

***Intracoronary Low-Dose Recombinant Tissue Plasminogen Activator in
Primary PCI for ST-Segment Elevation Myocardial Infarction and Large
Thrombus Burden:
A Randomized Double-Blind Trial***

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- Microvascular obstruction after primary PCI is common and affects nearly half of STEMI patients
- It results in larger infarct size, higher risk of heart failure, shock, and death
- Previous adjunctive therapies such as mechanical thrombectomy^{1,2} and intracoronary abciximab³ have failed to show benefit
- Facilitated PCI⁴ with systemic fibrinolytics increased bleeding risk without improving outcomes
- Intracoronary alteplase offers a targeted approach with potential to enhance microvascular perfusion safely.

Low-Dose Intracoronary Fibrinolysis Infusion with Delivery Catheter

- (1) Targets a highly effective therapy that is able to lyse clot in the microvascular circulation in the territory of the evolving infarction
- (2) Allows for a markedly reduced dose of fibrinolytic (approximately 12% of the systemic dose) thereby potentially reducing bleeding complications observed in facilitated PCI trials
- (3) unlike a mechanical thrombectomy strategy, it effectively penetrates the small vessels and microvascular circulation where thrombus may have embolized
- (4) A meta-analysis¹ of small trials^{2,3} suggested a possible benefit. However, a recent larger trial, **T-Time**⁴, where low-dose intracoronary alteplase was give through the guide catheter (rather than a delivery catheter) failed to show a benefit

Objective

To determine whether adjunctive intracoronary delivery of low dose alteplase reduces microvascular obstruction or major adverse cardiovascular events (MACE) in patients undergoing primary PCI for STEMI and high thrombus burden

Study Design: Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

Patients with Large Territory STEMI* undergoing Primary PCI + High Thrombus Burden (Grade 3-5) Within 6 (max 12) hours

* ≥ 2 mm STE in 2 contig anterior leads; or ≥ 2 mm STE 2 inferior leads + ST dep 2 contig ant/lat leads for total ST deviation ≥ 8 mm

Randomized

Excluded

- Active bleeding
- Lytic contra-indication
- Shock, LBBB
- Planned GP2b/3a

**Intracoronary Alteplase
10 mg**
(allocated n=69)
(received n=68)

**Intracoronary Alteplase
20 mg**
(allocated n=70)
(received n=69)

**Placebo
(Saline)**
(allocated n=71)
(received n=70)

Primary Outcome

Composite of MACE at 30 days, TIMI MBG 0/1, distal embolization, failure to achieve 50% ST segment resolution at 30 minutes

- Computer-based randomization, stratified by center.
- AFTER antegrade flow was established, a delivery catheter was inserted into the infarct related artery distal to the culprit lesion and study drug was infused over 3 minutes.
- Following administration of the study drug, primary PCI resumed as per standard practice.
- Unfractionated heparin (100 units/kg) was given
- A 12-lead ECG was performed at baseline and at 30 minutes following primary PCI.
- After discharge from initial hospitalization, patients were followed up at Day 30.

Primary Outcome

Composite of:

- MACE (CV death, MI, cardiogenic shock, new onset HF) at 30 days
- TIMI myocardial blush grade 0/1
- distal embolization
- failure to achieve $\geq 50\%$ ST-segment resolution at 30 minutes post-PCI

Safety outcomes

- **major bleeding** (defined as fatal, ICH, retroperitoneal, intraocular, requiring surgical intervention, Hb drop of 3g/dL, with each blood transfusion unit counting as 1 g/dL)
- **composite of major bleeding or clinically relevant bleeding at 30 days** (CRNMB defined as resulting in hospital admission, prolonged hospital stay or ≥ 1 unit of blood transfusion)

Secondary outcomes

1. Composite of MBG 0/1 or distal embolization
2. Individual components of primary outcome

- **Study Power:** 80% power for 48% RRR in alteplase combined dose groups vs placebo (est event rate=40%, $2\alpha=5\%$, 1% drop-out), 201 total participants required (67 in each group)
- **Coordinating Center:** Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada
- **ECG Core Lab:** Canadian VIGOUR Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB
- **Angiographic Core Lab:** PHRI, Hamilton, Canada
- **Analysis:** On-treatment analysis, modified Poisson regression
- **Follow-up (vital status):** 100% at 30 days

