SUPPLEMENTAL MATERIAL

Cangrelor, tirofiban and chewed or standard prasugrel regimens in patients with ST-segment elevation myocardial infarction: primary results of the FABOLUS FASTER trial.

Giuseppe Gargiulo et al.

SUPPLEMENTAL MATERIAL - TABLE OF CONTENTS

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Manuscript Responsibility:

Marco Valgimigli, MD, PhD and Giuseppe Gargiulo, MD, PhD wrote the first draft of the manuscript, which was critically reviewed and checked for consistency by the statistical committee. All remaining authors critically reviewed the manuscript.

Prof. Valgimigli submitted the manuscript for publication on behalf of the authors. Under the agreement between Insel Gruppe AG and the funding company, the manuscript was to be provided to MEDICURE (Canada) for review in advance of publication. However, MEDICURE did not have the right of refusal.

Supplementary Table I. Medications before and during PCI.

	Cangrelor [C] (N=40)	Tirofiban [T] (N=40)	chewed Prasugrel [cP] (N=21)	C vs T p-value	C vs cP p-value	T vs cP p-value	integral Prasugrel [iP] (N=21)	iP vs cP p-value
Unfractionated heparin								
Before catheterization	29 (73%)	27 (68%)	16 (76%)	0.808	1.000	0.564	17 (81%)	1.000
Bolus dose - UI/Kg	4965.5±680.5	4963.0±192.5	5218.8±836.0	0.985	0.277	0.133	4823.5±393.0	0.089
ACT performed	13 (48%)	14 (52%)	8 (53%)	1.000	1.000	1.000	9 (53%)	1.000
ACT value - seconds	163.6±31.9	147.5±20.9	154.1±41.0	0.130	0.559	0.618	156.7±14.6	0.864
During catheterization and PCI	39 (98%)	40 (100%)	20 (95%)	1.000	1.000	0.344	21 (100%)	1.000
First bolus dose - UI/Kg	5653.8±2173.9	6337.5±1865.3	6125.0±1848.7	0.137	0.412	0.678	6404.8±1921.1	0.638
Second bolus	16 (40%)	17 (43%)	10 (48%)	1.000	0.596	0.789	7 (33%)	0.530
Second Bolus dose - UI/Kg	3937.5±1579.8	3441.2±1967.6	3500.0±1699.7	0.432	0.511	0.938	3357.1±1313.8	0.855
Based on ACT performed	7 (44%)	10 (59%)	8 (80%)	0.494	0.109	0.406	6 (86%)	1.000
ACT value - seconds	201.6±34.1	204.0±30.7	213.6±53.7	0.880	0.619	0.638	217.8±40.5	0.875
Aspirin	39 (98%)	37 (93%)	18 (86%)	0.615	0.113	0.405	21 (100%)	0.232
Loaded	39 (98%)	37 (93%)	18 (86%)	0.615	0.113	0.405	21 (100%)	0.232
Loading dose	323.1±123.5	298.6±111.5	315.3±122.2	0.369	0.825	0.617	278.6±75.1	0.258
Route of administration				0.146	0.143	0.982		0.911
Intravenous	38 (100%)	35 (95%)	17 (94%)	0.240	0.321	1.000	20 (95%)	1.000
Oral	0 (0%)	2 (5%)	1 (6%)	0.240	0.321	1.000	1 (5%)	1.000
Morphine	22 (55%)	21 (53%)	9 (43%)	1.000	0.426	0.592	8 (38%)	1.000
Total dose - mg	5.1±2.7	4.8±2.7	6.6±4.8	0.716	0.304	0.221	5.5±6.0	0.693
Dose before catheter lab - mg	4.7±2.7	3.7±2.4	6.1±5.3	0.245	0.324	0.097	3.6±4.7	0.312
Other opioids	2 (5%)	2 (5%)	1 (5%)	1.000	1.000	1.000	2 (10%)	1.000

Data expressed as n %, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

Supplementary Table II. Angiographic and procedural details.

	Cangrelor [C] (N=40)	Tirofiban [T] (N=40)	chewed Prasugrel [cP] (N=21)	C vs T p-value	C vs cP p-value	T vs cP p-value	integral Prasugrel [iP] (N=21)	iP vs cl p-value
Time of procedure - minutes	60.38±29.96	59.90±22.44	65.00±30.79	0.936	0.573	0.465	60.90±22.25	0.629
Amount of contrast - ml	202.40±68.42	223.05±77.09	213.14±91.94	0.211	0.607	0.659	208.45±83.64	0.865
Culprit vessel				0.895	0.343	0.297		0.374
Left main artery	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
Left anterior descending artery	17 (43%)	19 (48%)	7 (33%)	0.822	0.586	0.414	11 (55%)	0.215
Left circumflex artery	4 (10%)	4 (10%)	5 (24%)	1.000	0.253	0.253	3 (15%)	0.697
Right coronary artery	19 (48%)	17 (43%)	9 (43%)	0.822	0.791	1.000	6 (30%)	0.520
Culprit lesion type				0.717	0.764	0.528		0.367
De novo	37 (93%)	37 (93%)	20 (95%)	1.000	1.000	1.000	19 (95%)	1.000
In-stent restenosis	1 (3%)	2 (5%)	0 (0%)	1.000	1.000	0.541	1 (5%)	0.488
Stent thrombosis	2 (5%)	1 (3%)	1 (5%)	1.000	1.000	1.000	0 (0%)	1.000
Graft	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
Culprit lesion length - mm	16.38±6.21	17.70±7.73	17.90±7.80	0.400	0.406	0.922	17.90±6.12	0.998
Culprit lesion diameter stenosis - %	95.85±6.26	92.92±14.82	95.81±6.48	0.254	0.981	0.400	96.95±4.44	0.517
Culprit post-procedural stenosis - %	0.0 (0.0; 5.0)	0.0 (0.0; 5.0)	0.0 (0.0; 5.0)	0.255	0.668	0.567	0.0 (0.0; 3.8)	0.510
Thrombus aspiration performed	12 (30%)	14 (35%)	6 (29%)	0.812	1.000	0.776	4 (20%)	0.719
Bifurcation	10 (25%)	9 (23%)	7 (33%)	1.000	0.555	0.376	5 (25%)	0.734
TIMI flow pre PCI culprit				0.493	0.186	0.098		0.200
0	21 (53%)	27 (69%)	11 (52%)	0.168	1.000	0.263	9 (45%)	0.758
1	6 (15%)	4 (10%)	7 (33%)	0.737	0.113	0.039	3 (15%)	0.277
2	9 (23%)	6 (15%)	1 (5%)	0.568	0.143	0.404	5 (25%)	0.093
3	4 (10%)	2 (5%)	2 (10%)	0.675	1.000	0.606	3 (15%)	0.663
TIMI flow post PCI culprit				0.219	0.437			
0	1 (3%)	0 (0%)	0 (0%)	1.000	1.000		0 (0%)	
1	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
2	2 (5%)	0 (0%)	0 (0%)	0.494	0.541		0 (0%)	
3	37 (93%)	39 (100%)	21 (100%)	0.241	0.545		20 (100%)	
Number of segments	2.35±1.56	2.77±1.48	3.05±1.16	0.215	0.077	0.466	2.45±1.54	0.167
Number of stents	1.82±1.31	2.00±0.99	2.29±1.35	0.499	0.197	0.361	2.00±0.92	0.434
Maximum stent diameter	3.30±0.67	3.29±0.45	3.50±0.50	0.974	0.229	0.113	3.24±0.59	0.131
Total stent length	47.32±40.35	52.39±29.72	61.48±38.17	0.542	0.194	0.321	54.15±31.73	0.509
Any overlapping stents	14 (37%)	18 (50%)	9 (43%)	0.348	0.782	0.784	11 (55%)	0.538
Nr of stents*	N = 69	N = 72	N = 48				N = 40	
Predilatation per stent	50 (72%)	51 (71%)	32 (67%)	0.734	0.994	0.762	33 (83%)	0.391
Postdilatation per stent	57 (83%)	63 (88%)	32 (67%)	0.312	0.593	0.166	35 (88%)	0.167

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests) or medians (interquartile 25%-75% range, p-values from Mann-Whitney U-test).
*P-values from mixed models accounting for stents nested within patients.
Seven patients did not receive stents: n=1 randomised to Cangrelor had distal occlusion and no wiring possible; n=1 randomised to Cangrelor, thrombus aspiration only; n=2 randomised to Tirofiban, thrombus aspiration only; n=1 randomised to Tirofiban, no PCI and planned CABG instead; n=1 randomised to integer Prasugrel had final diagnosis of Takotsubo, no segments identified, no PCI.

Supplementary Table III. Clinical outcomes up to 30 days of follow-up.

	Cangrelor [C] (N=40)	Tirofiban [T] (N=40)	chewed Prasugrel [cP] (N=21)	integral Prasugrel [iP] (N=21)	C vs T		C vs cP		T vs cP		iP vs cP	
					HR or RR (95% CI)	p-value	HR or RR (95% CI)	p-value	HR or RR (95% CI)	p-value	HR or RR (95% CI)	p-value
NACE	5 (12.5%)	3 (7.5%)	3 (14.8%)	0 (0.0%)	1.69 (0.40-7.09)	0.47	0.85 (0.20-3.56)	0.83	0.50 (0.10-2.47)	0.40	7.00 (0.38-127.51)	0.23
All-cause death	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1.01 (0.06-16.19)	0.99	1.59 (0.07-37.39)	1.00	1.59 (0.07-37.39)	1.00		
Cardiovascular death	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1.01 (0.06-16.19)	0.99	1.59 (0.07-37.39)	1.00	1.59 (0.07-37.39)	1.00		
Reinfarction (any)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
Definite or Probable Stent Thrombosis	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)			0.18 (0.01-4.23)	0.34	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
Definite Stent Thrombosis	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)			0.18 (0.01-4.23)	0.34	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
Probable Stent Thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
Repeat unplanned revascularisation (any)	2 (5.1%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	5.00 (0.25-100.93)	0.49	1.03 (0.09-11.41)	0.98	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
Urgent TVR	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)			0.18 (0.01-4.23)	0.34	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
TIA	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
Bleeding (any)	4 (10.0%)	2 (5.0%)	2 (10.1%)	0 (0.0%)	2.03 (0.37-11.06)	0.41	1.04 (0.19-5.70)	0.96	0.51 (0.07-3.64)	0.50	5.00 (0.25-98.14)	0.49
Intracranial bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
Gastrointestinal bleeding	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
BARC bleeding events												
type 2, 3 or 5	4 (10.0%)	2 (5.0%)	2 (10.1%)	0 (0.0%)	2.03 (0.37-11.06)	0.41	1.04 (0.19-5.70)	0.96	0.51 (0.07-3.64)	0.50	5.00 (0.25-98.14)	0.49
type 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
type 2	1 (2.6%)	2 (5.0%)	1 (4.8%)	0 (0.0%)	0.49 (0.04-5.37)	0.56	0.52 (0.03-8.30)	0.64	1.03 (0.09-11.31)	0.98	3.00 (0.13-69.61)	1.00
type 3a	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
type 3b	2 (5.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	5.00 (0.25-100.93)	0.49	1.05 (0.10-11.59)	0.97	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
type 3c	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
type 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
type 5a	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
type 5b	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
TIMI bleeding events												
major	3 (7.5%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	7.00 (0.37-131.22)	0.24	1.60 (0.17-15.35)	0.69	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
minor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
requiring medical attention	2 (5.1%)	2 (5.0%)	1 (4.8%)	0 (0.0%)	0.98 (0.14-6.96)	0.98	1.04 (0.09-11.50)	0.97	1.03 (0.09-11.31)	0.98	3.00 (0.13-69.61)	1.00
minimal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)								
GUSTO bleeding events												
severe	3 (7.5%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	7.00 (0.37-131.22)	0.24	1.60 (0.17-15.35)	0.69	0.18 (0.01-4.23)	0.34	3.00 (0.13-69.61)	1.00
moderate	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.00 (0.13-71.48)	1.00	1.59 (0.07-37.39)	1.00				
mild	1 (2.6%)	2 (5.0%)	1 (4.8%)	0 (0.0%)	0.49 (0.04-5.37)	0.56	0.52 (0.03-8.30)	0.64	1.03 (0.09-11.31)	0.98	3.00 (0.13-69.61)	1.00

Number of first events and raw percentages are reported (% of all randomized patients). Hazard ratios are estimated using the Cox regression method, except in the case of zero events when continuity corrected Risk Ratios. Proportional hazards were tested for outcomes with 2 or more events and were non-significant (p=0.92 for NACE, p=0.37 for death and cardiovascular death, p=0.65 for repeat unplnanned revascularization, p=0.55 for any bleeding). All p-values are from Fisher's exact test. All events were censored beyond 30 days. One patient randomised to Cangrelor had two bleeding events.
NACE defined as composite of death, non-fatal myocardial infarction, definite/probable stent thrombosis, non-fatal stroke and BARC 2, 3 or 5.

Supplementary Table IV. Pharmacodynamic effects of drugs measured by light transmittance aggregometry after ADP 20 µmol/l stimulation.

