

A Randomized Study of Early vs. Delayed Coronary Artery Bypass Surgery among Patients with Acute Coronary Syndromes Treated with Ticagrelor: The RAPID CABG Study



Derek YF So, George A Wells, Marie Lordkipanidze, Marc Ruel, Louis P Perrault, Aun Yeong Chong, Michel R Le May, Vincent Chan, Fraser Rubens, Jean-Francois Tanguay
on behalf of the RAPID CABG Investigators

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RAPID CABG

Trial Organization

Trial Steering Committee	Derek YF So, MD (PI), Jean-Francois Tanguay, MD (co-PI), Fraser Rubens, MD (co-PI), Marie Lordkipanidze PhD
Trial Adjudication Committee	Darryl Davis, MD, Richard Davies, MD, Anthony Poulin, MD
Data Safety Monitoring Committee	Girish Nair, MD, Sophie De Roock, MD
Platelet Function Lab	Marie Lordkipanidze PhD
Biostatistical Team	George A Wells, PhD (Director of Biostats), Lilly Chen, MSc

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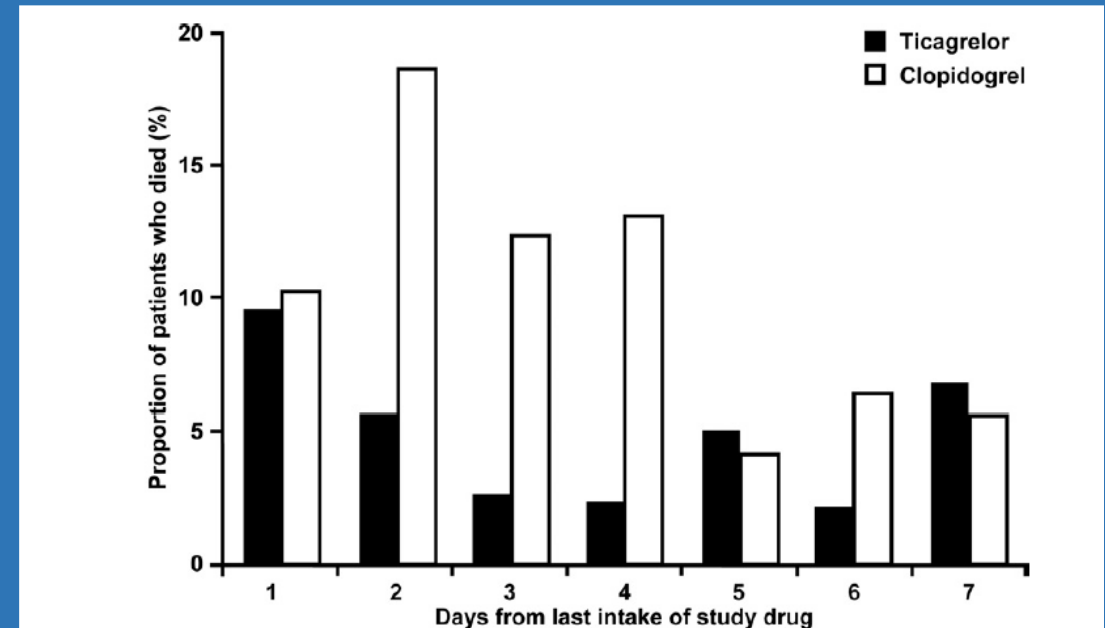




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Background (1):

- 10% of patients presenting with ACS require coronary artery bypass surgery (CABG)
- A major concern is perioperative bleeding among patients requiring CABG
- In the PLATO trial, patients undergoing CABG at 1 day or less after ticagrelor cessation had high mortality





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Background (2):

- Current North American guidelines (including ACC/AHA) advocate a waiting period of **at least 5 days after ticagrelor cessation** prior to non-urgent CABG