Baseline Characteristics

	Alteplase 10mg N=69	Alteplase 20mg N=70	Placebo N=71
Age (years)	63.8	61.1	63.1
Women	19 (27.5%)	15 (21.4%)	19 (26.8%)
MI location			
Anterior/Ant-lateral	35 (50.7%)	37 (52.9%)	31 (43.7%)
Inferior/Posterior	34 (49.3%)	33 (47.1%)	40 (56.3%)
Delivery Catheter			
Aspiration thrombectomy	46 (67%)	53 (75.7%)	51 (72%)
Over-the-wire balloon	14 (20%)	6 (8.6%)	10 (14.1%)
Micro-catheter	6 (8.7%)	5 (7.1%)	6 (8.5%)
Access			
Radial	66 (95.7%)	67 (95.7%)	66 (93.0%)
Femoral	3 (4.3%)	3 (4.3%)	5 (7.0%)

Symptom onset to rand (Median)=2.9 hours
Symptom onset to PCI (Median)=3 hours

	Alteplase 10mg N=69	Alteplase 20mg N=70	Placebo N=71
TIMI Thrombus Grade			
Grade 3	5 (7.2%)	6 (8.6%)	12 (16.9%)
Grade 4	14 (20.3%)	13 (18.6%)	16 (22.5%)
Grade 5	50 (72.5%)	51 (72.9%)	42 (59.2%)
TIMI Flow Grade Pre-PCI			
Grade 0	50 (72.5%)	51 (72.9%)	42 (59.2%)
Grade 1	3 (4.3%)	5 (7.1%)	6 (8.5%)
Grade 2	16 (23.2%)	14 (20.0%)	22 (31.0%)
Grade 3	0	0	1 (1.4%)
TIMI Flow prior to study drug infusion			
Grade 0	6 (8.7%)	0	1 (1.4%)
Grade 1	10 (14.5%)	10 (14.3%)	12 (16.9%)
Grade 2	36 (52.2%)	44 (62.9%)	32 (45.1%)
Grade 3	13 (18.8%)	11 (15.7%)	19 (26.8%)

Primary Outcome

Combined Alteplase Dose Groups vs Placebo

MACE at 30d, MBG 0/1, Distal Embolization or failure to achieve $\geq 50\%$ ST resolution at 30 min

Alteplase 10/20mg N=137	Placebo N=70	Relative Risk (95% CI)	P Value
73 (53.28%)	37 (52.86%)	1.00 (0.76-1.31)	0.99

