Reduction of Thrombus: Local vs. Systemic GPI Infusion

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Pros and Cons of Local GPI Delivery

- **Pros**
  - **Higher local concentration**
  - **More effective thrombus dissolution**
  - **Improved microvascular circulation**

- **Cons**
  - **Arrhythmia**
  - **Systemic effect**
  - **Invasive and delayed therapy**

Clinical outcome!

Variables to consider

- **Drug**

- **Timing**

- **Device**

- **Concomitant therapy**

- **Endpoints**

ICE (Intracoronary Eptifibatide) Trial

- **Single-center prospective randomized trial of 43 patients with ACS**

- **No STEMI patients treated with primary PCI**

- **No target lesion in an occluded vessel**

- **Intracoronary bolus of 180 ug/kg for 2 minutes via the guiding catheter, repeated 10 minutes later with a second bolus vs. Intravenous arm with two boluses of 180 ug/kg IV 10 minutes apart**

- **Both groups received continuous IV infusion at 2 ug/kg/min at the onset of the first bolus and both boluses prior to PCI.**
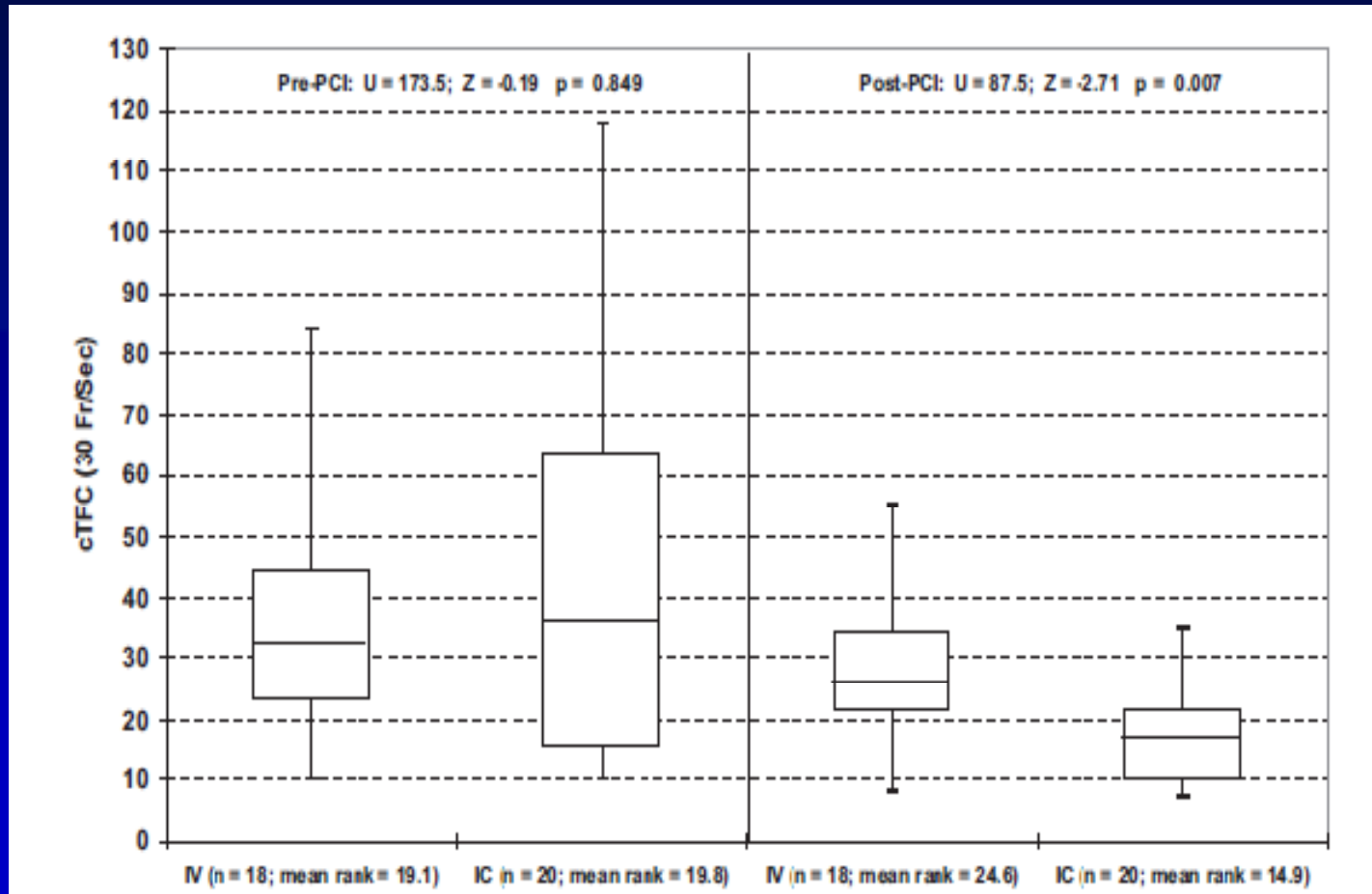
Results of ICE Trial