	Cangrelor [C] (N=40)	Tirofiban [C] (N=40)	chewed Prasugrel [cP] (N=21)	C vs T LS mean difference (95% CI)	C vs T p-value	C vs cP LS mean difference (95% CI)	C vs cP p-value	T vs cP LS mean difference (95% CI)	T vs cP p-value	integral Prasugrel [iP] (N=21)	cP vs iP LS mean difference (95% CI)	cP vs iP p-values
%IPA using LTA with ADP 20 µmol/L												
at 15 minutes	34.173±22.703	95.706±8.178	8.094±8.249	-61.534 (-69.719 to -53.348)	<0.001	26.079 (16.214 to 35.944)	<0.001	87.612 (77.747 to 97.477)	<0.001	4.094±5.487	4.000 (-7.297 to 15.297)	0.488
at 30 minutes*	34.124±22.505	95.002±8.996	10.472±11.040	-60.878 (-69.064 to -52.693)	<0.001	23.652 (13.787 to 33.517)	<0.001	84.530 (74.665 to 94.395)	<0.001	6.307±11.382	4.164 (-7.133 to 15.461)	0.470
at 1 hour	32.637±19.567	94.675±9.662	22.213±17.286	-62.038 (-70.223 to -53.852)	<0.001	10.424 (0.559 to 20.289)	0.038	72.462 (62.597 to 82.327)	<0.001	16.376±21.383	5.838 (-5.460 to 17.135)	0.311
at 2 hours	34.069±22.286	92.495±11.204	36.314±19.549	-58.427 (-66.612 to -50.241)	<0.001	-2.246 (-12.111 to 7.619)	0.655	56.181 (46.316 to 66.046)	<0.001	33.189±26.117	3.125 (-8.172 to 14.423)	0.588
at 3 hours	18.695±20.246 [38]	78.625±21.773	43.428±22.592	-60.589 (-68.847 to -52.330)	<0.001	-25.392 (-35.317 to -15.466)	<0.001	35.197 (25.332 to 45.062)	<0.001	48.496±24.822	-5.069 (-16.366 to 6.229)	0.379
at 4 to 6 hours	25.327±25.314 [38]	75.781±23.009	46.401±21.048	-51.113 (-59.372 to -42.855)	<0.001	-21.734 (-31.659 to -11.808)	<0.001	29.379 (19.515 to 39.244)	<0.001	49.269±24.957	-2.867 (-14.164 to 8.430)	0.619
>80% IPA with LTA with ADP 20 µmol/L												
at 15 minutes	5.0%	97.5%	0.0%	-0.913 (-1.003 to -0.823)	<0.001	0.026 (-0.046 to 0.099)	0.409	0.951 (0.896 to 1.006)	<0.001	0.0%		
at 30 minutes	5.0%	95.0%	0.0%	-0.892 (-0.989 to -0.795)	<0.001	0.026 (-0.046 to 0.099)	0.409	0.926 (0.854 to 0.999)	<0.001	0.0%		
at 1 hour	2.5%	92.5%	0.0%	-0.897 (-0.992 to -0.801)	<0.001	0.001 (-0.054 to 0.056)	0.966	0.901 (0.815 to 0.987)	<0.001	0.0%		
at 2 hours	7.5%	87.5%	0.0%	-0.790 (-0.941 to -0.639)	<0.001	0.051 (-0.035 to 0.137)	0.152	0.851 (0.745 to 0.957)	<0.001	4.8%	-0.024 (-0.119 to 0.071)	0.543
at 3 hours	2.6%	55.0%	4.8%	-0.545 (-0.715 to -0.376)	<0.001	0.003 (-0.055 to 0.060)	0.930	0.526 (0.370 to 0.683)	<0.001	9.5%	-0.071 (-0.200 to 0.057)	0.122
at 4 to 6 hours	5.3%	55.0%	9.5%	-0.518 (-0.695 to -0.340)	<0.001	0.029 (-0.047 to 0.105)	0.377	0.526 (0.370 to 0.683)	<0.001	4.8%	-0.024 (-0.119 to 0.071)	0.543
>90% IPA with LTA with ADP 20 µmol/L												
at 15 minutes	2.5%	95.0%	0.0%	-0.936 (-1.004 to -0.867)	<0.001	0.009 (-0.044 to 0.062)	0.708	0.934 (0.863 to 1.005)	<0.001	0.0%		
at 30 minutes	0.0%	90.0%	0.0%		<0.002			0.884 (0.789 to 0.980)	<0.001	0.0%		
at 1 hour	0.0%	90.0%	0.0%		<0.003			0.884 (0.789 to 0.980)	<0.001	0.0%		
at 2 hours	0.0%	80.0%	0.0%		<0.004			0.784 (0.658 to 0.910)	<0.001	0.0%		
at 3 hours	0.0%	42.5%	4.8%		<0.005		0.356	0.409 (0.254 to 0.564)	<0.001	0.0%		1.000
at 4 to 6 hours	0.0%	32.5%	4.8%		<0.006		0.356	0.309 (0.162 to 0.456)	<0.001	4.8%	-0.032 (-0.125 to 0.062)	0.365

Data expressed as means %IPA±standard deviations and least squares mean differences (95% confidence interval) with p-values from mixed models (for %IPA), interpretation of the p-values with Bonferroni correction.
IPA: [%PA at baseline time 0 - %PA at time point t] / %PA at baseline time 0.
In case of zero counts in one group: p-value from Fisher's exact test.
*Primary endpoint, all other endpoints are secondary endpoints.
LS mean difference for >80% and >90% expressed as proportions.

Supplementary Table V. Rates of high residual platelet reactivity at light transmittance aggregometry after ADP 20 and 5 µmol/l stimulation and at Multiplate ADP test.

	Cangrelor [C] (N=40)	Tirofiban [T] (N=40)	chewed Prasugrel [cP] N = 21	C vs T LS mean difference (95% CI)	C vs T p-value	C vs cP LS mean difference (95% CI)	C vs cP p-value	T vs cP LS mean difference (95% CI)	T vs cP p-value	integral Prasugrel [iP] (N=21)	cP vs iP LS mean difference (95% CI)	cP vs iP p-values
>59% using LTA with ADP 20 µmol/L												
at 15 minutes	57.5%	0.0%	100.0%		<0.001		<0.001		<0.001	95.2%		1.000
at 30 minutes*	55.0%	0.0%	90.5%		<0.001	-0.326 (-0.544 to -0.109)	0.012		<0.001	95.2%	-0.071 (-0.236 to 0.094)	0.370
at 1 hour	55.0%	0.0%	66.7%		<0.001	-0.088 (-0.332 to 0.157)	0.495		<0.001	81.0%	-0.177 (-0.426 to 0.073)	0.168
at 2 hours	50.0%	0.0%	38.1%		<0.001	0.126 (-0.132 to 0.383)	0.361		<0.001	52.4%	-0.155 (-0.466 to 0.156)	0.345
at 3 hours	81.6% [38]	7.5%	28.6%	0.733 (0.583 to 0.884)	<0.001	0.502 (0.288 to 0.715)	<0.001	-0.231 (-0.425 to -0.037)	0.030	19.0%	0.133 (-0.112 to 0.378)	0.296
at 4 to 6 hours	68.4% [38]	7.5%	33.3%	0.622 (0.470 to 0.774)	<0.001	0.350 (0.127 to 0.574)	0.009	-0.272 (-0.477 to -0.066)	0.014	19.0%	0.174 (-0.081 to 0.428)	0.186
>46% with LTA with ADP 5 µmol/L												
at 15 minutes	60.0%	0.0%	100.0%		<0.001		<0.001		<0.001	100.0%		0.133
at 30 minutes	55.0%	0.0%	100.0%		<0.001		<0.001		<0.001	90.5%		0.488
at 1 hour	55.0%	0.0%	90.5%		<0.001	-0.274 (-0.497 to -0.052)	0.022		<0.001	81.0%	0.095 (-0.168 to 0.359)	0.529
at 2 hours	55.0%	0.0%	61.9%		<0.001	-0.044 (-0.215 to 0.128)	0.639		<0.001	57.1%	0.024 (-0.203 to 0.251)	0.828
at 3 hours	84.2% [38]	7.5%	42.9%	0.685 (0.431 to 0.938)	<0.001	0.318 (-0.038 to 0.674)	0.002	-0.367 (-0.679 to -0.054)	0.005	33.3%	0.163 (-0.164 to 0.489)	0.347
at 4 to 6 hours	71.1% [38]	5.0%	52.4%	0.664 (0.535 to 0.793)	<0.001	0.120 (-0.127 to 0.367)	0.135	-0.544 (-0.795 to -0.294)	0.002	33.3%	0.284 (0.006 to 0.561)	0.133
AUC>46 using ADPtest												
at 15 minutes	8.6% [35]	8.3% [36]	83.3% [18]	0.016 (-0.134 to 0.166)	0.836	-0.746 (-0.946 to -0.546)	<0.001	-0.762 (-0.953 to -0.571)	<0.001	94.1% [17]	-0.093 (-0.275 to 0.089)	0.338
at 30 minutes	14.3% [35]	8.3% [36]	50.0% [18]	0.076 (-0.082 to 0.233)	0.360	-0.364 (-0.654 to -0.073)	0.009	-0.439 (-0.720 to -0.158)	0.001	94.1% [17]	-0.415 (-0.692 to -0.139)	0.011
at 1 hour	11.4% [35]	5.6% [36]	38.9% [18]	0.075 (-0.071 to 0.222)	0.322	-0.247 (-0.525 to 0.032)	0.046	-0.322 (-0.585 to -0.059)	0.007	70.6% [17]	-0.330 (-0.640 to -0.021)	0.066
at 2 hours	14.3% [35]	8.3% [36]	22.2% [18]	0.076 (-0.082 to 0.233)	0.360	-0.009 (-0.240 to 0.222)	0.939	-0.085 (-0.304 to 0.134)	0.433	17.6% [17]	0.035 (-0.243 to 0.312)	0.808
at 3 hours	48.5% [33]	19.4% [36]	22.2% [18]	0.245 (0.035 to 0.455)	0.015	0.266 (0.002 to 0.529)	0.060	0.021 (-0.206 to 0.247)	0.859	17.6% [17]	0.035 (-0.243 to 0.312)	0.808
at 4 to 6 hours	48.5% [33]	25.0% [36]	22.2% [18]	0.200 (-0.008 to 0.408)	0.050	0.266 (0.002 to 0.529)	0.060	0.066 (-0.160 to 0.292)	0.575	17.6% [17]	0.035 (-0.243 to 0.312)	0.808

Data expressed as counts (% of patients, p-values from mixed models) with least squares mean differences (95% confidence interval) with p-values from mixed models.
In case of zero counts in one group: p-value from Fisher's exact test.
LS mean difference for >80% and >90% expressed as proportions.
*Primary endpoint, all other endpoints are secondary endpoints.

Supplementary Table VI. Primary endpoint for the comparison chewed versus integral prasugrel stratified by patients receiving or not receiving opioids.

	chewed Prasugrel [cP] N = 21	integral Prasugrel [iP] N = 21	cP vs iP LS mean difference (95% CI)	cP vs iP p-value	cP vs iP interaction p-value
%IPA using LTA with ADP 20 µmol/L at 30min					
Opioids					**0.226**
no	14.407 ± 13.120 [11]	9.625 ± 14.150 [12]	4.782 (-10.606 to 20.170)	0.542	
yes	6.143 ± 6.312 [10]	1.884 ± 3.166 [9]	4.259 (-10.862 to 19.380)	0.581	

Supplementary Table VII. Platelet inhibition and aggregation with alternative assessments.

	Cangrelor [C] (N=40)	Tirofiban [T] (N=40)	chewed Prasugrel [cP] (N=21)	C vs T LS mean difference (95% CI)	C vs T p-value	C vs cP LS mean difference (95% CI)	C vs cP p-value	T vs cP LS mean difference (95% CI)	T vs cP p-value	integral Prasugrel [iP] (N=21)	cP vs iP LS mean difference (95% CI)	iP vs cP p-values
%IPA using LTA with ADP 5 µmol/L												
at 15 minutes	43.999±20.901	96.603±6.178	7.107±7.643	-52.604 (-60.461 to -44.746)	<0.001	36.893 (27.423 to 46.362)	<0.001	89.496 (80.027 to 98.966)	<0.001	4.424±6.716	2.682 (-8.162 to 13.527)	0.628
at 30 minutes	44.236±24.087	95.688±7.855	12.180±11.931	-51.451 (-59.309 to -43.594)	<0.001	32.057 (22.587 to 41.527)	<0.001	83.508 (74.039 to 92.978)	<0.001	7.188±13.198	4.991 (-5.853 to 15.836)	0.367
at 1 hour	41.727±22.179	96.111±7.739	23.294±15.595	-54.384 (-62.242 to -46.527)	<0.001	18.433 (8.963 to 27.902)	<0.001	72.817 (63.347 to 82.287)	<0.001	16.858±19.764	6.435 (-4.409 to 17.280)	0.245
at 2 hours	43.545±22.901	94.843±8.010	41.043±16.561	-51.298 (-59.155 to -43.440)	<0.001	2.502 (-6.967 to 11.972)	0.604	53.800 (44.330 to 63.270)	<0.001	39.209±27.069	1.833 (-9.011 to 12.678)	0.740
at 3 hours	19.383±21.383 [38]	83.728±18.819	49.045±18.840	-64.871 (-72.800 to -56.942)	<0.001	-30.189 (-39.717 to -20.660)	<0.001	34.683 (25.213 to 44.152)	<0.001	49.633±24.401	-0.588 (-11.432 to 10.257)	0.915
at 4 to 6 hours	28.001±25.739 [38]	80.752±18.831	50.252±17.746	-53.278 (-61.207 to -45.349)	<0.001	-22.777 (-32.306 to -13.248)	<0.001	30.501 (21.031 to 39.970)	<0.001	52.715±22.662	-2.464 (-13.308 to 8.381)	0.656
>80% IPA with LTA with ADP 5 µmol/L												
at 15 minutes	7.5%	97.5%	0.0%	-0.868 (-0.989 to -0.747)	<0.001	0.043 (-0.044 to 0.130)	0.250	0.943 (0.886 to 1.001)	<0.001	0.0%		
at 30 minutes	10.0%	95.0%	0.0%	-0.816 (-0.945 to -0.688)	<0.001	0.068 (-0.030 to 0.166)	0.095	0.918 (0.844 to 0.992)	<0.001	0.0%		
at 1 hour	7.5%	95.0%	0.0%	-0.850 (-0.972 to -0.728)	<0.001	0.043 (-0.044 to 0.130)	0.250	0.918 (0.844 to 0.992)	<0.001	0.0%		
at 2 hours	7.5%	95.0%	0.0%	-0.850 (-0.972 to -0.728)	<0.001	0.043 (-0.044 to 0.130)	0.250	0.918 (0.844 to 0.992)	<0.001	9.5%	-0.063 (-0.193 to 0.066)	0.195
at 3 hours	2.6%	60.0%	14.3%	-0.610 (-0.748 to -0.473)	<0.001	-0.005 (-0.065 to 0.054)	0.865	0.568 (0.413 to 0.723)	<0.001	4.8%	-0.016 (-0.112 to 0.080)	0.712
at 4 to 6 hours	5.3%	57.5%	4.8%	-0.551 (-0.717 to -0.385)	<0.001	0.021 (-0.056 to 0.098)	0.552	0.543 (0.387 to 0.699)	<0.001	9.5%	-0.063 (-0.193 to 0.066)	0.195
>90% IPA with LTA with ADP 5 µmol/L												
at 15 minutes	5.0%	95.0%	0.0%	-0.897 (-0.993 to -0.801)	<0.001	0.034 (-0.037 to 0.105)	0.245	0.934 (0.863 to 1.005)	<0.001	0.0%		
at 30 minutes	7.5%	92.5%	0.0%	-0.847 (-0.965 to -0.730)	<0.001	0.059 (-0.025 to 0.144)	0.083	0.909 (0.825 to 0.994)	<0.001	0.0%		
at 1 hour	2.5%	90.0%	0.0%	-0.875 (-0.981 to -0.768)	<0.001	0.009 (-0.044 to 0.062)	0.708	0.884 (0.789 to 0.980)	<0.001	0.0%		
at 2 hours	5.0%	87.5%	0.0%	-0.823 (-0.949 to -0.698)	<0.001	0.034 (-0.037 to 0.105)	0.245	0.859 (0.754 to 0.964)	<0.001	4.8%	-0.032 (-0.125 to 0.062)	0.365
at 3 hours	2.6%	47.5%	4.8%	-0.451 (-0.619 to -0.283)	<0.001	0.010 (-0.045 to 0.066)	0.677	0.459 (0.303 to 0.615)	<0.001	0.0%		1.000
at 4 to 6 hours	2.6%	45.0%	4.8%	-0.425 (-0.592 to -0.258)	<0.001	0.010 (-0.045 to 0.066)	0.677	0.434 (0.278 to 0.590)	<0.001	0.0%		1.000
%IPA using LTA with TRAP 5 µmol/L												
at 15 minutes	22.878±27.099 [39]	95.303±5.764	14.614±18.135	-72.425 (-82.220 to -62.631)	<0.001	8.264 (-3.520 to 20.045)	0.169	80.690 (68.960 to 92.419)	<0.001	7.494±13.959	7.120 (-6.312 to 20.552)	0.299
at 30 minutes	25.862±27.754 [39]	94.819±5.719	20.284±21.329	-68.957 (-78.752 to -59.162)	<0.001	5.577 (-6.200 to 17.358)	0.353	74.535 (62.810 to 86.264)	<0.001	9.097±14.410	11.188 (-2.244 to 24.620)	0.103
at 1 hour	25.264±27.790 [39]	95.375±7.152	18.186±14.209	-70.111 (-79.906 to -60.316)	<0.001	7.079 (-4.700 to 18.859)	0.239	77.189 (65.460 to 88.919)	<0.001	16.824±19.346	1.362 (-12.070 to 14.794)	0.842
at 2 hours	36.621±33.259 [39]	95.622±6.249	38.150±27.906	-59.001 (-68.796 to -49.206)	<0.001	-1.529 (-13.310 to 10.251)	0.799	57.471 (45.740 to 69.201)	<0.001	34.338±28.039	3.813 (-9.619 to 17.245)	0.578