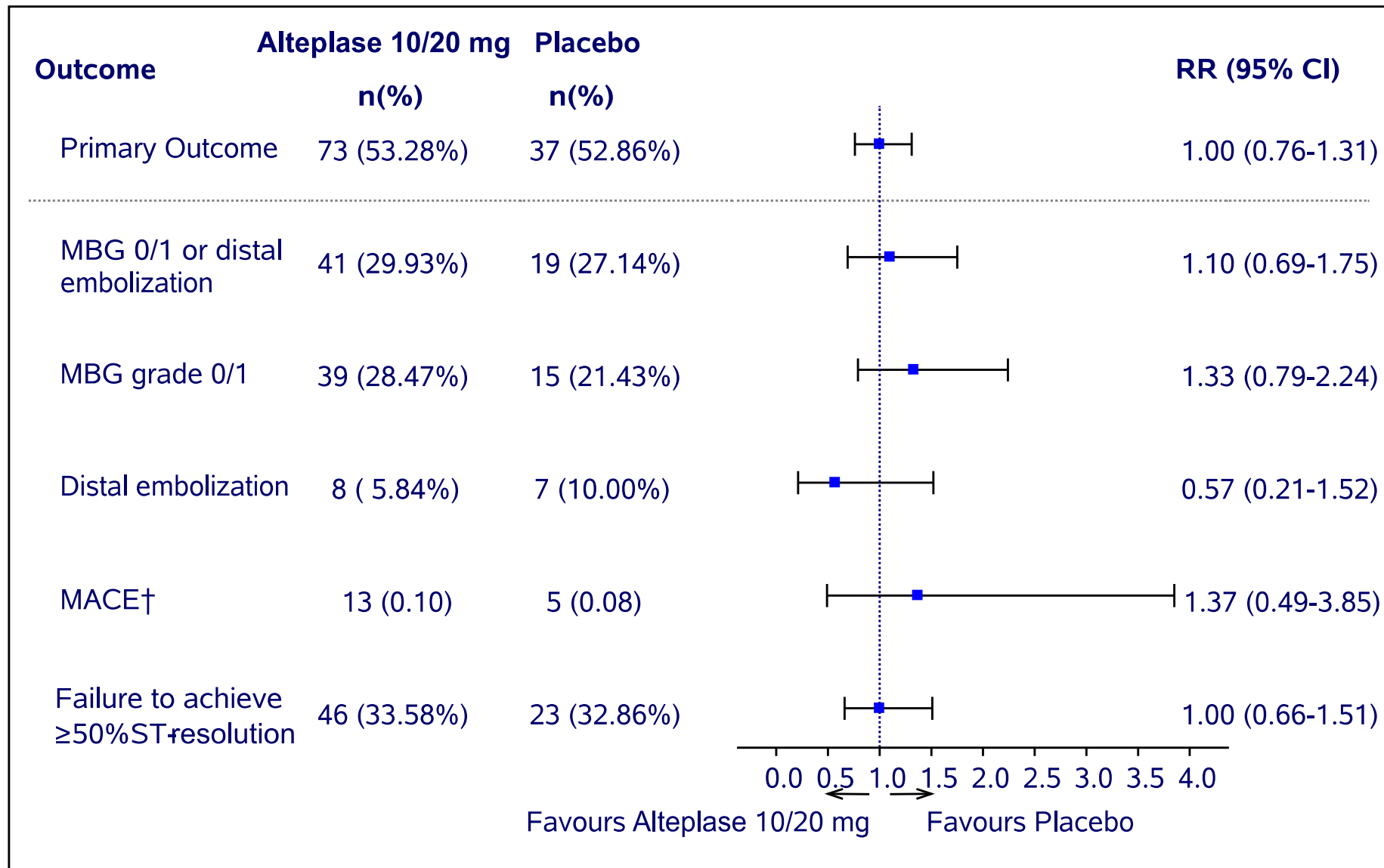
Primary Outcome

Individual Alteplase Dose Groups vs Placebo

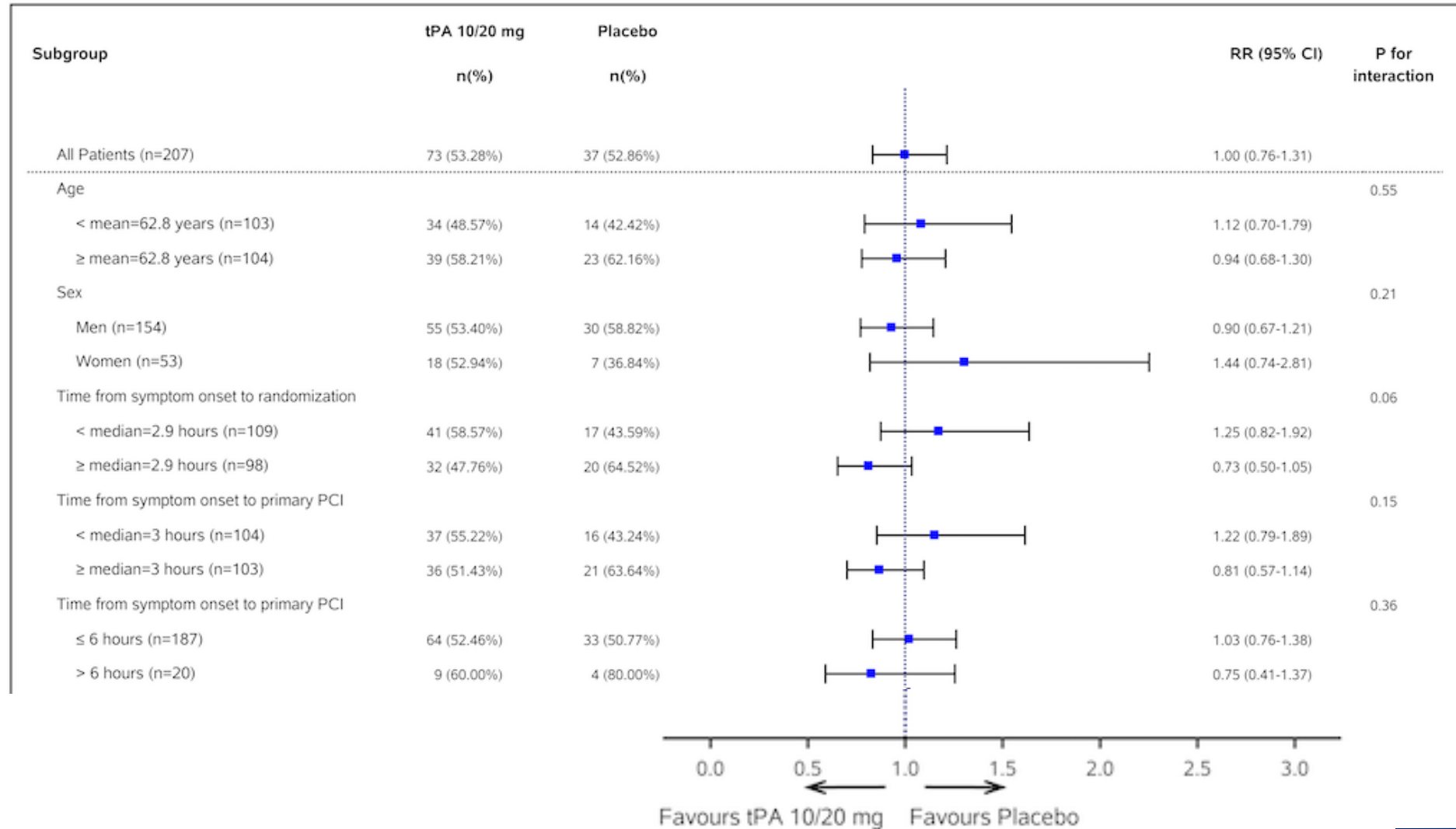
MACE at 30 days, MBG 0/1, Distal Embolization or failure to achieve $\geq 50\%$ ST resolution at 30 min

Alteplase 10 mg N=68	Alteplase 20 mg N=69	Placebo N=70	Alteplase 10 mg vs Placebo	Alteplase 20 mg vs Placebo
			RR (95% CI)	RR (95% CI)
32 (47.06%)	41 (59.42%)	37 (52.86%)	0.89 (0.64-1.25) P=0.50	1.12 (0.84-1.51) P=0.44