- **No angiographic, electrophysiological, or other adverse findings attributable to the intracoronary administration of eptifibatide.**

- **The systemic inhibition of platelet aggregation was similar in both groups.**

- **The local platelet GP IIb/IIIa receptor occupancy in the coronary sinus was significantly higher in the intracoronary group for both boluses (after first bolus, $94\pm9\%$ vs $51\pm15\%$; after second bolus, $99\pm2\%$ vs $91\pm4\%$, p=0.001).**

  Circulation 2010;121:784-791

Improved post-PCI cTFC with IC Integrilin

INFUSE-AMI

- **Anterior STEMI (proximal or mid LAD occlusion)**

- **Angiomax as the anticoagulant**

- **IC Abciximab via ClearWay RX Catheter or No Abciximab**

- **With or without aspiration thrombectomy**

Reperfusion Indices

|	IC	-IC		+Asp	-Asp	
TIMI flow after PCI[c]						
0/1	7/229 (3.1)	2/223 (0.9)	.18	4/229 (1.7)	5/223 (2.2)	.75
2	13/229 (5.7)	17/223 (7.6)	.41	13/229 (5.7)	17/223 (7.6)	.41
3	209/229 (91.3)	204/223 (91.5)	.94	212/229 (92.6)	201/223 (90.1)	.36
Corrected TIMI frame count after PCI, median (IQR)[c]	20 (16-26)	20 (16-26)	.62	20 (16-26)	20 (16-26)	.40
MBG 0/1 after PCI[c]	44/228 (19.3)	40/223 (17.9)	.71	38/229 (16.6)	46/222 (20.7)	.26
MBG 2/3 after PCI[c]	184/228 (80.7)	183/223 (82.1)	.71	191/229 (83.4)	176/222 (79.3)	.26
ST-segment resolution at 60 min, median (IQR), %[c,d]	69.8 (46.0-85.5)	74.1 (52.6-88.2)	.30	71.2 (45.2-87.2)	74.4 (55.8-87.4)	.37
Complete, >70%	101/202 (50.0)	108/187 (57.8)	.13	101/199 (50.8)	108/190 (56.8)	.23
Partial, 30%-70%	73/202 (36.1)	49/187 (26.2)	.04	65/199 (32.7)	57/190 (30.0)	.57
Absent, <30%	28/202 (13.9)	30/187 (16.0)	.55	33/199 (16.6)	25/190 (13.2)	.34

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Modest Reduction in Infarct Size and Mass by IC RX

Table 3. Thirty-Day Cardiac Magnetic Resonance Imaging Results for the Pooled Randomized Groups					
	Intracoronary Abciximab[a] (n = 188)	No Intracoronary Abciximab[a] (n = 184)	P Value	Aspiration Thrombectomy[b] (n = 186)	No Aspiration Thrombectomy[b] (n = 186)	P Value
Infarct size, median [IQR], % of total LV mass[c]	15.1 [6.8-22.7] (n = 181)	17.9 [10.3-25.4] (n = 172)	.03	17.0 [9.0-22.8] (n = 174)	17.3 [7.1-25.5] (n = 179)	.51
Total LV myocardial mass, median [IQR], g	128.6 [106.6-152.4] (n = 181)	130.4 [109.9-155.9] (n = 172)	.55	128.3 [108.9-149.8] (n = 174)	132.0 [107.6-156.1] (n = 179)	.50
Infarct mass, median [IQR], g	18.7 [7.4-31.3] (n = 184)	24.0 [12.1-34.2] (n = 175)	.03	20.3 [9.7-31.7] (n = 178)	21.0 [9.1-34.1] (n = 181)	.36
Total abnormal wall motion score, median [IQR]	7.0 [2.0-10.0] (n = 188)	8.0 [3.0-10.0] (n = 184)	.08	7.5 [2.0-10.0] (n = 186)	7.5 [2.0-10.0] (n = 186)	.89
Left ventricular ejection fraction, median [IQR], %	50.2 [44.2-57.9] (n = 182)	48.9 [42.3-56.7] (n = 179)	.22	49.6 [43.3-56.8] (n = 181)	49.5 [41.8-57.6] (n = 180)	.66