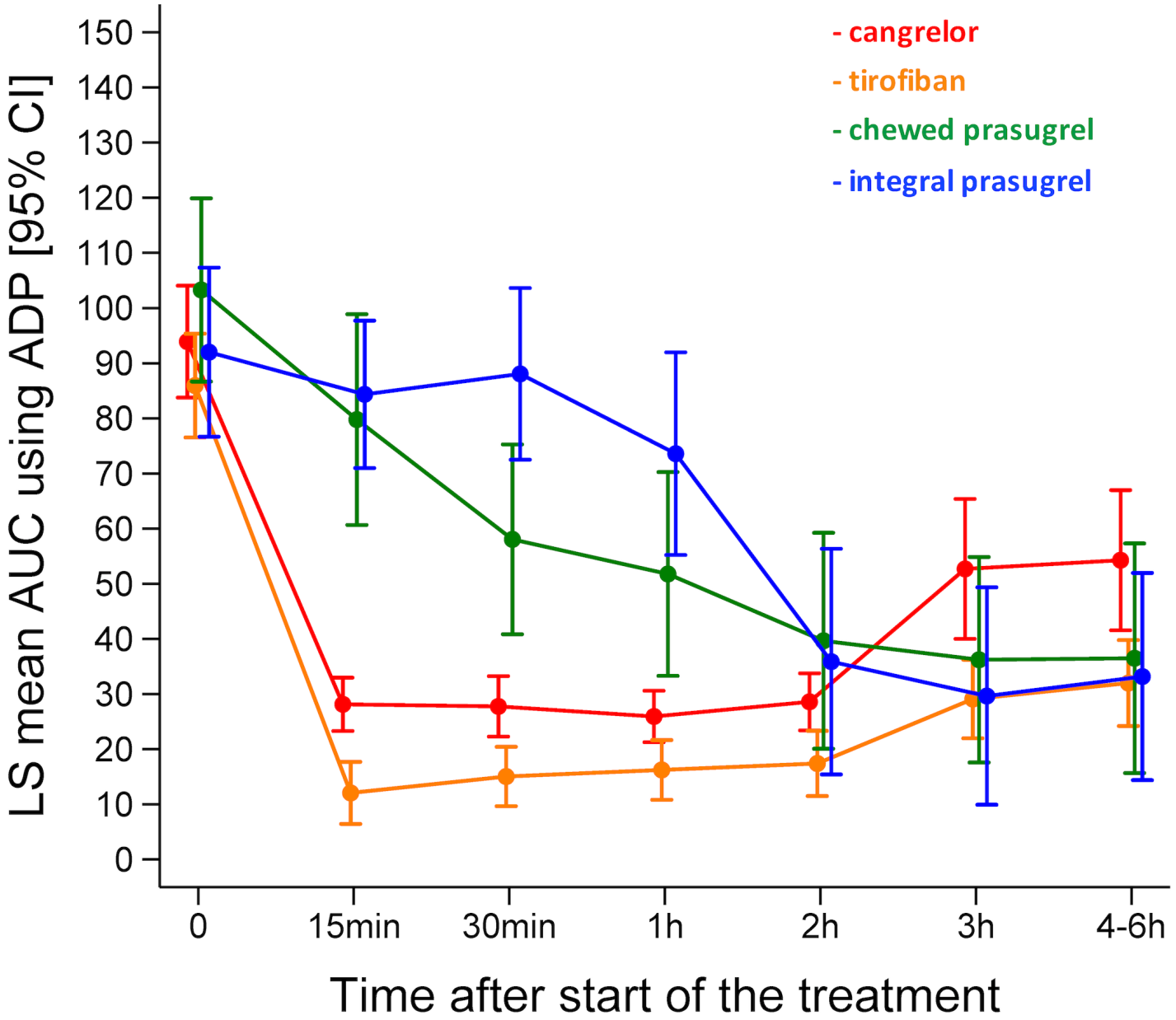
at 3 hours	28.929±32.646 [37]	92.722±10.245	39.586±25.347	-63.476 (-73.364 to -53.588)	<0.001	-10.339 (-22.200 to 1.519)	0.087	53.137 (41.410 to 64.866)	<0.001	39.341±31.325	0.245 (-13.188 to 13.677)	0.972
at 4 to 6 hours	31.166±32.143 [37]	89.567±13.026	49.162±27.289	-58.084 (-67.972 to -48.196)	<0.001	-17.679 (-29.540 to -5.821)	0.003	40.405 (28.680 to 52.134)	<0.001	40.521±32.926	8.641 (-4.791 to 22.074)	0.207
>80% IPA with LTA with TRAP 5 µmol/L												
at 15 minutes	5.1% [39]	97.5%	0.0%	-0.915 (-1.003 to -0.827)	<0.001	0.004 (-0.075 to 0.082)	0.926	0.927 (0.866 to 0.988)	<0.001	0.0%		
at 30 minutes	7.7% [39]	95.0%	0.0%	-0.867 (-0.977 to -0.757)	<0.001	0.029 (-0.062 to 0.121)	0.485	0.902 (0.825 to 0.979)	<0.001	0.0%		
at 1 hour	5.1% [39]	95.0%	0.0%	-0.891 (-0.990 to -0.792)	<0.001	0.004 (-0.075 to 0.082)	0.926	0.902 (0.825 to 0.979)	<0.001	0.0%		
at 2 hours	15.4% [39]	95.0%	4.8%	-0.792 (-0.926 to -0.658)	<0.001	0.106 (-0.013 to 0.225)	0.034	0.902 (0.825 to 0.979)	<0.001	14.3%	-0.095 (-0.249 to 0.059)	0.109
at 3 hours	16.2% [37]	95.0%	9.5%	-0.788 (-0.924 to -0.653)	<0.001	0.115 (-0.010 to 0.239)	0.027	0.902 (0.825 to 0.979)	<0.001	9.5%	-0.048 (-0.179 to 0.083)	0.383
at 4 to 6 hours	13.5% [37]	92.5%	14.3%	-0.790 (-0.931 to -0.649)	<0.001	0.088 (-0.029 to 0.204)	0.074	0.877 (0.788 to 0.967)	<0.001	14.3%	-0.095 (-0.249 to 0.059)	0.109
>90% IPA with LTA with TRAP 5 µmol/L												
at 15 minutes	5.1% [39]	87.5%	0.0%	-0.815 (-0.953 to -0.677)	<0.001	0.020 (-0.056 to 0.095)	0.573	0.843 (0.736 to 0.950)	<0.001	0.0%		
at 30 minutes	5.1% [39]	85.0%	0.0%	-0.786 (-0.931 to -0.640)	<0.001	0.020 (-0.056 to 0.095)	0.573	0.818 (0.703 to 0.933)	<0.001	0.0%		
at 1 hour	0.0% [39]	90.0%	0.0%		<0.001			0.868 (0.770 to 0.966)	<0.001	0.0%		
at 2 hours	5.1% [39]	87.5%	0.0%	-0.815 (-0.953 to -0.677)	<0.001	0.020 (-0.056 to 0.095)	0.573	0.843 (0.736 to 0.950)	<0.001	0.0%		
at 3 hours	5.4% [37]	75.0%	9.5%	-0.680 (-0.822 to -0.538)	<0.001	0.022 (-0.057 to 0.101)	0.531	0.718 (0.581 to 0.856)	<0.001	9.5%	-0.063 (-0.193 to 0.066)	0.195
at 4 to 6 hours	8.1% [37]	60.0%	9.5%	-0.512 (-0.689 to -0.336)	<0.001	0.049 (-0.044 to 0.142)	0.209	0.568 (0.413 to 0.723)	<0.001	4.8%	-0.016 (-0.112 to 0.080)	0.712
%IPA using LTA with TRAP 15 µmol/L												
at 15 minutes	19.095±16.305	88.86 ±7.194	5.034±6.722	-69.768 (-77.130 to -62.407)	<0.001	14.061 (5.189 to 22.932)	0.002	83.829 (74.958 to 92.701)	<0.001	6.382±6.749	-1.348 (-11.508 to 8.812)	0.795
at 30 minutes	15.606±14.500	87.726±10.695	9.602±11.081	-72.120 (-79.481 to -64.759)	<0.001	6.004 (-2.868 to 14.875)	0.185	78.124 (69.252 to 86.995)	<0.001	5.956±8.640	3.646 (-6.514 to 13.805)	0.482
at 1 hour	16.966±17.009	89.082±9.156	11.211±12.807	-72.116 (-79.477 to -64.755)	<0.001	5.755 (-3.117 to 14.626)	0.204	77.871 (69.000 to 86.742)	<0.001	13.631±16.281	-2.420 (-12.580 to 7.739)	0.641
at 2 hours	20.243±21.105	82.320±15.578	20.298±14.952	-62.078 (-69.439 to -54.716)	<0.001	-0.055 (-8.926 to 8.817)	0.990	62.023 (53.151 to 70.894)	<0.001	17.824±17.383	2.473 (-7.686 to 12.633)	0.633
at 3 hours	14.824±19.882 [38]	66.079±26.981	24.464±21.448	-51.435 (-58.871 to -43.999)	<0.001	-9.819 (-18.752 to -0.885)	0.031	41.616 (32.744 to 50.487)	<0.001	21.191±17.866	3.273 (-6.887 to 13.432)	0.528
at 4 to 6 hours	14.945±17.773 [38]	58.980±25.595	23.76 ±23.485	-44.214 (-51.650 to -36.778)	<0.001	-8.999 (-17.933 to -0.066)	0.048	35.215 (26.343 to 44.086)	<0.001	23.105±19.266	0.660 (-9.499 to 10.820)	0.899
>80% IPA with LTA with TRAP 15 µmol/L												
at 15 minutes	0.0%	95.0%	0.0%		<0.001			0.934 (0.863 to 1.005)	<0.001	0.0%		
at 30 minutes	0.0%	80.0%	0.0%		<0.001			0.784 (0.658 to 0.910)	<0.001	0.0%		
at 1 hour	2.5%	87.5%	0.0%	-0.848 (-0.961 to -0.735)	<0.001	0.009 (-0.044 to 0.062)	0.708	0.859 (0.754 to 0.964)	<0.001	0.0%		
at 2 hours	5.0%	65.0%	0.0%	-0.606 (-0.765 to -0.447)	<0.001	0.034 (-0.037 to 0.105)	0.245	0.634 (0.485 to 0.784)	<0.001	0.0%		

at 3 hours	0.0% [38]	37.5%	4.8%		<0.001		0.356	0.359 (0.208 to 0.511)	<0.001	0.0%		1.000
at 4 to 6 hours	0.0% [38]	20.0%	4.8%		0.005		0.356	0.184 (0.058 to 0.310)	<0.001	0.0%		1.000
>90% IPA with LTA with TRAP 15 µmol/L												
at 15 minutes	0.0%	40.0%	0.0%		<0.001			0.384 (0.231 to 0.538)	<0.001	0.0%		
at 30 minutes	0.0%	47.5%	0.0%		<0.001			0.459 (0.303 to 0.615)	<0.001	0.0%		
at 1 hour	0.0%	45.0%	0.0%		<0.001			0.434 (0.278 to 0.590)	<0.001	0.0%		
at 2 hours	0.0%	30.0%	0.0%		<0.001			0.284 (0.140 to 0.428)	<0.001	0.0%		
at 3 hours	0.0% [38]	25.0%	4.8%		0.001		0.356	0.234 (0.098 to 0.370)	<0.001	0.0%		1.000
at 4 to 6 hours	0.0% [38]	12.5%	4.8%		0.055		0.356	0.109 (0.004 to 0.214)	0.011	0.0%		1.000
AUC using ADPtest												
at 0 minutes	93.914±29.544 [35]	85.944±27.835 [36]	103.278±33.406 [18]	7.970 (-4.584 to 20.524)	0.213	-9.363 (-24.702 to 5.975)	0.232	-17.333 (-32.600 to -2.067)	0.026	92.000±29.833 [17]	11.278 (-6.608 to 29.163)	0.217
at 15 minutes	28.143±14.082 [35]	12.083±16.640 [36]	79.778±38.426 [18]	16.060 (3.506 to 28.613)	0.012	-51.635 (-66.974 to -36.296)	<0.001	-67.694 (-82.961 to -52.428)	<0.001	84.353±25.993 [17]	-4.575 (-22.461 to 13.310)	0.616
at 30 minutes	27.771±15.960 [35]	15.056±15.901 [36]	58.056±34.610 [18]	12.716 (0.162 to 25.270)	0.047	-30.284 (-45.623 to -14.945)	<0.001	-43.000 (-58.266 to -27.734)	<0.001	88.059±30.275 [17]	-30.003 (-47.889 to -12.118)	0.001
at 1 hour	25.943±13.597 [35]	16.250±16.002 [36]	51.778±37.162 [18]	9.693 (-2.861 to 22.247)	0.130	-25.835 (-41.174 to -10.496)	0.001	-35.528 (-50.794 to -20.261)	<0.001	73.588±35.744 [17]	-21.810 (-39.696 to -3.925)	0.017
at 2 hours	28.600±15.063 [35]	17.417±17.474 [36]	39.667±39.379 [18]	11.183 (-1.370 to 23.737)	0.081	-11.067 (-26.406 to 4.272)	0.157	-22.250 (-37.516 to -6.984)	0.004	35.882±39.796 [17]	3.784 (-14.101 to 21.670)	0.678
at 3 hours	52.697±35.773 [33]	29.111±21.056 [36]	36.222±37.465 [18]	23.673 (11.028 to 36.317)	<0.001	16.562 (1.148 to 31.975)	0.035	-7.111 (-22.378 to 8.155)	0.361	29.647±38.339 [17]	6.575 (-11.310 to 24.461)	0.471
at 4 to 6 hours	54.273±35.838 [33]	32.000±23.018 [36]	36.500±41.870 [18]	22.360 (9.715 to 35.004)	0.001	17.860 (2.446 to 33.273)	0.023	-4.500 (-19.766 to 10.766)	0.563	33.176±36.528 [17]	3.324 (-14.562 to 21.209)	0.716
AUC using TRAPtest												
at 0 minutes	139.457±30.896 [35]	133.444±34.675 [36]	142.778±36.263 [18]	6.013 (-9.206 to 21.231)	0.439	-3.321 (-21.916 to 15.275)	0.726	-9.333 (-27.841 to 9.174)	0.323	143.824±27.044 [17]	-1.046 (-22.728 to 20.637)	0.925
at 15 minutes	120.886±33.432 [35]	20.389±19.830 [36]	136.167±38.580 [18]	100.497 (85.278 to 115.716)	<0.001	-15.281 (-33.876 to 3.314)	0.107	-115.778 (-134.285 to -97.270)	<0.001	149.353±30.704 [17]	-13.186 (-34.869 to 8.496)	0.233
at 30 minutes	112.829±37.058 [35]	21.500±15.680 [36]	125.278±39.528 [18]	91.329 (76.110 to 106.547)	<0.001	-12.449 (-31.044 to 6.146)	0.189	-103.778 (-122.285 to -85.270)	<0.001	137.529±33.928 [17]	-12.252 (-33.934 to 9.431)	0.268
at 1 hour	110.257±32.598 [35]	25.333±19.136 [36]	124.000±37.321 [18]	84.924 (69.705 to 100.143)	<0.001	-13.743 (-32.338 to 4.852)	0.147	-98.667 (-117.174 to -80.159)	<0.001	131.000±37.809 [17]	-7.000 (-28.682 to 14.682)	0.527
at 2 hours	103.886±34.917 [35]	23.278±17.262 [36]	109.000±47.219 [18]	80.608 (65.389 to 95.827)	<0.001	-5.114 (-23.710 to 13.481)	0.590	-85.722 (-104.230 to -67.215)	<0.001	106.824±37.738 [17]	2.176 (-19.506 to 23.859)	0.844
at 3 hours	122.485±44.355 [33]	51.806±26.780 [36]	108.444±33.007 [18]	71.244 (55.940 to 86.547)	<0.001	14.605 (-4.060 to 33.269)	0.125	-56.639 (-75.146 to -38.132)	<0.001	103.765±41.329 [17]	4.680 (-17.003 to 26.362)	0.672
at 4 to 6 hours	120.909±38.645 [33]	69.361±35.090 [36]	104.611±46.357 [18]	52.112 (36.809 to 67.416)	<0.001	16.862 (-1.802 to 35.527)	0.077	-35.250 (-53.757 to -16.743)	<0.001	109.824±35.910 [17]	-5.212 (-26.895 to 16.470)	0.638