ACC/AHA

CLASS I

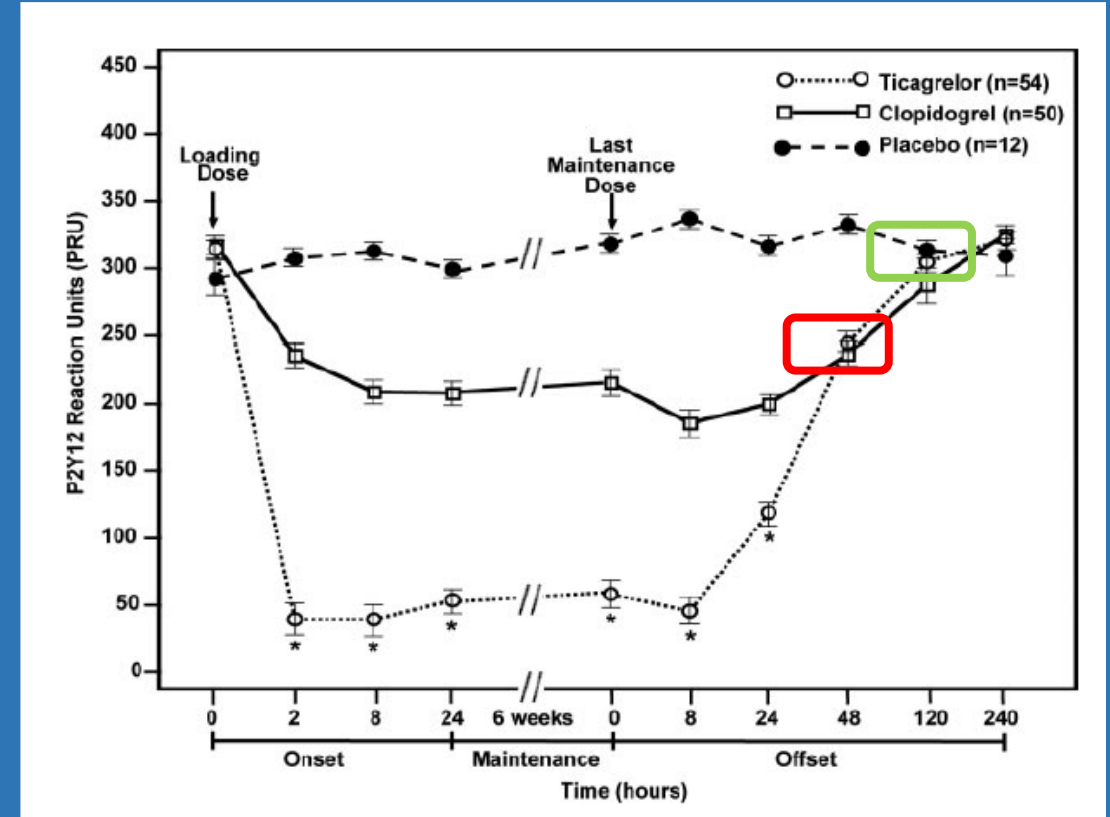
LEVEL B

- The 2017 European Society of Cardiology (ESC) guidelines advocate a waiting period of at least **3 days after ticagrelor cessation** for non-urgent CABG

ESC

CLASS 2a

LEVEL B



Hillis LD et al. 2011. Circulation 2011;124:e652-735
Mehta SR et al. 2018. Can J Cardiol 2018;34:214-33
Valgimigli M et al. 2018. Eur Heart J 2018;39:213-60
Gurbel et al. 2009. Circulation; 120(25)2577-85



RAPID CABG

Study Design and Hypothesis:

RAPID CABG is a physician-initiated multi-center randomized study evaluating the safety of early surgery at **2 to 3 days after ticagrelor cessation** compared to a delay of **5 to 7 days**, among patients presenting with ACS who require non-emergent CABG

- > 18 y.o. with Acute Coronary Syndromes (unstable angina, NSTEMI, STEMI) received ticagrelor
- Exclusions: 1) Patients with stenting for culprit lesions, 2) requiring urgent surgery (<24hrs), 3) requiring valve surgery