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INFUSE-AMI: Infarct size at 30 days

Infarct Size (%LV)

14.7	17.3	18.6	17.6

Legend:
- Asp + IC
- - Asp + IC
- Asp - IC
- - Asp - IC
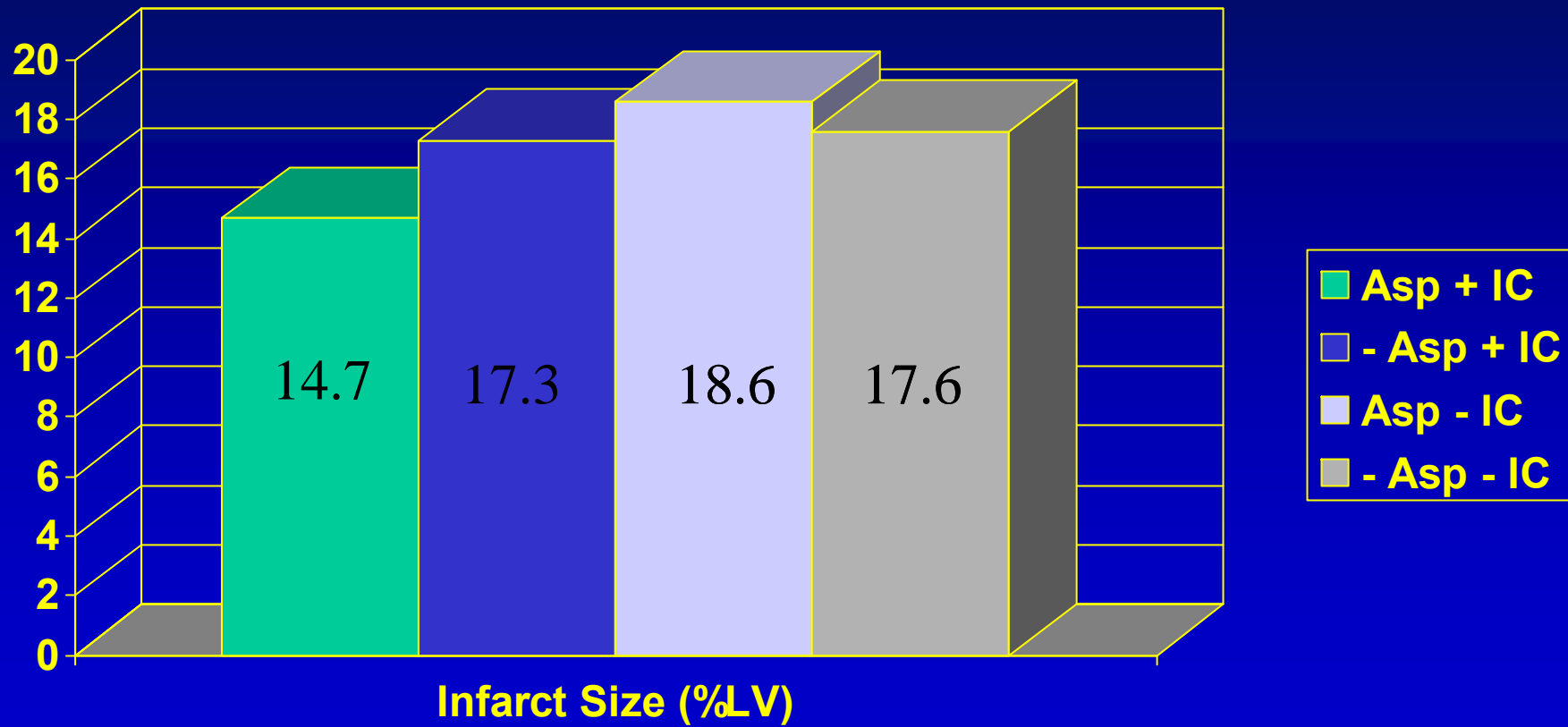
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Table 4. Clinical Efficacy and Safety End Points at 30 Days for the Pooled Randomized Groups