Data expressed as LTA: means %IPA±standard deviations (p-values from mixed models); AUC means U units±standard deviations (p-values from mixed models); >80% and >90% IPA: counts (% of patients, p-values from mixed models). P-values are interpreted using Bonferroni correction.

LS mean difference for >80% and >90% expressed as proportions. AUC: area under the curve; one site (Ferrara University Hospital enrolling 14 patients) did not perform Multiplate so AUC not available. In case of zero counts in one group: p-value from Fisher's exact test.

Supplementary Figure I. Pharmacodynamic effects of drugs measured by Multiplate after ADP stimulation.



<<Facilitation through Aggrastat or cangrelor Bolus and infusion Over prasugreL: a mUlticenter randomized open-label trial in patientS with ST-elevation myocardial inFarction referred for primAry percutaneouS inTERvention. FABOLUS FASTER trial>>

Clinical Study Protocol

Study Type:	*Clinical trial with Investigational Medicinal Product (IMP)*
Study Categorisation:	*Risk category A*
Study Registration:	*www.clinicaltrials.gov: NCT02978040*
Sponsor-Investigator:	*Inselspital - Bern University Hospital, 3010 Bern, Switzerland* *Marco Valgimigli, MD, PhD, marco.valgimigli@insel.ch*
Investigational Medicinal Product:	*Tirofiban (Aggrastat®), Cangrelor, Prasugrel.*
Protocol Version and Date:	*Version 2, 06.12.2016*

The Sponsor-Investigator and trial statistician have approved the protocol version 2 dated 06.12.2016, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Coordinating-Investigator:

Marco Valgimigli, MD, PhD, Head of Clinical research, Cardiology, Bern University Hospital, Bern, Switzerland

Place/Date _____ Signature _____

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	*Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134, Firenze (IT)*
Principal investigator	*Guido Parodi, MD, PhD*

Place/Date	Signature

Site	*Cardiovascular Institute, Azienda Ospedaliero-Universitaria S. Anna,Via Aldo Moro, 8 - 44124 Cona, Ferrara (IT)*
Principal investigator	*Gianluca Campo, MD*

Place/Date	Signature

Site	*Dipartimento di Cardiologia, Cardiochirurgia ed Emergenze Cardiovascolari, Azienda Ospedaliero-Universitaria Federico II,Via Pansini, 5 - 80131 Napoli (IT)*
Principal investigator	*Giovanni Esposito, MD, PhD*

Place/Date	Signature

Site	*Institute de Cardiologie – INSERM UMRS-ICAN 1166; Group Hospitalier Pitié-Salpetrière, 47-83, Bd de l'hopital, 75013, Paris (FR)*
Principal investigator	*Jean-Philippe Collet, MD, PhD*

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Table of Contents

STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Inselspital - Bern University Hospital, 3010 Bern, Switzerland
Study Title:	Facilitation through Aggrastat or cangrelor Bolus and infusion Over prasugreL: a mUlticenter randomized open-label trial in patientS with ST-elevation myocardial inFarction referred for primAry percutaneouS inTERvention.
Short Title:	FABOLUS FASTER trial
Protocol Version and Date:	Version 2 / 06.12.2016
Trial registration:	*www.clinicaltrials.gov* : NCT02978040
Study category and Rationale	Clinical trial of medicinal products, risk category A: all products are authorized in Switzerland and their use is according to the prescribing information.
Clinical Phase:	Phase 4
Background and Rationale:	Primary PCI is the main reperfusion therapy in patients with ST-elevation myocardial infarction. Ancillary pharmacological therapy includes dual antiplatelet therapy with aspirin and an inhibitor of P2Y12 receptor, responsible of ADP-mediated platelet activation. Ticagrelor and prasugrel are the most recent and efficient oral P2Y12 inhibitors available to date. However, in STEMI even prasugrel and ticagrelor could have a significant delay of onset of action. Early in-ambulance administration can increase the inhibition of P2Y12 receptor, however, the benefits versus risks balance remain uncertain. Recently, small-scale independent studies suggested that chewed or crushed loading dose of ticagrelor or prasugrel can achieve more pronounced platelet inhibition compared with standard whole tablets soon after drug administration. Yet, the delay in platelet inhibition remains considerable even after chewed or crushed loading dose of newer oral P2Y12 inhibitors and suboptimal modulation of platelet reactivity at the time of primary intervention may persist. Tirofiban and cangrelor are intravenous drugs with a more rapid onset and offset of action (compared with oral agents). Both agents have been extensively tested in clinical trials including patients with STEMI. However, the comparative speed of action of cangrelor as opposed to tirofiban and to chewed or integer loading dose of prasugrel is unknown.
Objective(s):	To assess the inhibition of platelet aggregation in the early phase of primary PCI (i.e. 30 minutes after start of treatment as primary study endpoint) and up to 6 hours (secondary endpoints). To evaluate the clinical effect of different regimens on platelet inhibition: tirofiban bolus + infusion, cangrelor bolus + infusion, prasugrel chewed loading dose, prasugrel integer loading dose. Other secondary objectives will include adverse clinical events in the overall patient population and the assessment of infarct size and micro-vascular damage by using cardiac magnetic resonance in a subset of patients who will consent to participate into this sub-study.

Outcome(s):	Primary outcome is platelet inhibition assessed with light transmission aggregometry (LTA) in platelet rich plasma with the addition of ADP 20 µmol/l at 30 minutes from drug administration (bolus or oral loading dose). Secondary outcomes include LTA using TRAP at 5 and 15 µmol/l, as well as ADP at 5 µmol/l at all different time points and up to 6 hours and ADP at 20 µmol/l at time points before and later than 30 minutes (15 minutes, 1h, 2h, 3h, 4-6h). Other secondary endpoints will include residual platelet reactivity assessed with Multiplate® technology at all time frames and after ADP and TRAP as agonists, the degree of ST resolution and residual ST segment elevation immediately after intervention and at 90 minutes thereafter, angiographic parameters of reperfusion, including final TIMI flow, corrected TIMI frame count and myocardial blush, adverse clinical ischemic and bleeding events at 48 hours and 30 days. In a subset of included patients, micro-vascular damage at cardiac magnetic resonance imaging modality will be also assessed. Cost-effectiveness analysis will be also carried out by investigating direct and indirect costs in relation to outcomes.
Study design:	Randomized open-label multicenter trial.
Inclusion / Exclusion criteria:	Patients with ST-elevation myocardial infarction referred for primary PCI. Key exclusion criteria are: unconsciousness or other conditions that make the patient incapable of receiving integer oral loading dose of prasugrel, bleeding diathesis, recent administration of fbrinolotycs or GPI or P2Y12 inhibitors or cangrelor, chronic dialysis, previous intracranial haemorrhage, previous stroke or recent TIA, known hypersensitivity to study drugs, need for oral anticoagulant therapy, pregnancy or breast-feeding, limited life expectancy.
Measurements and procedures:	All patients will receive aspirin before primary PCI (150-300 mg orally or 80-150 mg i.v., then 81-325 mg daily) and then will be randomized to 3 different treatment regimens: tirofiban, cangrelor or prasugrel; patients in the prasugrel group will be subsequently randomized to integer oral tablets or chewed oral tablets loading dose at the beginning of primary PCI. In each patient, 7 blood samples will be obtained at different time points (the first before starting of the procedure (baseline), then, counting from drug bolus termination (tirofiban and cangrelor arms) or oral loading dose of prasugrel, at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and between 4 to 6 hours thereafter). ECG will be recorded before and soon after PCI and 90 minutes thereafter. Patients providing consent to participate at the imaging sub-study, will perform cardiac magnetic resonance at 3±1 days (within hospitalization) and 5±1 months. Clinical data collection (vital signs, therapy, clinical events and other data) is scheduled at 30 days.
Study Product / Intervention:	Cangrelor will be administered according to current European label as follows: as bolus of 30 µg/Kg followed by infusion at 4 µg/Kg/min for 2 h (or to the end of PCI); at the end of infusion, oral prasugrel at loading dose of 60 mg will be administrated, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines. As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

Control Interventions (if applicable):	Tirofiban will be administrated according to current European guidelines as follows: as 25 µg/Kg bolus followed by infusion at 0.15 µg/Kg/min for 2 h (or to the end of PCI) (infusion rate of 0.075 µg/Kg/min for patients with creatinine clearance < 60 ml/min); at the end of infusion, oral prasugrel at loading dose of 60 mg will be administrated, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines. As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated. In the prasugrel arm no intravenous anti-platelet drug will be administered. Patients will be randomized to oral integer prasugrel or chewed oral prasugrel at an identical loading dose of 60 mg, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines; As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 70-100 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.
Number of Participants with Rationale:	Total number of patients with primary endpoint assessment: 120 40 patients in the tirofiban group 40 patients in the cangrelor group 40 patients in the prasugrel group (20 integer, 20 chewed) Sample size is calculated to state non-inferiority of cangrelor compared with tirofoban, superiority of both tirofiban and cangrelor compared with integer prasugrel and to show superiority of chewed prasugrel compared to integer.
Study Duration:	1 year
Study Schedule:	February 2017 February 2018
Investigator(s):	Dr. Marco Valgimigli, Inselspital Universitätsspital, Freiburgstrasse 4, 3010 Bern (CH) Dr. Guido Parodi, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134, Firenze (IT) Dr. Gianluca Campo, Cardiovascular Institute, Azienda Ospedaliero-Universitaria S. Anna, Via Aldo Moro, 8 - 44124 Cona, Ferrara (IT) Dr. Giovanni Esposito, Azienda Ospedaliero-Universitaria Federico II, Via Pansini 5, 80131, Napoli (IT) Dr. Jean-Philippe Collet, Institute de Cardiologie – INSERM UMRS-ICAN 1166; Group Hospitalier Pitié-Salpetrière, 47-83, Bd de l'hopital, 75013, Paris (FR)
Study Centre(s):	Inselspital Bern University Hospital, Bern (CH), Azienda Ospedaliero-Universitaria Careggi, Firenze (IT), Azienda Ospedaliero-Universitaria S. Anna, Ferrara (IT), Azienda Ospedaliero-Universitaria Federico II, Napoli (IT), Group Hospitalier Pitié-Salpetrière, Paris (FR).

Statistical Considerations:	Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of at least 94% with i.v. antiplatelet therapy, with a standard deviation of 8%, a non-inferiority margin of 9%, with an alpha of 0.016, 40 patients per group will give 99% of power to show non-inferiority of cangrelor compared to tirofiban. If non-inferiority of cangrelor will not be met, then the superiority of tirofiban over cangrelor will be tested (pre-specified secondary endpoint). Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, this study will have 100% of power to show both superiority of tirofiban (n=40) compared to chewed prasugrel (n=20) and superiority of cangrelor (n=40) compared to chewed prasugrel (n=20). Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, 20 patients per group will give 82% of power to show superiority of chewed prasugrel compared with integer prasugrel.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

ADP	Adenosine diphosphate
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area under the curve
BARC	Bleeding Academic research Consortium
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CTCAE	Common terminology criteria for adverse events
CTU	Clinical Trials Unit
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPI	Glycoprotein IIb/IIIa inhibitors
GUSTO	Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries trial
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
Ho	Null hypothesis
IMP	Investigational Medicinal Product
ISO	International Organisation for Standardisation
LTA	Light Transmission Aggregometry
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
STEMI	ST elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction trial
TRAP	Thrombin receptor-activating peptides

STUDY SCHEDULE

Study Periods	*Enrol lment*	*Treatment, Intervention Period*					*In-Hospital course*				*Follow-up*	
Time point	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Time	*0*	*End of PCI*	*15 min*	*30 min*	*1 h*	*2 h*	*3 h*	*4-6 h*	*48 h*	*3 days*	*30 days*	*5±1 months*
Patient Information and Informed Consent	*x*											
Demographics	*x*											
Medical History	*x*											
In- /Exclusion Criteria	*x*											
Physical Examination	*x*										*x*	
Vital Signs	*x*					*x*			*x*		*x*	
Randomisation	*x*											
ECG	*x*	*x*				*x*						
Administer Study Medication	*x*		*x*	*x*	*x*	*x*						
*MRI**										*x**		*x**
*Primary Variables **	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
*Secondary Variables**	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
Concomitant Therapy, Intervention	*x*					*x*					*x*	
Adverse Events						*x*			*x*	*x**	*x*	

* This will be performed only in patients providing consent to participate to the imaging sub-study.