Hypothesis: Early Surgery is noninferior to Delayed Surgery for severe or massive perioperative bleeding

- Noninferiority margin of 8% for severe/massive bleeding based on:
 - Association of massive perioperative blood loss to mortality
 - Balancing concerns for ischemic outcomes while patients are off a P2Y12 inhibitor
- Powered for an alpha of 0.05

143 Patients Enrolled – Randomized 1:1
ACS patients treated with ticagrelor
deemed to require CABG after angiography

72 patients allocated to Early Surgery (Day 2-3) ITT 71 patients allocated to Delayed Surgery (Day 5-7)

1 patient refused surgery
• Treated medically

2 patients refused surgery
• both treated with PCI

71 patients **MITT** 69 patients

6 patients went later than assigned window for logistic/medical reasons

7 patients went earlier than assigned window
• 5 medical reasons
• 2 physician reasons

65 patients **PP** 58 patients

4 patients went later than assigned window for logistic/medical reasons

Primary Outcome: Severe/Massive Bleeding by Universal Definition of Perioperative Bleeding (UDPB): Class 3 or 4

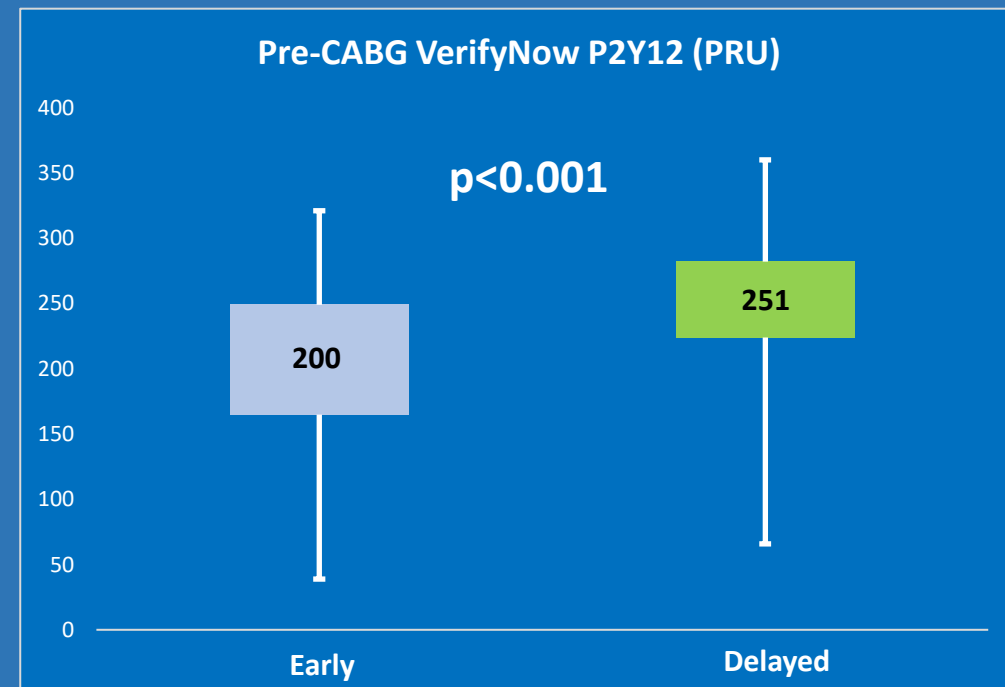
ITT: Intention to Treat
MITT: Modified Intention to Treat
PP: Per Protocol



Baseline Characteristics:

Baseline Characteristics	Early CABG (N= 71)	Delayed CABG (N= 69)
Age, yrs	63.2±9.8	64.7±9.3
Male	57 (80.3%)	57 (82.6%)
BMI, kg/m ²	29.9±5.5	28.1±5.3
Non-STE-ACS at presentation	68 (95.8%)	61 (88.4%)
Risk Factors		
Hypertension	52 (73.2%)	47 (68.1%)
Dyslipidemia	44 (62.0%)	50 (72.5%)
Diabetes	31 (43.7%)	30 (43.5%)
Smoking (current)	32 (45.1%)	25 (36.2%)
Family History of CAD	40 (56.3%)	42 (60.9%)
Reason for CABG		
Left main disease	2 (2.8%)	3 (4.4%)
Multi-vessel disease	66 (93.0%)	64 (92.7%)
Unfavorable PCI Anatomy	3 (4.2%)	2 (2.9%)