	No. of Events (%)[a]					
	Intracoronary Abciximab[b] (n = 229)	No Intracoronary Abciximab[b] (n = 223)	P Value	Aspiration Thrombectomy[c] (n = 229)	No Aspiration Thrombectomy[c] (n = 223)	P Value
Efficacy End Points						
MACCE	11 (4.8)	7 (3.2)	.36	7 (3.1)	11 (5.0)	.31
MACE	16 (7.0)	15 (6.8)	.91	15 (6.6)	16 (7.2)	.81
Death	8 (3.5)	5 (2.3)	.42	7 (3.1)	6 (2.7)	.81
Reinfarction	1 (0.5)	2 (0.9)	.56	1 (0.5)	2 (0.9)	.55
New-onset severe heart failure	7 (3.1)	10 (4.5)	.44	8 (3.5)	9 (4.1)	.77
Rehospitalization for heart failure	0	2 (0.9)	.15	0	2 (0.9)	.15
Stroke	1 (0.4)	0	.32	0	1 (0.5)	.31
Clinically driven TVR	2 (0.9)	3 (1.4)	.65	1 (0.5)	4 (1.8)	.17
Stent thrombosis, definite or probable	2 (0.9)	2 (0.9)	.99	3 (1.4)	1 (0.5)	.33
Acute, <24 h	0	0		0	0	
Subacute, 1-30 d	2 (0.9)	2 (0.9)	.99	3 (1.4)	1 (0.5)	.33
Bleeding End Points						
HORIZONS-AMI major bleeding	11 (4.9)	8 (3.6)	.50	9 (4.0)	10 (4.6)	.79
TIMI major or minor bleeding	5 (2.2)	4 (1.8)	.75	3 (1.3)	6 (2.8)	.30
TIMI major	5 (2.2)	1 (0.5)	.11	2 (0.9)	4 (1.8)	.40
TIMI minor	0	3 (1.4)	.08	1 (0.5)	2 (0.9)	.55
GUSTO bleeding, any	15 (6.75)	12 (5.5)	.58	12 (5.3)	15 (6.8)	.51
GUSTO severe	10 (4.4)	9 (4.1)	.84	9 (4.0)	10 (4.5)	.77
GUSTO moderate	3 (1.3)	0	.09	2 (0.9)	1 (0.5)	.58
GUSTO mild	2 (0.9)	3 (1.4)	.64	1 (0.4)	4 (1.8)	.17
Any blood product transfusion	4 (1.8)	1 (0.5)	.18	2 (0.9)	3 (1.4)	.64
Thrombocytopenia, in-hospital[d]	2/196 (1.0)	2/179 (1.1)	.99	1/186 (0.5)	3/189 (1.6)	.62

