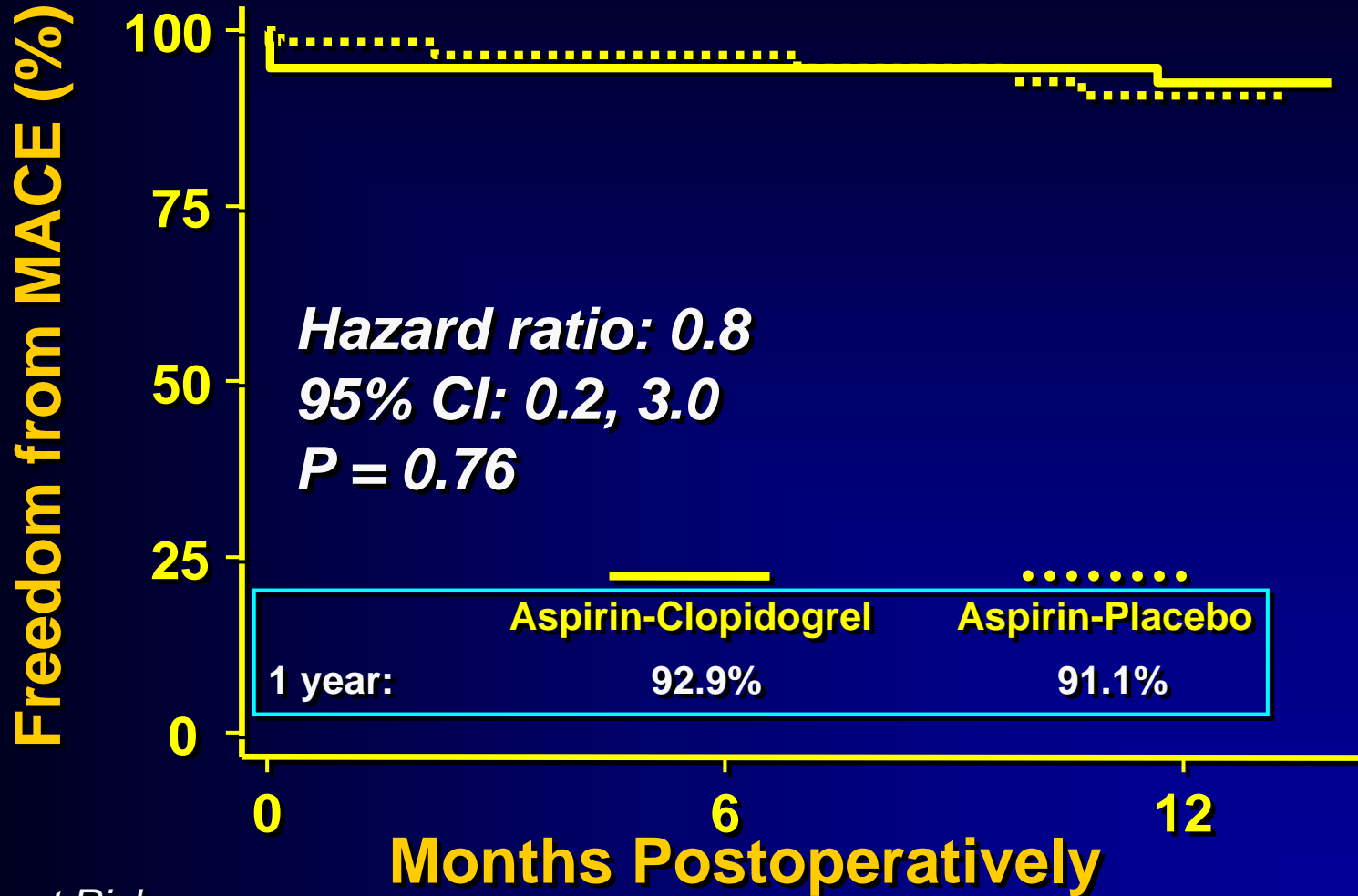
	Aspirin- Clopidogrel (N=56)	Aspirin- Placebo (N=57)	P Value
<b>Overall patency (%)</b>	<b>95.2%</b>	<b>95.5%</b>	<b>1.00</b>
<b>ITA patency (%)</b>	<b>96.6%</b>	<b>100%</b>	<b>0.50</b>
<b>SVG patency (%)</b>	<b>94.3%</b>	<b>93.2%</b>	<b>0.78</b>



# 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 death (%)</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 did not lead to a significant reduction in 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

- ✦ We did not find a significant difference in the process of SVG intimal hyperplasia when aspirin plus clopidogrel was compared to aspirin monotherapy after CABG



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# Thank You