Surgical Characteristics	Early CABG (N= 71)	Delayed CABG (N= 69)
Bypass Graft Conduits		
Total number of grafts, N, median (Q1, Q3)	3 (2,3)	3 (2,3)
LITA	70 (98.6%)	69 (100.0%)
2 nd Arterial Graft	37 (52.1%)	37 (53.6%)
Saphenous Vein Graft, median (Q1, Q3)	1 (0,2)	1 (1,2)



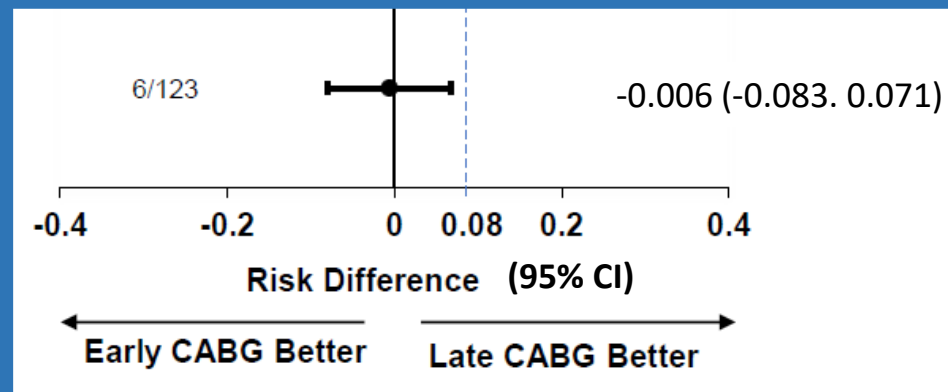
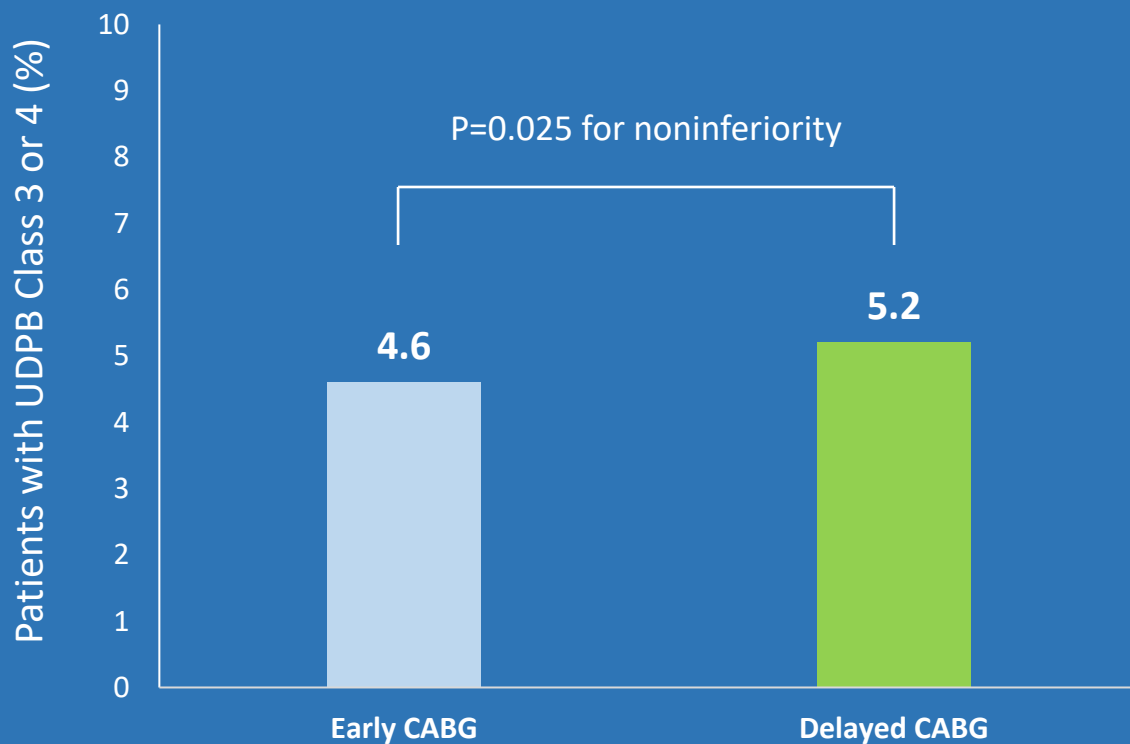
Median Time from Last Ticagrelor dose to CABG, days, median (Q1, Q3)