** Venous blood will be sampled and processed with APACT 4004 Light Transmission Aggregometry and Multiplate; platelets will be stimulated with different agents and concentration (ADP 5-20 umol/l and TRAP 5-15 umol/l for Light Transmission Aggregometry, ADPtest and TRAPtest for Multiplate)

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

This is an Investigator Initiated Trial, the Sponsor is Inselspital - Bern University Hospital, 3010 Bern, Switzerland.

1.2 Principal Investigator(s)

Coordinating Investigator:

Marco Valgimigli, MD, PhD - Inselspital Universitätsspital, Freiburgstrasse 4, 3010 Bern (CH). Phone +41 31 632 3077

Local Principal Investigators

Guido Parodi, MD, PhD - Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134, Firenze (IT). Phone +39 055 794 7966

Gianluca Campo, MD - Cardiovascular Institute, Azienda Ospedaliero-Universitaria S. Anna, Via Aldo Moro, 8 - 44124 Cona, Ferrara (IT). Phone +39 3493757919

Giovanni Esposito, MD, PhD - Azienda Ospedaliero-Universitaria Federico II, Via Pansini 5, 80131 Napoli (IT). Phone:+39 0817463075

Jean-Philippe Collet, MD, PhD - Institute de Cardiologie – INSERM UMRS-ICAN 1166; Group Hospitalier Pitié-Salpetrière, 47-83, Bd de l'hopital, 75013, Paris (FR). Phone +33.1.42.16.29.62

1.3 Statistician ("Biostatistician")

Clinical Trials Unit – University of Bern - Finkenhubelweg 11, 3012 Bern, Phone +41 31 631 35 56

1.4 Any other relevant Committee, Person, Organisation, Institution

Clinical Events Committee for Adjudication of adverse events will be composed by:

- Dr. Pascal Vranckx, Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium
- Dr. Sergio Leonardi, Unità Operativa Complessa Cardiologia, Dipartimento CardioToracoVascolare, Fondazione IRCCS Policlinico San Matteo, Vial Golgi 2, 27100 Pavia, Italy.
- Dr. Salvatore Curello, Unità operativa Emodinamica, Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

www.clinicaltrials.gov : NCT02978040

2.2 Categorisation of study

Category A

This is an interventional study with medicinal products. The IMP used during the study (tirofiban, cangrelor and prasugrel) are authorised in Switzerland and used in accordance with the prescribing information. Loading dose of Prasugrel tablets will be chewed in 20 patients.

2.3 Competent Ethics Committee (CEC)

Responsible investigators at each site ensure that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report shall be submitted within one year after study end.

2.4 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the

Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.5 Declaration of interest

The study will be conducted with intellectual, financial and property independence, no conflict of interest needs to be declared.

2.6 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved.

The formal consent of a participant using the approved consent form must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment, the following informed consent process will be applied:

1) If the patient is conscious he/she will be asked for written consent prior to the randomization.

2) Unconscious patients are excluded from the study.

The three drugs used in this trial are approved for PCI in patients with acute myocardial infarction. From a patient's point of view, the main question about the potential participation to the trial concerns his/her willingness to enable the blood samples to be analysed for platelet tests and the medical data related to the intervention (and during the follow-up) to be used for this research project.

The different options listed above for the informed consent process will ensure that, independently from the emergency intervention, enough time, is given to the participant to decide whether or not to participate to the trial.

2.7 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.8 Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.9 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be

documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Anti-thrombotic therapy is crucial in the management of ST elevation myocardial infarction (STEMI) treated with primary PCI (10). Multiple pathways are involved in platelet activation, adhesion, aggregation and fibrin synthesis, hence several anti-thrombotic agents are used in the acute phase of STEMI (11). The combination of aspirin and oral inhibitors of ADP-activated platelet P2Y12 receptor (the most recent are prasugrel and ticagrelor) has been shown to reduce ischemic recurrences and it is strongly recommended as the current gold standard of therapy (10). However, high residual platelet activity has been reported up to 4 hours after loading dose of prasugrel or ticagrelor, with a large inter-individual variability, depending on drug used, intestinal absorption, bioavailability, etc (12). Early in-ambulance administration can increase the inhibition of P2Y12 receptor, however only little clinical benefit has been shown (13). Recently, two small-scale independent studies suggested that crushed loading dose of ticagrelor or prasugrel can achieve more pronounced platelet inhibition compared with standard whole tablets soon after drug administration (14, 15). The MOJITO (Mashed Or Just Integral pill ofTicagrelOr) trial found that in 82 patients a crushed loading dose of ticagrelor achieved a more pronounced platelet inhibition (tested with VerifyNow system) at 1 hour from oral administration compared with integral tablets (14). Similarly, the CRUSH trial enrolled 52 STEMI patients undergoing primary PCI and found that crushed prasugrel leads to faster drug absorption, and consequently, more prompt and potent antiplatelet effects (demonstrated by VerifyNow and whole blood vasodilator-stimulated phosphoprotein [VASP] assays) compared with whole tablet ingestion (15). More importantly, another recent study, the IPAAD-Tica (The inhibition of platelet-aggregation after administration of three different ticagrelor formulations) compared integer, chewed and crushed oral administration of ticagrelor showing that chewed ticagrelor tablets provided faster platelet inhibition than integer tablets (16). Ninety nine patients with stable angina were randomly assigned, in a 3:1:1 fashion, to one of the 3 groups (integer, crushed or chewed tablets) and platelet reactivity was assessed with VerifyNow before, 20 and 60 min after loading dose (high residual platelet reactivity (HRPR) was defined as >208 P2Y12 reaction units (PRU)). Chewed ticagrelor tablets resulted in significantly lower PRU values compared to crushed or integer tablets at 20 and 60min. Crushed ticagrelor loading dose resulted in significantly lower PRU values compared to integer tablets at 20 min whereas no difference was observed at 60 min. At 20 min, no patients had HRPR with chewed ticagrelor compared to 68% with integer and 30% with crushed ticagrelor loading dose ($p<0.01$) (16).

Several intravenous antiplatelet agents have been used in STEMI to facilitate primary PCI through reducing early ischemic complication. Glycoprotein IIb/IIIa inhibitors (GPI) act on the final pathway of platelet aggregation, preventing the formation of fibrinogen-bridges between platelets (17), they achieve a great platelet activity inhibition at the cost of an increased risk of bleeding, hence current guidelines recommend to use them during primary PCI in selected situations (18,19). Among GPI, **tirofiban** is a non-peptide tyrosine derivate that strongly inhibits platelet aggregation and has a relatively rapid dissociation from the receptor with a half-life of 2-4 hours, hence the drug action can be reversed within hours from infusion discontinuation (17). **Cangrelor**, a recently approved inhibitor of ADP-induced platelet aggregation, may be considered in P2Y12 inhibitor–naive patients undergoing PCI, including primary PCI. It achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus plus infusion, the plasma half-life is approximately 3 to 5 minutes and platelet function is fully restored within 1 hour after cessation of infusion (20).

Use of intravenous drug on top of oral therapy with aspirin and P2Y12 inhibitors confers the benefit of a more rapid and stronger inhibition of platelet function. However they may increase risk of bleeding, depending on patient characteristics and bleeding definition, so the optimal use of these drugs with the optimal benefit-risk ratio is still unknown.

3.2 Investigational Products and Indication

Tirofiban is a competitive GP IIb/IIIa inhibitor (GPI) with high specificity and affinity for the GP IIb/IIIa receptor. It is a small molecule, non-peptide tyrosine derivative, it dissociates from the receptor relatively rapidly, with a half-life of 2–4 hours, and its action is therefore reversed within hours after the completion of infusion (17). Such reversibility may have significant implications with regard to bleeding. It is currently recommended at a dosage of 25 µg/Kg for bolus over 3 minutes followed by infusion of 0.15 µg/Kg/min (reduced dose in case of renal impairment), in selected patients with STEMI at the time of primary PCI when using unfractionated heparin during procedure (ACCF/AHA 2013 Guidelines on STEMI, class of recommendation IIa, level of evidence B; ESC/EACTS 2014 Guidelines on myocardial revascularization, as bail-out in case of thrombotic complications, class of recommendation IIa, level of evidence C) (18,19).

Cangrelor is an ATP-analogue that binds reversibly and with affinity the P2Y12 receptor. It achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus of 30 µg/Kg plus infusion at 4 µg/Kg/min, the plasma half-life is approximately 3 to 5 minutes and platelet function is fully restored within 1 hour after cessation of infusion (20). Both European Medicines Agency and Food and Drug Administration recently (2015) approved its use in P2Y12 inhibitor-naive patients undergoing PCI, including primary PCI. Oral thienopyridines can be administrated at the end of cangrelor infusion (21).

Prasugrel is a third-generation oral thienopyridine that allows a consistent, more efficient (than clopidogrel) conversion to the active metabolite that irreversibly inhibits P2Y12 platelet receptor (22); in a study with STEMI patients treated with bivalirudin during primary PCI the mean delay from loading dose of 60 mg and reduction of platelet activity (assessed as Platelet Reactive Units with VerifyNow system) was 3 hours, with high residual platelet reactivity found in 44% patients after 2 hours (12); when a reversal of platelet inhibition is required in patients on maintenance dose, a 7-days interruption is needed (18). Prasugrel is recommended in patients with STEMI undergoing primary PCI (loading dose of 60 mg, followed by 10 mg daily; class of recommendation I, level of evidence B according to both ACCF/AHA 2013 Guidelines on STEMI and ESC/EACTS 2014 Guidelines on myocardial revascularization). It is contraindicated in patients with prior stroke or transient ischemic attack; in patients older than 75 years or with body weight less than 60 Kg can be used with a maintenance dose of 5 mg daily (18,19).

3.3 Preclinical Evidence

Not applicable, all the drugs used in this study have been previously approved for use in humans in the context of STEMI.

3.4 Clinical Evidence to Date

Dual antiplatelet therapy (DAPT) with aspirin and a last generation oral P2Y12 inhibitor is to date the gold standard for patients with STEMI undergoing primary PCI (10). In the pre-specified STEMI-sub-study of TRITON TIMI 38 trial, prasugrel, compared to clopidogrel, showed reduction of the primary end-point (composite of cardiovascular death, non-fatal myocardial infarction or stroke) as well as cardiovascular mortality alone and also stent thrombosis; differently from the main study, there was no significant increase in terms of non-CABG related bleeding eventss with prasugrel (23).

Tirofiban, along with other GPI, was already extensively used with clinical benefit in patients undergoing primary PCI before the routine use of DAPT (24). More recently, in the On-TIME 2 trial a strategy of routine upstream use of tirofiban, compared to placebo (blinded bail-out possibility), improved the primary end-point of ST resolution and reduced the rate of thrombotic bail-out, without a significant increase in bleeding events (25). In association with prasugrel or clopidogrel, tirofiban was directly compared with prasugrel only in the FABOLUS PRO trial, showing a more than doubled platelet inhibition after 30 minutes from drug administration (26).

Cangrelor as compared with clopidogrel showed in the large CHAMPION PHOENIX trial a reduction in adverse ischemic events at 48 hours after PCI, mainly driven by a reduction in non-fatal myocardial infarction and stent thrombosis (no significant difference in death nor in ischemia driven revascularization), without significant increase in GUSTO and TIMI bleeding events. Importantly, the results were consistent in the STEMI cohort, without significant interaction with the clinical presentation (21).

3.5 Dose Rationale

Prasugrel and cangrelor will be administrated at the dosage regimen and duration as indicated in international guidelines (18,19) and as approved by international associations of drug monitoring (EMA, FDA).

Tirofiban will be administrated with the “high bolus (25 µg/Kg) and infusion (0.15 µg/Kg/min) dose”, that is the dosage regimen at which tirofiban has been showed to be non-inferior compared with abciximab (this regimen is also recommended by international guidelines). In case of creatinine clearance ≤ 60 ml/min, a reduced rate of infusion at 0.075 µg/Kg/min will be used (10). The duration of infusion will be 2 hours (or up to the end of primary PCI, if longer), as in FABOLUS PRO trial, where the 2-h infusion followed by prasugrel administration showed high platelet inhibition up to 24 hours (26).

3.6 Explanation for choice of comparator

The main comparison will be aimed to show non-inferiority of cangrelor compared with tirofiban. Currently, therapy with cangrelor is to be considered in patients not receiving pre-treatment with a P2Y12 inhibitor undergoing PCI, in order to reduce the risk of subsequent periprocedural myocardial infarction and stent thrombosis. Both cangrelor and tirofiban have a fast onset and offset of action. In a third arm patients will receive only prasugrel which is the current standard of care. The aim of this further comparison is to show that both tirofiban and cangrelor might be superior in terms of platelet inhibition, without an excess of adverse clinical events. The last comparison will be within the prasugrel group, in which standard way of administration of loading dose (oral integer tablet) will be compared with oral chewed tablet loading dose administration, which is hypothesized to offer a faster platelet inhibition.

3.7 Risks / Benefits

The main risk after antiplatelet drug administration is related to bleeding events. Common measure of good clinical practice will be adopted to minimize this risk, including the limitation to use heparin after procedure, and discouraging drug cross-over. However, patients with recent or current bleeding are excluded. If necessary, in case of severe bleeding, early discontinuation of tirofiban or cangrelor infusion will be allowed.

No clinical sequelae have been noted in patients who accidentally received cangrelor overdosage in the trials.

Tirofiban has been previously reported to be associated with a slightly increased risk of thrombocytopenia (17); use of short infusion (2 hours) and exclusion of patients with previous thrombocytopenia following GPI administration should minimize this risk. However, platelet count will be monitored accordingly to clinical practice in case of GPI administration (platelet count after 6 hours from the start of treatment) and drug infusion will be immediately stopped in case of uncontrolled severe bleeding.

For patient participating to the imaging substudy with the cardiac MRI, the risks associated with the injection of the contrast medium include: headache, nausea and dizziness for a brief time after the injection as well as a feeling of coldness at the injection site (1 in 100). Less often (1 in 1000), an itchy skin rash might appear and usually settle down within an hour or so. Very rarely (1 in 10'000) a severe allergic (anaphylactic) reaction might occur. Rarely, a nephrogenic systemic fibrosis could occur (in patients with severe kidney disease). The potential benefit of an additional MRI investigation include the evaluation of the cardiac function in a more accurate way than using clinical observation only.

3.8 Justification of choice of study population

Patients with STEMI referred for primary PCI represent a particular situation of patients with emergency need for treatment. The more rapid is the treatment, the better is the outcome. For this reason, to study the rapidity of different pharmacologic regimens in reaching their antiplatelet effect is of paramount clinical relevance for these study population.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to compare the efficacy of cangrelor vs tirofiban, the efficacy of both to standard therapy (prasugrel at standard administration route) and the potential advantages of administrating a chewed loading dose of prasugrel as compared with standard integer tablet administration in patients undergoing primary PCI for STEMI.