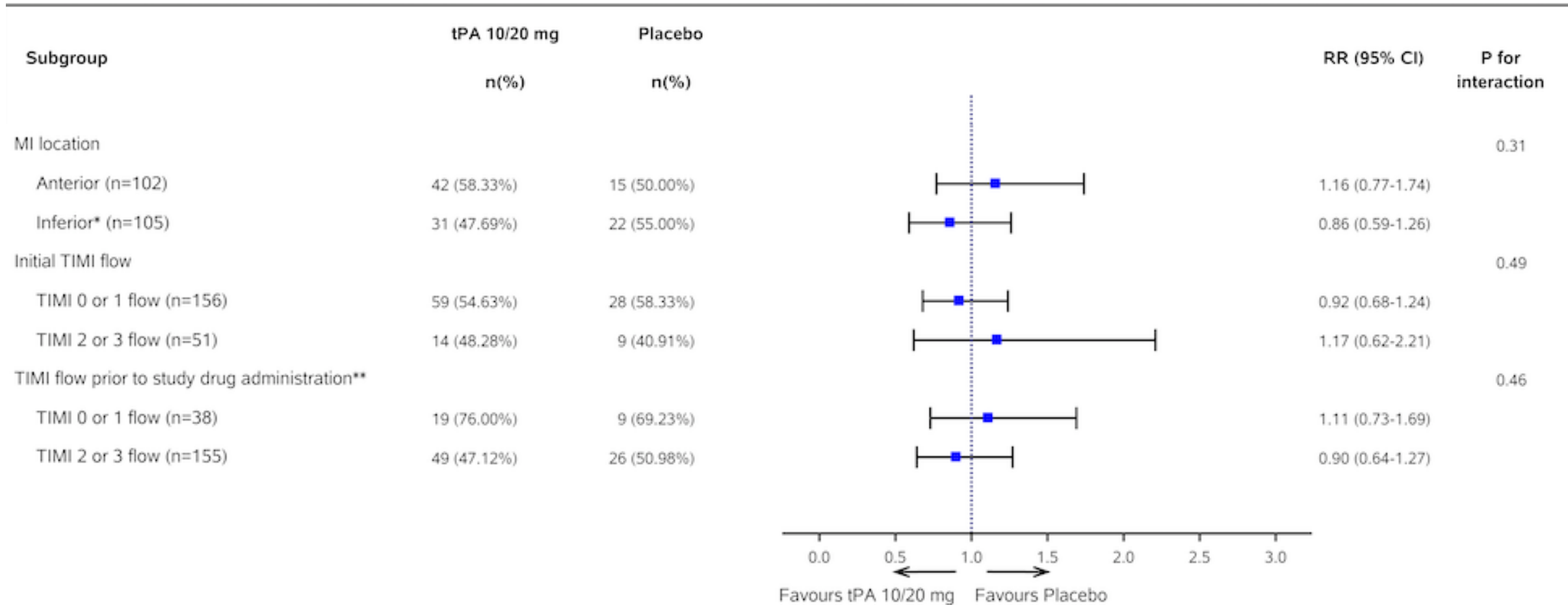
Primary and Secondary Outcomes



Pre-specified Subgroups



Pre-specified Subgroups



Safety

Alteplase 10/20 mg N=	Alteplase 10 mg N=68	Alteplase 20 mg N=69	Placebo N=70	Alteplase 10/20 mg vs Placebo
				RR (95% CI)
Major Bleeding	0	0	0	-
CRNMB	0	1	0	-
Ventricular Fibrillation*	5	9	1	6.86, 95% CI 0.91-51.4 P=0.06

*All cases of VF were transient and successfully defibrillated. There was **no increase** in mortality or the primary outcome in those with vs without VF
CRNMB=clinically relevant non-major bleed

Outcome	No VF	VF	P
	n(%) / N[Rate(CI)]	n(%) / N[Rate(CI)]	
Primary Outcome	104 (54.17%)	6 (40.00%)	0.29
Composite of MBG grade 0/1 or distal embolization or failure to achieve ≥50% ST-segment resolution	96 (50.00%)	6 (40.00%)	0.46
Composite of MBG grade 0/1 or distal embolization	57 (29.69%)	3 (20.00%)	0.56
MBG grade 0/1	53 (27.60%)	1 (6.67%)	0.12
Distal embolization	13 (6.77%)	2 (13.33%)	0.30
Failure to achieve ≥50% ST-segment resolution*	66 (34.38%)	3 (20.00%)	0.26
Time to the first occurrence of MACE	17 [0.10 (0.06 - 0.15)]	1 [0.07 (0.00 - 0.40)]	>0.99
Time to CV death	9 [0.05 (0.02 - 0.09)]	0	n/a
Time to Myocardial re-infarction	5 [0.03 (0.01 - 0.06)]	0	n/a
Time to Cardiogenic Shock	4 [0.02 (0.01 - 0.06)]	1 [0.07 (0.00 - 0.40)]	0.32
Time to new onset heart failure	4 [0.02 (0.01 - 0.06)]	0	n/a
All-cause mortality at 30 days	9 (4.69%)	1 (6.67%)	0.54