Much More Work to be Done

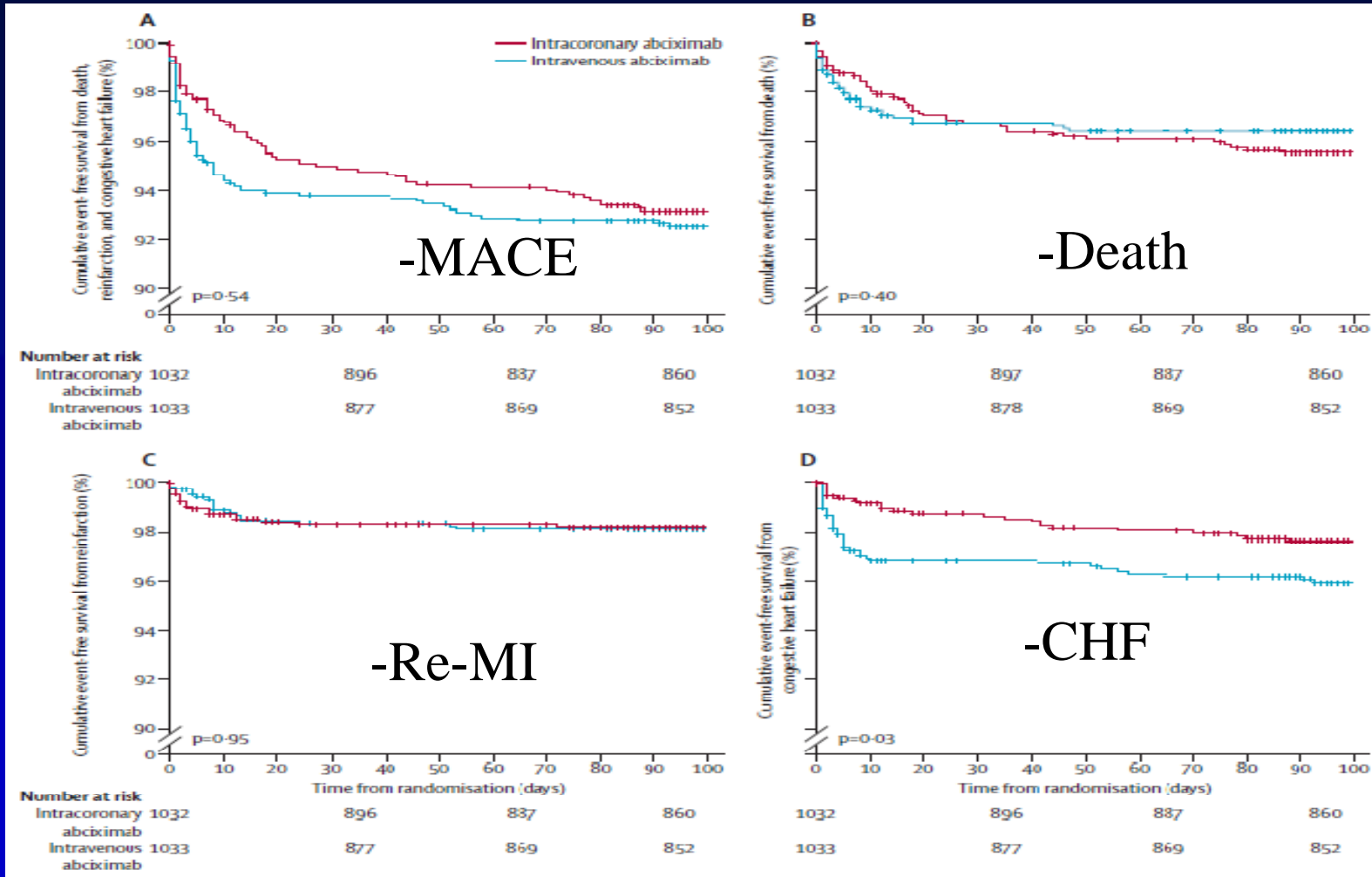|	
TIMI 3 Flow	**91.4%**
MBG ≥2	**81.4%**
Complete STR @ 60 min	**53.7%**

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Pre-AIDA STEMI Randomized Study (N=154)
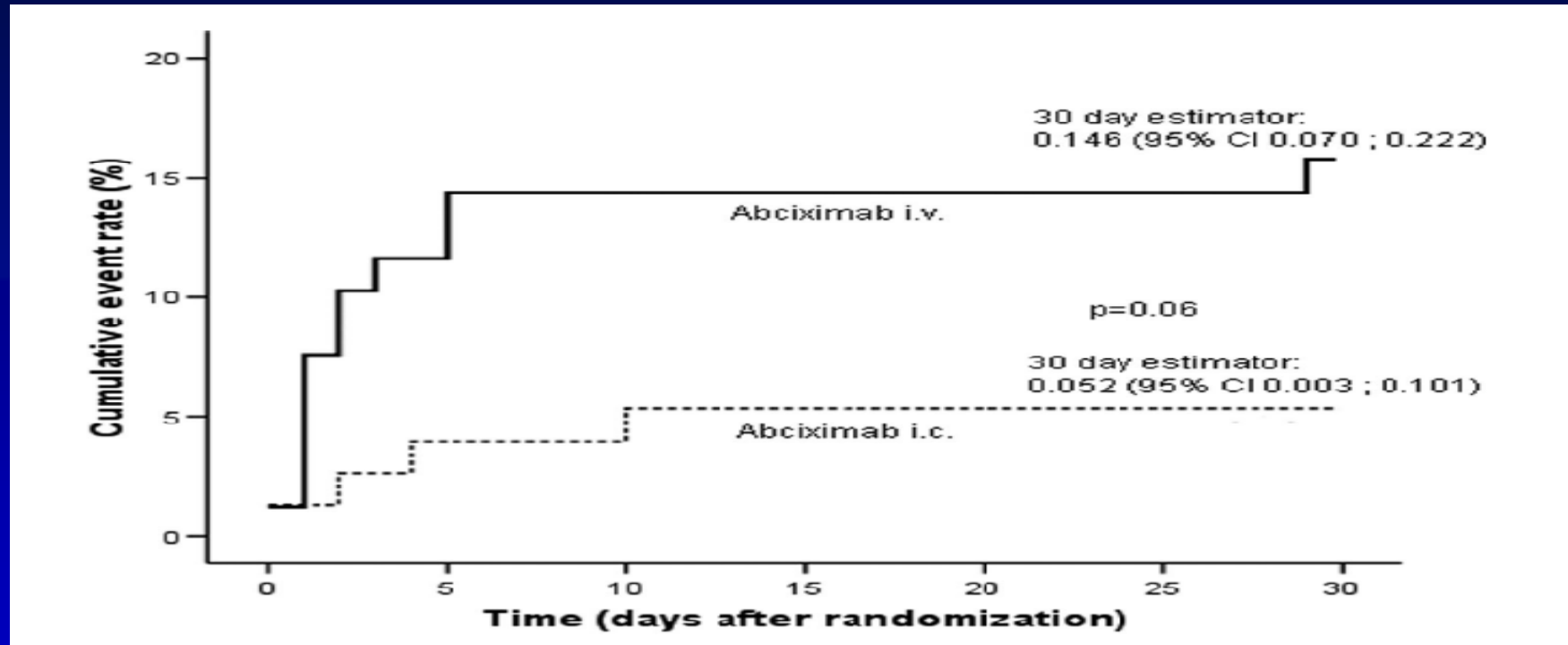
Significant reduction in infarct size and microvascular obstruction