4.2 Primary Objective

The main objective is to evaluate the clinical effect of 3 different regimens on platelet inhibition: tirofiban bolus + infusion, cangrelor bolus + infusion, prasugrel chewed loading dose, prasugrel integer loading dose by assessing the inhibition of platelet aggregation in the early phase of primary PCI (i.e. 30 minutes after start of treatment as primary study endpoint) and up to 6 hours (secondary endpoints).

4.3 Secondary Objectives

Other secondary objectives will include adverse clinical events in the overall patient population, the assessment of microvascular reperfusion with angiography and ECG, and assessment of infarct size and microvascular damage by using cardiac magnetic resonance in a subset of patients who will consent to participate into this sub-study.

4.4 Safety Objectives

Safety objective is to show that there is no significant difference in terms of bleeding up to 48 hours from randomization across the three regimens.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary end-point of the study is the percentage of inhibition of platelet activity (IPA) at light transmission aggregometry (LTA) in a platelet-rich plasma stimulated with ADP 20 µmol/l after 30±5 minutes from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose (at the beginning of the primary PCI) in the prasugrel only arm.

5.2 Secondary Outcomes

Secondary end-points include:

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 20 µmol/l at time 0 (before any drug administration, as baseline), at 15±5 minutes, at 1 hour ±5 minutes, at 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose in the prasugrel only arm (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 5 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with thrombin receptor agonist peptide (TRAP) 5 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with TRAP 15 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

area under the curve (AUC) at impedance aggregometry (Multiplate® Electrode Aggregometry) in whole blood with ADPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (AUC unit >46, that is the threshold for high platelet reactivity in patients undergoing PCI);

AUC at impedance aggregometry in whole blood with TRAPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours.

5.3 Other Outcomes of Interest

Effect of drugs on microvascular reperfusion will be evaluated with:

- Corrected TIMI frame count at the end of PCI
- Proportion of patients with TIMI flow <3 at the end of PCI
- ST resolution and residual ST-elevation at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI (pre-PCI, end-PCI, and 90 min after PCI)
- In patients participating to the imaging sub-study also:

  A) Infarct size at cardiac MRI at 3±1 days from primary PCI and at 5±1 months from primary PCI

  B) Intramyocardial haemorrhage at cardiac MRI at 3±1 days from primary PCI and at 5±1 months from primary PCI

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis. Cost-effectiveness analysis will be also carried out by inputting direct and indirect costs in relation to outcomes assessed both in terms of clinical events, surrogate markers of outcomes, such as ST segment elevation resolution or infarct size at MRI as well with respect to degree of platelet inhibition.

5.4 Safety Outcomes

Main safety outcomes are:

- Bleeding Academic Research Consortium (BARC) bleeding grade 2, 3 and 5 at 48 hours and 30 days
- Thrombolysis in Myocardial Infarction (TIMI) bleeding scale at 48 hours and 30 days
- Global Use of Strategies To Open occluded arteries (GUSTO) bleeding scale at 48 hours and 30 days
- Net adverse clinical events (NACE) defined as the composite of death, non-fatal myocardial infarction, definite/probable stent thrombosis, non-fatal stroke, and BARC 2, 3, or 5 at 48 hours and 30 days.

6. STUDY DESIGN

6.1 General study design and justification of design

This will be a multicenter, open-label, prospective, randomized study in patients with STEMI undergoing primary PCI with the aim to show, on top of aspirin, the non-inferiority of cangrelor compared with tirofiban in terms of early platelet inhibition and the superiority of both drugs compared with chewed prasugrel at the beginning of PCI; finally platelet inhibition of oral chewed prasugrel loading dose will be compared with integer oral loading dose.

Once the patient is judged eligible and the informed consent has been signed, the patient will be randomly assigned in a 1:1:1 fashion to tirofiban (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel), cangrelor (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel) or prasugrel 60 mg (40 patients, at the beginning of the PCI). The first randomization will be stratified according to center and to time of symptoms-PCI (<3 hours, 3-6 hours, >6 hours). Patients in the prasugrel arm will undergo a second 1:1 randomization to chewed oral loading dose of prasugrel or integer oral loading dose.

Treatment will be administrated as open-label for patients and treating physician, however results of laboratory tests, ECG, coronary angiography, cardiac MRI and clinical events will be managed by investigators unaware of actual treatment.

Blood samples for platelet inhibition assessment will be collected from the randomization up to 6 hours. Blood samples will be anticoagulated with 0.129 mol/l sodium citrate collected for platelet reactivity. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 70 g, will be stimulated with 5 and 20 mol/l ADP and 5 and 15 mol/l thrombin receptor agonist peptide (TRAP), and aggregation will be assessed using light transmittance aggregometry (LTA). The 100% line will be set using platelet poor plasma and the 0 baseline established with platelet rich plasma (adjusted from 18 _ 109/l up to 30 _ 109/l)

For patients participating at the imaging sub-study, a cardiac magnetic resonance imaging is planned at day 3±1 and at 5±1 months. A dedicated visit to assess vital signs and status is scheduled at 30 days after primary PCI.

6.2 Methods of minimising bias

Randomization will be performed via a web-based interactive randomization system, based on a computer-generated random sequence with a random block size stratified according to center and to the time from symptoms onset-PCI time (< 3 hours, 3-6 hours, > 6 hours).

Site investigator will report anonymized results of aggregation test, ECG, coronary angiography, cardiac MRI and clinical visit to the CoreLab, for blinded adjudication of end-points.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all the following inclusion criteria are eligible for the study:

- Signed Informed Consent
- Age greater than 18 years old
- Have symptoms of acute myocardial ischemia (i.e. new persistent anginal pain) that were lasting at least 20 min with an electrocardiographic ST-segment elevation > 1 mm in 2 or more contiguous ECG leads, or with a new (or presumably new) left bundle branch block or ST segment depression of ≥1 mm in ≥2 of leads V1-3 with a positive terminal T wave
- Referred for primary PCI either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia

The presence of anyone of the following exclusion criteria will lead to exclusion of the participant:

- Unconsciousness
- Other conditions that make the patient incapable receiving integer loading dose of prasugrel
- Any contraindication and/or known hypersensitivity or allergy to aspirin, prasugrel, intravenous unfractionated heparin, cangrelor, tirofiban
- Any contraindication to primary PCI
- Administration of GPI or P2Y12-inhibitors or cangrelor < 7 days
- Chronic dialysis
- Recent (< 15 days) or current major bleeding
- Recent (< 15 days) major surgery
- Administration of fibrinolytics < 30 days
- Current use or indication to oral anticoagulant
- Previous stroke or TIA
- Inability to follow the procedures of the study (language problems, psychological disorders, dementia) or comorbidities associated with less than 6 months survival (active malignancies drug or alcohol abuse, etc.)
- Women who are pregnant or breast feeding or with potential to become pregnant during the course of the study (age < 55 years and last menstruation within the last 12 months) and did not undergo tubal ligation, ovariectomy or hysterectomy
- Participation in another study with investigational drug within the 30 days preceding and during the present study
- Enrolment of the investigator, his/her family members, employees and other dependent persons

7.2 Recruitment and screening

Patients will be screened at the admission. After adequate explanation, patients accepting to participate will sign the informed consent form and will be enrolled in the study by dedicated staff previously identified at each center. See 9.1 for additional details.

Study participants will not receive any payment or compensation for participation in the study.

7.3 Assignment to study groups

Randomization will be performed with a web-based interactive randomization system.

7.4 Criteria for withdrawal / discontinuation of participants

Patients can be withdrawn from the study at every time from the enrolment if any of the following criteria occurs: withdrawal of informed consent, non-compliance, safety issue (i.e. unexpected risk related to study procedure), premature interruption of the study, presence of any exclusion criteria that was not known at the time of enrolment.

8. STUDY INTERVENTION

8.1 Identity of Investigational Medicinal Products

8.1.1 Experimental Intervention

Cangrelor (Kengrexal®) is available as 50 mg powder concentrate vials for solution for infusion. For reconstitution, to each 50 mg/vial, 5 ml of sterile water for injection are added, then the so reconstituted solution is diluted with 250 ml sodium chloride 0.9% solution for injection or glucose 5% solution for injection (this dilution will generate a concentration of 200 µg/ml and should be sufficient for at least two hours of dosing as required). The solution is then visually inspected for particulate matter after reconstitution. Cangrelor is administrated via an intravenous line, the bolus is administered rapidly (<1 minute), from the diluted bag via manual intravenous push or pump, the infusion starts immediately after administration of the bolus.

8.1.2 Control Intervention

Tirofiban (Aggrastat®) concentrate is available in 50 ml vials of a clear, colourless concentrated solution; 1 ml of concentrate for infusion solution contains 281 µg of tirofiban hydrochloride monohydrate which is equivalent to 250 µg tirofiban. Aggrastat® concentrate must be diluted to the same strength of Aggrastat® solution: 50 ml are drawn from a 250 ml container of sterile 0.9% saline or 5% glucose in water and replaced with 50 ml Aggrastat® (from one 50 ml puncture vial) to make up a concentration of 50 µg/ml; before use the created solution is well mixed and visually inspected for visible particles or discolouration; then it is administrated intravenously with a calibrated infusion set.

Prasugrel (Efient®) is available as film-coated tablet of 5 mg (yellow and double-arrow shaped tablets, debossed with “5 MG” on one side and “4760” on the other) or 10 mg (beige and double-arrow shaped tablets, debossed with “10 MG” on one side and “4759” on the other). Prasugrel is intended for oral use, may be administrated with or without food. In the “chewed prasugrel” arm, the patient will be instructed to chew one 60 mg prasugrel pill for at least 10–15 s followed by oral administration of 150 mL of water as previously described (16).

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

Cangrelor is administrated intravenously as a bolus of 30 µg/Kg (in 1 minute) followed by a 2-hours (or up to the end of primary PCI, if longer) infusion at a 4 µg/Kg/min rate, as in CHAMPION PHOENIX trial (21). At the end of the infusion a loading dose of 60 mg Prasugrel will be administrated orally, followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

8.2.2 Control Intervention

Tirofiban is administrated intravenously as a bolus of 25 µg/Kg (in 3 minutes) followed by a 2-hours (or up to the end of primary PCI, if longer) infusion at a 0.15 µg/Kg/min rate (0.075 µg/Kg/min in case of creatinine clearance < 60 ml/min), as in FABOLUS PRO trial (26). At the end of the infusion a loading dose of 60 mg Prasugrel will be administrated orally, followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

In the prasugrel-only arm, a loading dose of 60 mg Prasugrel is administrated orally (chewed or integer, accordingly to the second randomization) as soon as possible after randomization, as in TRITON-TIMI 38 trial (for STEMI) (23), followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

8.3 Dose modifications

Tirofiban, cangrelor and prasugrel administration can be discontinued in advance if an unexpected risk related to drugs rises up or in case of overt unmanageable bleeding, according to the responsible physician or investigator judgement.

8.4 Concomitant Interventions

As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg for Cangrelor and Tirofiban groups or 70-100 UI/Kg for Prasugrel group, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

Any urgent treatment that is needed (physician judgement) is allowed. Interventions that can increase bleeding risk (including minor surgery) that are not urgent will be postponed for at least 6 months after primary PCI, if possible.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Screening will be performed immediately before primary PCI. Potential patients will be informed about the study and asked for participation. Subjects are considered provisionally enrolled with the signature on the written informed consent form, however a subject will only proceed to the baseline evaluations and index procedure if all initial and applicable procedure related to eligibility criteria are met. A copy of the informed consent form with the patient's information document will be given to the patient.

Patients who have signed the informed consent form and meeting all inclusion and exclusion criteria will be included in the study and randomized before primary PCI. Patients will be followed-up at 30 days. A detailed summary of the study time schedule is provided in the Table of the "STUDY SCHEDULE" section.

The following evaluations will be performed at baseline:

- Demographics;
- Relevant medical history (general medical, cardiac, neurologic and renal history; cardiovascular history; risk factors (e.g. dyslipidemia, hypertension, diabetes mellitus, tobacco use); history of peripheral vascular disease, stroke, transient ischemic attack)
- Ischemic/anginal status assessment (according to the Canadian Cardiovascular Society (CCS) classification;
- Current cardiovascular and diabetic medications, including antiplatelet/anticoagulant medications;
- Physical examination, including weight, height, arterial blood pressure and heart rate;
- Routine laboratory tests within 24 hours prior to or immediately after the index procedure, including complete blood count, blood chemistry (Na, K, creatinine, urea), glucose (HbA1c if patient with known diabetes), lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), CK, CK-MB and troponin (T/I, or high sensitive, according to local practice).

After randomization, patients will receive the randomized treatment and will undergo primary PCI (see Figure 1).
Before, during and after primary PCI several blood samples will be drawn at specific time points for aggregation analyses (7 blood samples, see Figure 2).
12-lead ECGs will be recorded and encoded for adjudication at baseline, immediately after PCI and at 90 minutes after PCI and during hospitalization.

Coronary angiograms will be digitalized and encoded for adjudication.

Vital status and adverse clinical events will be assessed at 48 hours.

Patients will be asked to come back for a visit after 30days. A physical examination including a measurement of the vital signs will be performed. Information regarding AE/SAE and the current medication will be collected.

Patients providing consent to participate at the imaging substudy, will undergo a cardiac MRI with injection of contrast medium (Gadolinium) at 3±1 days and 5±1 months.

Figure 1.