1. VF during intracoronary drug infusion
 - May have been due to too rapid of an injection of study drug or other property of reconstituted alteplase
 - All successfully defibrillated with no CV deaths, no increase in mortality, primary outcome or any other adverse event
2. Sub-optimal flow during study drug administration could impede drug from reaching microcirculation
 - There was *no difference* in outcomes based on flow pre study drug administration and delivery catheter should partially offset this

Why was intracoronary lytic not effective?

- increased myocardial hemorrhage?
- increased thrombosis secondary to thrombin and platelet activation despite use of high dose heparin and potent P2Y12?

Conclusions

In patients with large territory STEMI and high thrombus burden, intracoronary delivery of low-dose alteplase compared with placebo:

- Did not reduce the composite primary outcome of MACE or microvascular obstruction
- Did not reduce myocardial blush grade or distal embolization
- Did not improve failure to achieve $\geq 50\%$ ST-segment resolution
- Resulted in more episodes of VF (all successfully defibrillated)
- Did not increase major or clinically significant bleeding

Overall, STRIVE does not support the routine administration of this therapy

1. Microvascular obstruction after primary PCI *remains the single most important unresolved issue* limiting the efficacy of primary PCI
2. Taken in the context of T-Time and other trials, STRIVE essentially closes the door on low-dose intracoronary lytic

Variations on administering IC lytic (eg after stent deployment in patients with high IMR) are being studied
3. Intracoronary low dose lytic now joins facilitated PCI, intracoronary abciximab, adenosine, nitroprusside and mechanical thrombectomy and others as once promising therapies that failed to improve microvascular obstruction after STEMI

Acknowledgments

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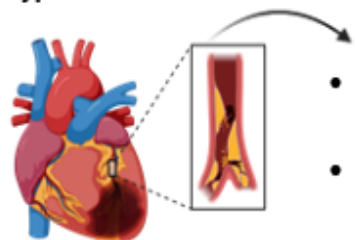
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Hypothesized Mechanism

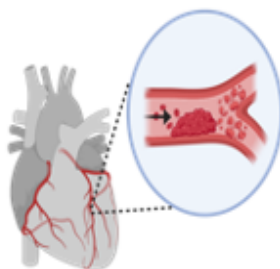


Distal embolization occurs in ~50% primary PCI

- Microvascular obstruction
- Reduced myocardial perfusion
- Larger infarct size



Alteplase is a fibrin-specific tissue plasminogen inhibitor that dissolves thrombus



Would direct intracoronary administration of alteplase reduce microvascular obstruction and reduce MACE?

In patients undergoing primary PCI for STEMI with large thrombus burden, the use of intracoronary alteplase did not improve the composite of MACE or microvascular obstruction

STRIVE Trial Design

Population (n=210):

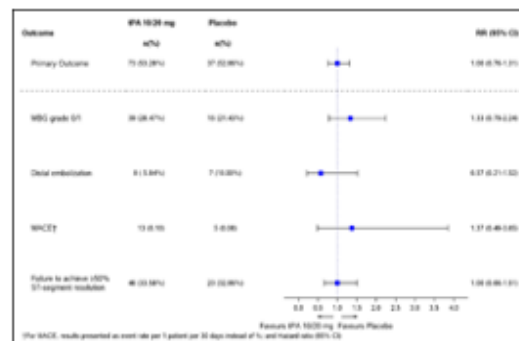
Large Territory STEMI and high thrombus burden

Intervention:

Intracoronary Alteplase (10 mg or 20 mg) vs. placebo (saline)



Observed Findings



Primary Outcome: MACE at 30 days, myocardial blush grade 0/1, distal embolization or failure to achieve ≥50% ST-segment resolution



Higher trend of ventricular fibrillation with combined alteplase group compared to placebo