*Circulation 2008;118:49-57*

AIDA STEMI: N=2065

A

	Intracoronary		Intravenous		Weight	Risk ratio M–H, random, 95% CI
	Events	N	Events	N		
AIDA STEMI	42	935	34	932	53·3%	1·23 (0·79–1·92)
CRYSTAL AMI[30]	0	25	1	23	2·7%	0·31 (0·01–7·20)
Iversen[16]	2	185	9	170	10·5%	0·20 (0·04–0·93)
CICERO[6]	5	271	7	263	17·1%	0·69 (0·22–2·16)
Dominguez-Rodriguez[15]	0	25	0	25	..	Not estimable
Thiele[7]	4	77	4	77	12·9%	1·00 (0·26–3·86)
Bellandi[9]	1	22	1	232	3·6%	1·05 (0·07–15·70)
Total (95% CI)	54	1540	56	1513	100·0%	0·86 (0·51–1·46)

Heterogeneity: $\tau^2=0.08$; $\chi^2=6.05$; df=5 (p=0·30); $I^2=17\%$
Test for overall effect: Z=0·56 (p=0·58)

0·01   0·1   1   10   100
Intracoronary better   Intravenous better
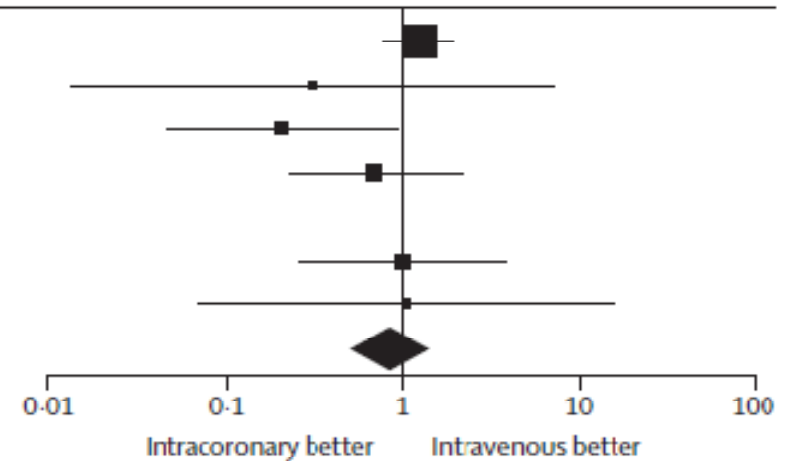
B