3.0 (2.0,3.0)

6.0 (5.0,7.0)

Primary and Secondary Bleeding Outcomes:

Severe/Massive Perioperative Bleeding (Class 3 or 4 UDPB)



Other Bleeding Outcomes	Early CABG (N=65)	Delayed CABG (N=58)
Class 3 (severe)	3 (4.6%)	3 (5.2%)
Class 4 (massive)	0	0
TIMI CABG bleeding	2 (3.1%)	0
BARC 4	2 (3.1%)	0
BARC 5	0	0

* Analysis on per protocol population



Bleeding and Transfusion Parameters:

Bleeding Parameters	Early CABG (N=65)	Delayed CABG (N=58)
Delayed Sternal Closure	0	0
Chest tube blood loss within 12hrs, mL, median (Q1, Q3)	470 (330,650)	495 (380,610)
Re-exploration / Tamponade	1 (1.5%)	0
RBC Transfusion	10 (15.4%)	8 (13.8%)
FFP Transfusion	0	3 (5.2%)
Platelet Transfusion	9 (13.9%)	4 (6.9%)
Use of Cryoprecipitate	0	0
Use of Prothrombin complex/fibrinogen	1 (1.5%)	0
Use of recombinant activated factor VII (rFVIIa)	0	0

Ischemic Outcomes:

Ischemic Outcomes Prior to Assigned Surgical Date		
	Early CABG (N=71)	Delayed CABG (N=69)
Complications Prior To Assigned Surgical Date	0	6 (8.7%)
Myocardial Infarction	0	1
Recurrent Angina	0	4
Ventricular Tachycardia	0	1
Cumulative 6-month Ischemic Outcomes		
MACE (All-cause death, non-fatal MI, Stroke, Recurrent angina, stroke, repeat revascularization)	4 (5.6%)	9 (13.0%)*
Cardiovascular Death	0	0
All-cause Death	1	1
Non-fatal Myocardial Infarction	0	2
Stroke	2	1
Recurrent Angina	0	5
Repeat Revascularization	1	1

Median Length of Stay: Randomization to Discharge	Early CABG (N=71)	Delayed CABG (N=69)
Days, median (Q1, Q3)	9 (7, 13)	12 (10,15)

*Analysis per MITT population; * 1 patient with in-hospital and post discharge myocardial infarction*



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Summary of Findings:

- Early surgery 2-3 days after ticagrelor cessation was non-inferior in incurring severe or massive perioperative bleeding compared to waiting 5-7 days
- There were no differences in TIMI CABG, BARC Types 4 or 5 bleeding
- Patients in the delayed group had ischemic events requiring earlier surgery
- The early surgery group had a reduced length of hospital stay by 3 days



RAPID CABG

Conclusions:

RAPID CABG is the first and only RCT evaluating safety of early surgery:

“ In patients with ACS, an early surgical strategy, 2 to 3 days after ticagrelor cessation, was noninferior in incurring severe or massive bleeding compared to delaying surgery until 5 to 7 days.”