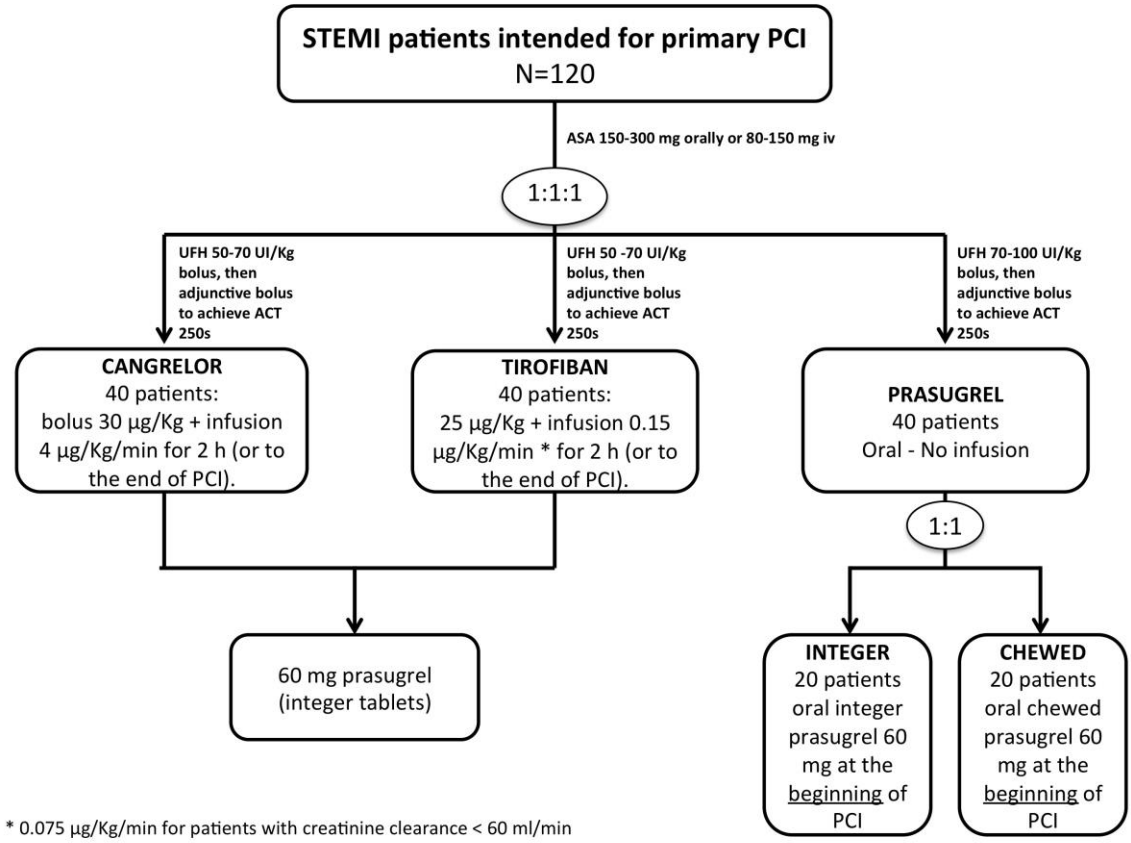
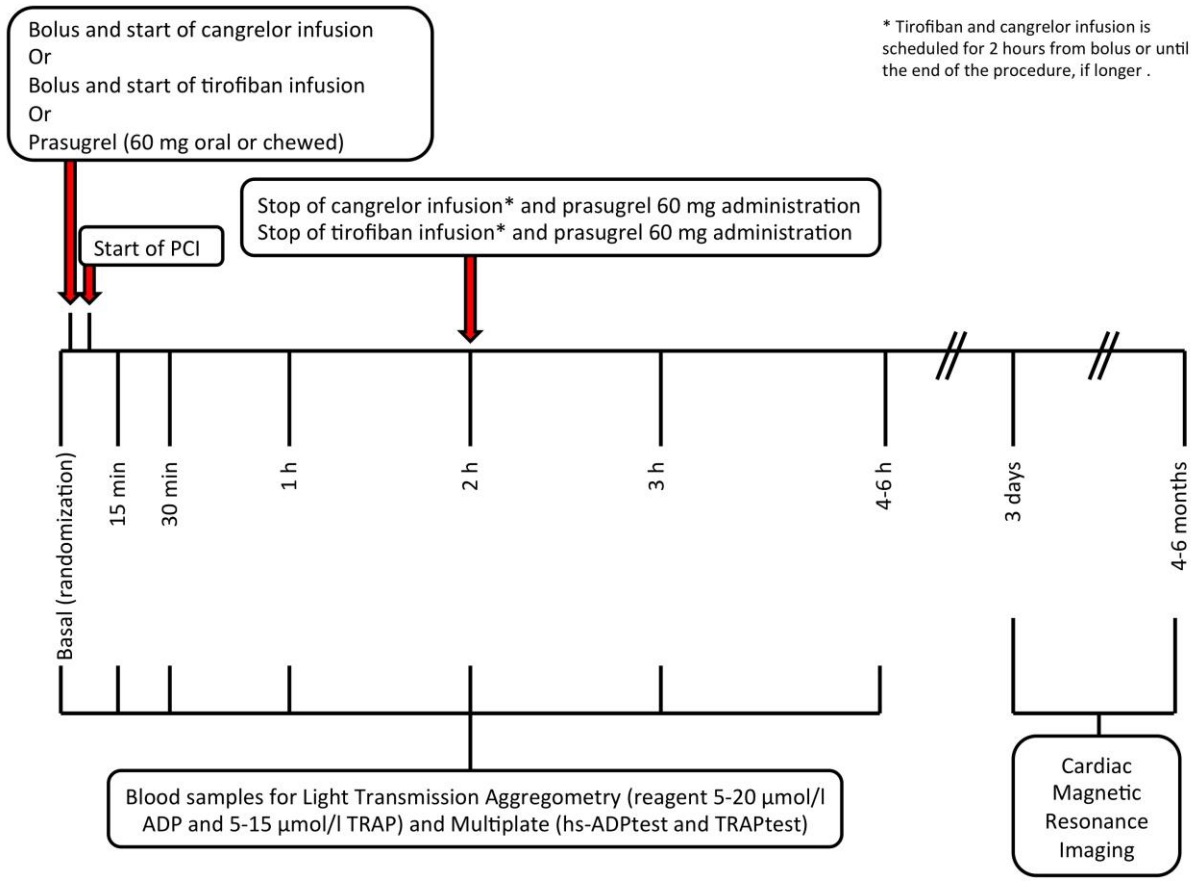

STEMI patients intended for primary PCI
N=120
ASA 150-300 mg orally or 80-150 mg iv
1:1:1
UFH 50-70 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
UFH 50 -70 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
UFH 70-100 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
CANGRELOR
40 patients:
bolus 30 µg/Kg + infusion 4 µg/Kg/min for 2 h (or to the end of PCI).
TIROFIBAN
40 patients:
25 µg/Kg + infusion 0.15 µg/Kg/min * for 2 h (or to the end of PCI).
PRASUGREL
40 patients
Oral - No infusion
1:1
60 mg prasugrel (integer tablets)
INTEGER
20 patients oral integer prasugrel 60 mg at the beginning of PCI
CHEWED
20 patients oral chewed prasugrel 60 mg at the beginning of PCI
* 0.075 µg/Kg/min for patients with creatinine clearance < 60 ml/min

Figure 2.



9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome is the percentage of inhibition of platelet aggregation in a sample of platelet-rich plasma stimulated with 20 µmol/l ADP assessed with Light Transmission Aggregometry after 30 minutes of termination of tirofiban bolus or cangrelor bolus or administration of oral 60 mg of prasugrel.

9.2.2 Assessment of secondary outcomes

At the following time point percentage of platelet inhibition will be assessed with ADP 5 and 20 µmol/l, with TRAP 5 and 15 µmol/l: time 0 (baseline), 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, 3 hours ±5 minutes, 4-6 hours.

At the same time points platelet inhibition will compared between the three arms using AUC at impedance aggregometry (Multiplate® Electrode Aggregometry) in whole blood stimulated with ADP test and TRAP test.

9.2.3 Assessment of other outcomes of interest

12-lead ECG will be recorded at baseline, soon after PCI and 90±30 minutes from the end of PCI, to assess ST resolution (∆% variation of the sum of ST elevation) and residual ST elevation (sum of the absolute values of the 12-lead elevation/depression).

Corrected TIMI frame count and proportion of patients with TIMI flow < 3 at the end of PCI will be derived by two independent expert interventional cardiologists.

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days (dedicated outpatient visit or at least telephone contact). They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis.

For patients participating at the imaging sub-study, cardiac MRI will be performed at 3±1 days from primary PCI and at 5±1 months from primary PCI in order to assess infarct size and intramyocardial haemorrhage.

9.2.4 Assessment of safety outcomes

BARC bleeding grade 2, 3 and 5, TIMI scale and GUSTO scale bleeding at 48 hours and 30 days (blinded adjudication)

Net adverse clinical events defined as the composite of death, definite/probable stent thrombosis and BARC 2-3-5 (blinded adjudication) at 48 hours and 30 days

9.2.4.1 Adverse events

For every suspected adverse event, investigator will be asked to collect time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment.

9.2.4.2 Laboratory parameters

Platelet count reduction under 90,000/mm^3 after 2-6 hour will be considered suggestive for drug-induced thrombocytopenia. Further therapeutic measures will be taken at the physician's discretion.

Hemoglobin and other parameters will be assessed as per local policy.

9.2.4.3 Vital signs

Heart rate, blood pressure, body temperature, respiratory rate, glycemia, invasive hemodynamic measures will be collected at the physician discretion.

ECG will be recorded at the beginning of the procedure, soon after PCI and 90±30 minutes after the end of PCI.

9.2.5 Assessments in participants who prematurely stop the study

Data of withdrawn participants will be collected up to the time of withdrawn. After analysis, the data will be anonymized. The blood specimen collected up to the time of withdrawn will be analysed and destroyed afterwards. After the procedure, all patients will be prescribed the same pharmacologic treatment (irrespective of the study and irrespective of withdraw) corresponding to the standard of care for patients with STEMI treated with primary PCI.

9.3 Procedures at each visit

Vital status and adverse clinical events will be assessed at 30 days, with a dedicated outpatient visit (follow up visit) or at least a telephone contact.

Cardiac MRI at 5±1 months (for patients consenting to participate to the specific substudy).

10. SAFETY REPORTING

During the entire duration of the study, all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and electronic case report forms (eCRF).

Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. [ICH E2A]

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

The "Common Terminology Criteria for Adverse Events CTCAE Version 4.0" terminology will be used.

10.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAE

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study.

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days.

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator within 7 days.

Reporting of SUSAR

In order to identify possible SUSAR, the Sponsor-Investigator will re-evaluate SAE with the Investigator:

- the causality to the Investigational Medicinal Products
- the expectedness of the occurrence

The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. A SUSAR needs to be reported to the Ethics Committee within 7 days, if the event is fatal or within 15 days (all other events).

All SUSAR and SAE will be reported to the Ethics Committee by the Sponsor-Investigator in the Annual Safety report.

10.3 Follow up of (Serious) Adverse Events

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

11. STATISTICAL METHODS

Statistical considerations

11.1 Hypothesis

Null hypothesis A (H_{0A}): cangrelor (bolus followed by infusion) induces a weaker platelet inhibition compared with tirofiban (bolus followed by infusion) after 30 minutes from bolus termination.

Null hypothesis B (H_{0B}): there is no differences between the platelet inhibition induced by both cangrelor and tirofiban (analysed as pooled effect if non-inferiority will be met or analysed for tirofiban only if non-inferiority of cangrelor vs tirofiban will not be met) compared with that induced by chewed prasugrel 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (prasugrel).

Null hypothesis C (H_{0C}): there is no difference between platelet inhibition induced by chewed prasugrel 60 mg compared with integer prasugrel 60 mg after 30 minutes from prasugrel administration.

Alternative hypothesis A (H_{1A}): cangrelor (bolus followed by infusion) induces a platelet inhibition after 30 minutes from bolus termination that is non-inferior to that induced by tirofiban (bolus followed by infusion).

Alternative hypothesis B (H_{1B}): both cangrelor and tirofiban (analysed together if non-inferiority will be met or analysed for tirofiban only group if non-inferiority of cangrelor vs tirofiban will not be met) induces a stronger platelet inhibition compared with chewed prasugrel 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (prasugrel).

Alternative hypothesis C (H_{1C}): chewed prasugrel 60 mg induces a stronger platelet inhibition compared with integer prasugrel 60 mg after 30 minutes from oral administration.

11.2 Determination of Sample Size

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of at least 94% with i.v. antiplatelet therapy, with a standard deviation of 8%, a non-inferiority margin of 9%, with an alpha of 0.016, 40 patients per group will give 99% of power to show non-inferiority of cangrelor compared to tirofiban. If non-inferiority of cangrelor will not be met, then the superiority of tirofiban over cangrelor will be tested (pre-specified secondary endpoint).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, this study will have 100% of power to show both superiority of tirofiban (n=40) compared to chewed prasugrel (n=20) and superiority of cangrelor (n=40) compared to chewed prasugrel (n=20).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, 20 patients per group will give 82% of power to show superiority of chewed prasugrel compared with integer prasugrel.

11.3 Statistical criteria of termination of trial

No statistical interim analyses are planned.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The analysis will be performed according to the intention to treat principle. In patients in the Prasugrel arm in whom bailout intravenous antiplatelet (Tirofiban) is deemed necessary, these patients will be excluded from the analysis which will be performed as modified intention to treat (mITT) considering patients receiving only the randomized treatment. For the primary end-point only patients with a valid value of 30 minutes inhibition of platelet activity will be considered; for the other end-points all the patients randomized will be included.

11.4.2 Primary Analysis

Inhibition of platelet activity (% of IPA at LTA or AUC unit at Multiplate, as continuous variables) will be compared between the groups with ANOVA with Bonferroni post-hoc test.

The proportion of patients with >80% of IPA and >90% of IPA in the three groups will be compared with χ^2 test.

11.4.3 Secondary Analyses

Extent of infarct size at cardiac MRI will be compared between treatment groups with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with multivariable linear regression.

Rate of intramyocardial haemorrhage at cardiac MRI will be compared with χ^2 test and hazard ratios calculated with multivariable logistic regression

Corrected TIMI frame count at the end of PCI will be compared with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with multivariable linear regression

Proportion of patients with TIMI flow < 3 at the end of PCI will be compared with χ^2 test and hazard ratios calculated with multivariable logistic regression

Rate of ST resolution ≥70% at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be compared to baseline ECG with χ^2 test and hazard ratios calculated with multivariable logistic regression

Residual ST elevation at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be calculated by the sum of the absolute values of the 12-lead elevation/depression data and then differences between treatments will be tested with both the nonparametric Wilcoxon rank sum test and a t-test.

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis, bleeding events, net adverse clinical event. Rate of events will be compared with χ^2 test and hazard ratios calculated with multivariable logistic Cox-proportional-hazard model.

11.4.4 Deviation(s) from the original statistical plan

Any deviation from the planned analyses will be reported in the final trial report.

11.5 Handling of missing data and drop-outs

Patients with missing data for the primary end-point will be excluded from the primary analysis.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

The Local Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual enrolled in the study.

An web-based electronic data capture (EDC) system will be used for the study (database technology Oracle Mysql), that fulfils the legal requirements and guidelines. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff. eCRFs documenting SAEs should be submitted via the EDC system within 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment or follow-up visit.

The subject's anonymity will be maintained and the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable legal requirements. Patients data will be encoded:

- Subjects will be identified only by their assigned study number, initials and year of birth on all CRFs
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
- The investigator will maintain all study documents in strict confidence.
- CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified. Copy of coronary angiogram, cardiac MRI and ECG will be stored at the main site in Bern.

All data will be cleared of any sensible personal information, patients will be identified by their assigned study number. For end-point adjudication data will be examined without any form of identification (blinded).

12.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, SAEs, AEs and concomitant medication, and results of relevant examinations. The investigator assures that source documents are appropriately stored and completed. The patient's file will reveal that this patient is a study participant by entering the following details: study name, protocol number, date of enrolment, informed consent obtained prior to any study specific procedure. Each follow up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that medical files and Case Record Forms are accessible for inspection by authorities and monitoring visits.

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. All data will be stored at the main site in Bern.

12.3 Data management

Clinical Trial Unit (CTU) – Bern University, will be in charge for data management and analysis.

Every investigator has access to data of patients enrolled in the own site. CTU in Bern has access to all patient

data and can lock patient's data at the end of the trial. Once locked, data can no longer be modified by site investigator.