	Intracoronary		Intravenous		Weight	Risk ratio M–H, random, 95% CI
	Events	N	Events	N		
AIDI STEMI	17	935	17	932	61·8%	1·00 (0·51–1·94)
Iversen[16]	5	185	8	170	22·8%	0·57 (0·19–1·72)
CICERO[6]	3	271	4	263	12·4%	0·73 (0·16–3·22)
Dominguez-Rodriguez[15]	0	25	0	25	..	Not estimable
Thiele[7]	0	77	2	77	3·0%	0·20 (0·01–4·10)
Total (95% CI)	25	1493	31	1467	100·0%	0·81 (0·48–1·36)

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.60$, df=3 (p=0·66); $I^2=0\%$
Test for overall effect: Z=0·81 (p=0·42)

0·01   0·1   1   10   100
Intracoronary better   Intravenous better
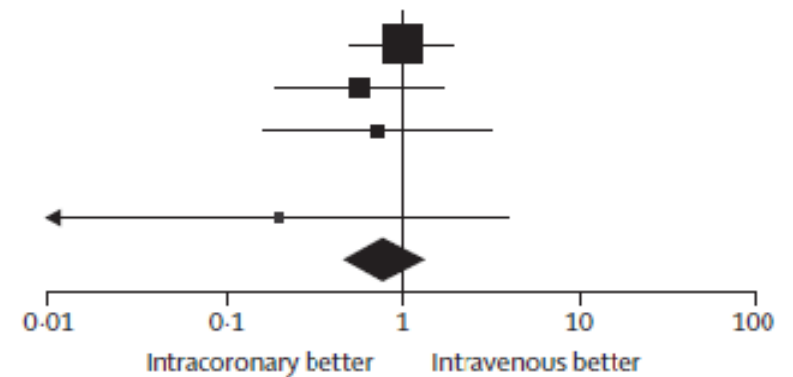
Lancet 2012;379:923-31

Pre-AIDA STEMI vs AIDA STEMI

- Smaller sample size

- Older patients

- No preloading with thienopyridines

- No thrombectomy

- Longer ischemic time

Potential Mechanism of No Sustained Benefit

- "At late sampling after 30 minutes, no significant differences were found between (iv vs. ic abciximab) groups for both platelet reactivity and GP IIb/IIIa receptor occupancy." (Clin Res Cardiol 2012;101:117-24)

- "Platelet glycoprotein IIb/IIIa receptor occupancy was significantly greater with ic vs iv administration (of integrilin): first bolus, $94\pm9\%$ vs $51\pm15\%$, p<0.001; and second bolus, $99\pm2\%$ vs $91\pm4\%$, p=0.001." (Circulation 2010;121:784-791)

Benefit of Upstream IV Integrilin
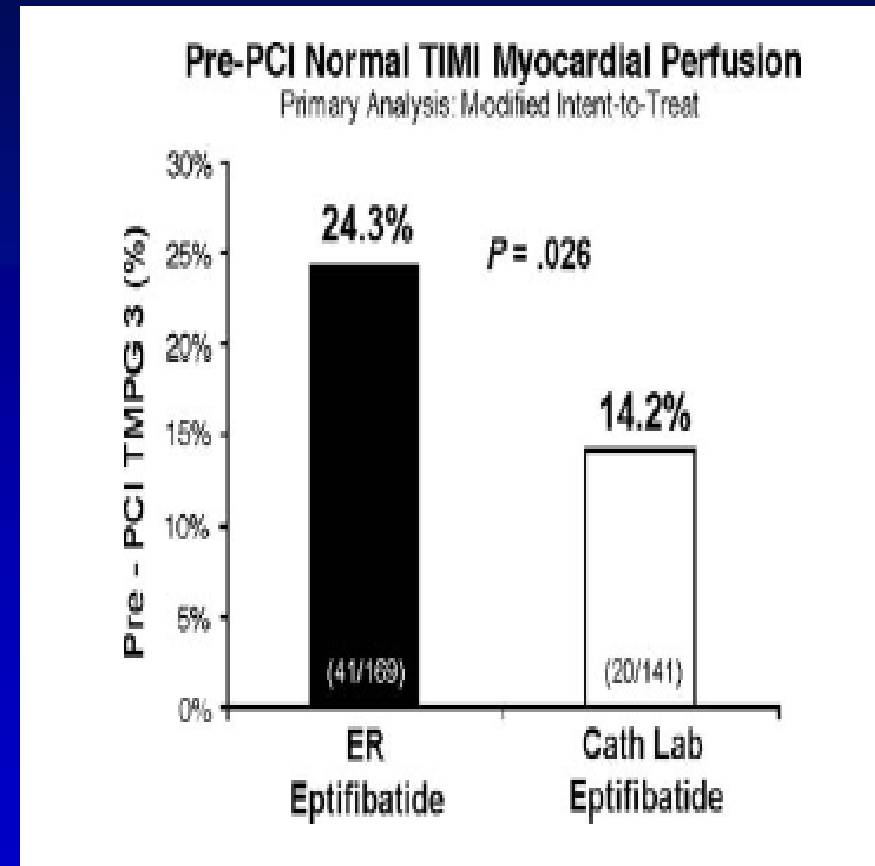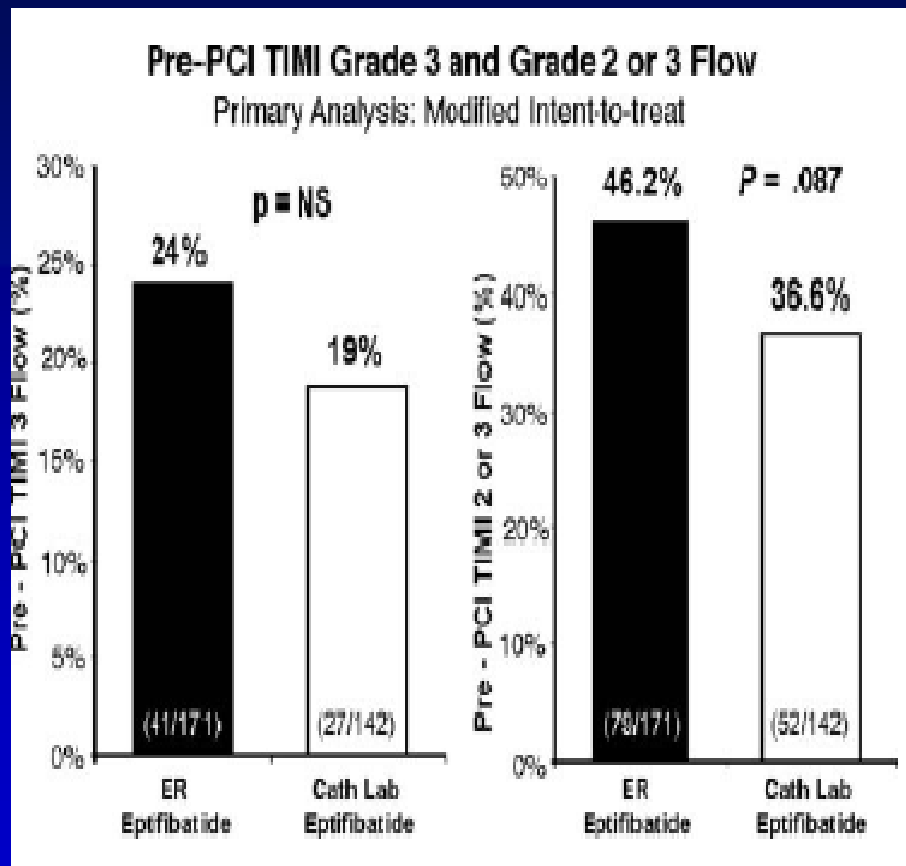
Am Heart J 2006;152:668-75

"The present updated meta-analysis showed that IC administration of abciximab is associated with significant benefits in myocardial perfusion, but not in clinical outcome at short-term follow-up as compared to IV abciximab administration, without any excess of major bleedings in STEMI patients undergoing primary PCI.

IC abciximab administration cannot be routinely recommended, but may be considered in high-risk patients."

Atherosclerosis 2012;Mar 7

IC GP IIb/IIIa Inhibitor Therapy

Safety	**+**
Acute efficacy	**±**
Long-term benefit	**-**
Routine Recommendation	**-**
Select, high-risk patients	**±**
Type of agent	**-**

Proposed Algorithm for the Future

- **Upstream intravenous GPI therapy with ACS Dx**

- **If (+) high-risk angiographic features with thrombus, intracoronary GPI therapy without manipulating the thrombus/lesion**

- **Manual aspiration with a low-profile catheter**

- **Angioplasty of the lesion with a dual angioplasty/local infusion catheter, followed by minimally traumatic stent implantation**

- **Combination pharmacologic/mechanical therapy to achieve normal myocardial perfusion prior to conclusion of the procedure**