12.4 Monitoring

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and that the protocol is followed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Informed Consent Forms for each study participant;
- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.
- Periodic on-site visits and, if necessary, remote monitoring of data.

12.5 Audits and Inspections

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP), and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also CEC) and questions should be answered during inspections. All involved parties must keep the participant data strictly confidential.

12.6 Confidentiality, Data Protection

Direct access to source documents will be permitted for monitoring, audits and inspections. Clinical Trial Unit – Bern has full access to protocol, dataset and statistical codes, during and after the study.

12.7 Storage of biological material and related health data

Biological samples for main endpoints of platelet aggregation will be analysed within few hours from collection. Each participating centre will perform its own platelet aggregation analysis. In addition, 3 samples (plasma, serum and DNA) for each patient will be stored in each centre at -80°C up to one year after study end for future researches. Patients will be adequately informed and will provide consent to this storage of biological material.

13. PUBLICATION AND DISSEMINATION POLICY

After the database has been closed, findings will be shared and discussed with all of the investigators for the study. An estimated timeline for creation of an abstract will be defined at that time. An abstract of the completed study, after input from all the authors, will be submitted to the most important and representative international meetings. A manuscript of the study, having received input from all of the authors, is tentatively scheduled for submission in a renowned international medical journal. Authorship will be selected according to the requirements of the New England Journal of Medicine (http://www.icmje.org/). These indicate that every author provided such contribution to the clinical trial and the subsequent publication that he can take public responsibility for the integrity of the entire work. Therefore the credit for authorship requires substantial contributions to:

1. The conception and design or analysis and interpretation of the data.

2. The drafting of the article or critical revision for important intellectual content.

3. Final approval of the version to be published.

Authors must have fundamentally taken part in all of the 3 aspects.

For the main publication each of the 5 main centers will obtain at least 1 authorship, if the above mentioned requirements 1-3 are met. Prior to sub-publication consultation and agreement of the coordinating investigator and the steering committee are mandatory.

14. FUNDING AND SUPPORT

This study is an Investigator Initiated Trial supported by a grant from Medicure Inc, 2-1250 Waverley Street, Winnipeg, Manitoba, CANADA R3T 6C6.

15. INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

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<<Facilitation through Aggrastat or cangrelor Bolus and infusion Over prasugreL: a mUlticenter randomized open-label trial in patientS with ST-elevation myocardial inFarction referred for primAry percutaneouS inTERvention. FABOLUS FASTER trial>>

Clinical Study Protocol

Study Type:	*Phase III Clinical trial with Investigational Medicinal Product (IMP)*
Study Categorisation:	*Risk category A*
Study Registration:	*www.clinicaltrials.gov: NCT02978040;* *EudraCT number: 2017-001065-24*
Sponsor-Investigator:	*Inselspital - Bern University Hospital, 3010 Bern, Switzerland* *Marco Valgimigli, MD, PhD, marco.valgimigli@insel.ch*
Investigational Medicinal Product:	*Tirofiban (Aggrastat®), Cangrelor, Prasugrel.*
Protocol number/code	*FABOLUS-FASTER*
Protocol Version and Date:	*Version 5.0, 19.04.2018*

The Sponsor-Investigator and trial statistician have approved the protocol version 2 dated 06.12.2016, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Coordinating-Investigator:

Marco Valgimigli, MD, PhD, Head of Clinical research, Cardiology, Bern University Hospital, Bern, Switzerland

Bern, 19.04.2018	
Place/Date	Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site

Principal investigator

Place/Date	Signature

Table of Contents

ABBREVIATIONS

ADP	Adenosine diphosphate
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area under the curve
BARC	Bleeding Academic research Consortium
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CTCAE	Common terminology criteria for adverse events
CTU	Clinical Trials Unit
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPI	Glycoprotein IIb/IIIa inhibitors
GUSTO	Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries trial
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
Ho	Null hypothesis
IMP	Investigational Medicinal Product
ISO	International Organisation for Standardisation
LTA	Light Transmission Aggregometry
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
STEMI	ST elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction trial
TRAP	Thrombin receptor-activating peptides

STUDY SCHEDULE

Study Periods	*Enrol lment*	*Treatment, Intervention Period*					*In-Hospital course*				*Follow-up*	
Time point	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Time	*0*	*End of PCI*	*15 min*	*30 min*	*1 h*	*2 h*	*3 h*	*4-6 h*	*48 h*	*3 days*	*30 days*	*5±1 months*
Patient Information and Informed Consent	*x*											
Demographics	*x*											
Medical History	*x*											
In- /Exclusion Criteria	*x*											
Physical Examination	*x*										*x*	
Vital Signs	*x*					*x*			*x*		*x*	
Randomisation	*x*											
ECG	*x*	*x*				*x*						
Administer Study Medication	*x*		*x*	*x*	*x*	*x*						
*MRI**										*x**		*x**
*Primary Variables *****	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
*Secondary Variables***	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
Concomitant Therapy, Intervention	*x*					*x*					*x*	
Adverse Events						*x*			*x*	*x**	*x*	

* This will be performed only in patients providing consent to participate to the imaging sub-study.

** Venous blood will be sampled and processed for both pharmacokinetic (plasma stabilized and stored for prasugrel active metabolite dosing) and pharmacodynamic analyses (platelets will be stimulated with different agents and concentration: ADP 5-20 umol/l and TRAP 5-15 umol/l for Light Transmission Aggregometry, ADPtest and TRAPtest for Multiplate).

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

This is an Investigator Initiated Trial, the Sponsor is Inselspital - Bern University Hospital, 3010 Bern, Switzerland.

1.2 Principal Investigator(s)

Coordinating Investigator:

Marco Valgimigli, MD, PhD - Inselspital Universitätsspital, Freiburgstrasse 4, 3010 Bern (CH). Phone +41 31 632 3077

Local Site Investigators, see the attachment

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1.3 Statistician ("Biostatistician")

Clinical Trials Unit – University of Bern - Finkenhubelweg 11, 3012 Bern, Phone +41 31 631 35 56

1.4 Any other relevant Committee, Person, Organisation, Institution

Clinical Events Committee for Adjudication of adverse events will be composed by:

- Dr. Pascal Vranckx, Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium
- Dr. Sergio Leonardi, Unità Operativa Complessa Cardiologia, Dipartimento CardioToracoVascolare, Fondazione IRCCS Policlinico San Matteo, Vial Golgi 2, 27100 Pavia, Italy.
- Dr. Salvatore Curello, Unità operativa Emodinamica, Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy.

Data and Safety Monitoring Board (DSMB):

An independent DSMB will monitor the progress of the trial and ensure that the safety of subjects enrolled in the trial is not compromised. The DSMB will consist of 2 physicians experienced in clinical trials, but not participating in this study and 1 statistician:

- Chair: Enrico Frigoli, MD, Clinical Trial Unit (CTU) of Bern, Switzerland
- Member: Roberto Diletti, MD, Thoraxcenter, Rotterdam, The Netherlands
- Member: Alexios Karagiannis, PhD, Clinical Trial Unit (CTU) of Bern, Switzerland

Since all the drugs in the study and their regimens are approved and used on-label but chewed prasugrel, DSMB will specifically monitor the safety of chewed prasugrel as compared to other approved drug regimens. Therefore, for patients randomized to chewed prasugrel arm, the pre-specified rule to interrupt the study will be the occurrence of 2 extra major bleeding (defined as BARC bleeding 3b), or the occurrence of 1 extra episode of intracranial bleeding (BARC 3c) or 1 extra fatal bleeding (BARC 5) or the occurrence of 2 extra stent thrombosis events in the prasugrel chewed group compared with prasugrel integer. The comparator arm for this assessment will be the standard prasugrel integer group. The DSMB will also evaluate the occurrence of any possible combination among those above mentioned adverse events and may decide to stop the study even if the above criteria will not be formally met in case a combination of both ischemic and bleeding events clusters in the chewed as compared to integer prasugrel arm.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

www.clinicaltrials.gov : NCT02978040; EudraCT number: 2017-001065-24

2.2 Categorisation of study

Category A

This is an interventional study with medicinal products. The IMP used during the study (tirofiban, cangrelor and prasugrel) are authorised in Switzerland and Europe and used in accordance with the prescribing information.

Loading dose of Prasugrel tablets will be chewed in 20 patients.

2.3 Competent Ethics Committee (CEC)

Responsible investigators at each site ensure that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report shall be submitted within one year after study end.

2.4 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.5 Declaration of interest

The study will be conducted with intellectual, financial and property independence, no conflict of interest needs to be declared.

2.6 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved.

The formal consent of a participant using the approved consent form must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment, the following informed consent process will be applied:

1) If the patient is conscious he/she will be asked for written consent prior to the randomization.

2) Unconscious patients are excluded from the study.

The three drugs used in this trial are approved for PCI in patients with acute myocardial infarction. From a patient's point of view, the main question about the potential participation to the trial concerns his/her willingness to enable the blood samples to be analysed for platelet tests and the medical data related to the intervention (and during the follow-up) to be used for this research project.

The different options listed above for the informed consent process will ensure that, independently from the emergency intervention, enough time, is given to the participant to decide whether or not to participate to the trial.

2.7 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.8 Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.9 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Anti-thrombotic therapy is crucial in the management of ST elevation myocardial infarction (STEMI) treated with primary PCI (10). Multiple pathways are involved in platelet activation, adhesion, aggregation and fibrin synthesis, hence several anti-thrombotic agents are used in the acute phase of STEMI (11). The combination of aspirin and oral inhibitors of ADP-activated platelet P2Y12 receptor (the most recent are prasugrel and ticagrelor) has been shown to reduce ischemic recurrences and it is strongly recommended as the current gold standard of therapy (10). However, high residual platelet activity has been reported up to 4 hours after loading dose of prasugrel or ticagrelor, with a large inter-individual variability, depending on drug used, intestinal absorption, bioavailability, etc (12). The delayed onset and attenuated antiplatelet effects, which have been consistently observed in STEMI patients treated with oral P2Y12 receptor inhibitors, have been attributed to impaired drug absorption resulting in reduced drug bioavailability. Therefore, strategies to increase bioavailability of orally administered P2Y12 receptor inhibitors have been advocated for STEMI patients, such as increasing the dosing regimen or crushing and chewing tablets. Early in-ambulance administration can increase the inhibition of P2Y12 receptor, however only little clinical benefit has been shown (13). Recently, two small-scale independent studies suggested that crushed loading dose of ticagrelor or prasugrel can achieve more pronounced platelet inhibition compared with standard whole tablets soon after drug administration (14, 15). The MOJITO (Mashed Or Just Integral pill ofTicagrelOr) trial found that in 82 patients a crushed loading dose of ticagrelor achieved a more pronounced platelet inhibition (tested with VerifyNow system) at 1 hour from oral administration compared with integral tablets (14). Similarly, the CRUSH trial enrolled 52 STEMI patients undergoing primary PCI and found that crushed prasugrel leads to faster drug absorption, and consequently, more prompt and potent antiplatelet effects (demonstrated by VerifyNow and whole blood vasodilator-stimulated phosphoprotein [VASP] assays) compared with whole tablet ingestion (15). Importantly, in the CRUSH study, pharmacokinetic analysis showed that crushed prasugrel was associated with faster drug absorption, leading to higher plasma concentrations of prasugrel active metabolite (P-AM) at 30 min and 1 h and similar concentrations by 2 h. The Tmax for P-AM was 0.8 h (0.5 to 4.0 h) and 3 h (0.5 to 24.0 h) in the crushed and whole tablets groups, respectively. Maximal P-AM plasma concentrations, measured as Cmax, were increased by approximately 80% with crushed compared with whole prasugrel tablets. Although exposure to P-AM during overall study time course was similar between treatments, exposure to P-AM during the first 2 h after LD was roughly 3.5-fold higher with crushed prasugrel (15). Another recent study, the IPAAD-Tica (The inhibition of platelet-aggregation after administration of three different ticagrelor formulations) compared integer, chewed and crushed oral administration of ticagrelor showing that chewed ticagrelor tablets provided faster platelet inhibition than integer tablets (16). Ninety nine patients with stable angina were randomly assigned, in a 3:1:1 fashion, to one of the 3 groups (integer, crushed or chewed tablets) and platelet reactivity was assessed with VerifyNow before, 20 and 60 min after loading dose (high residual platelet reactivity (HRPR) was defined as >208 P2Y12 reaction units (PRU)). Chewed ticagrelor tablets resulted in significantly lower PRU values compared to crushed or integer tablets at 20 and 60min. Crushed ticagrelor loading dose resulted in significantly lower PRU values compared to integer tablets at 20 min whereas no difference was observed at 60 min. At 20 min, no patients had HRPR with chewed ticagrelor compared to 68% with integer and 30% with crushed ticagrelor loading dose ($p<0.01$) (16).

Several intravenous antiplatelet agents have been used in STEMI to facilitate primary PCI through reducing early ischemic complication. Glycoprotein IIb/IIIa inhibitors (GPI) act on the final pathway of platelet aggregation, preventing the formation of fibrinogen-bridges between platelets (17), they achieve a great platelet activity inhibition at the cost of an increased risk of bleeding, hence current guidelines recommend to use them during

primary PCI in selected situations (18,19). Among GPI, tirofiban is a non-peptide tyrosine derivate that strongly inhibits platelet aggregation and has a relatively rapid dissociation from the receptor with a half-life of 2-4 hours, hence the drug action can be reversed within hours from infusion discontinuation (17). Cangrelor, a recently approved inhibitor of ADP-induced platelet aggregation, may be considered in P2Y12 inhibitor–naive patients undergoing PCI, including primary PCI. It achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus plus infusion, the plasma half-life is approximately 3 to 5 minutes and platelet function is fully restored within 1 hour after cessation of infusion (20).

Use of intravenous drug on top of oral therapy with aspirin and P2Y12 inhibitors confers the benefit of a more rapid and stronger inhibition of platelet function. However they may increase risk of bleeding, depending on patient characteristics and bleeding definition, so the optimal use of these drugs with the optimal benefit-risk ratio is still unknown.

3.2 Investigational Products and Indication

Tirofiban is a competitive GP IIb/IIIa inhibitor (GPI) with high specificity and affinity for the GP IIb/IIIa receptor. It is a small molecule, non-peptide tyrosine derivative, it dissociates from the receptor relatively rapidly, with a half-life of 2–4 hours, and its action is therefore reversed within hours after the completion of infusion (17). Such reversibility may have significant implications with regard to bleeding. It is currently recommended at a dosage of 25 μg/Kg for bolus over 3 minutes followed by infusion of 0.15 μg/Kg/min (reduced dose in case of renal impairment), in selected patients with STEMI at the time of primary PCI when using unfractionated heparin during procedure (ACCF/AHA 2013 Guidelines on STEMI, class of recommendation IIa, level of evidence B; ESC/EACTS 2014 Guidelines on myocardial revascularization, as bail-out in case of thrombotic complications, class of recommendation IIa, level of evidence C) (18,19).

Cangrelor is an ATP-analogue that binds reversibly and with affinity the P2Y12 receptor. It achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus of 30 μg/Kg plus infusion at 4 μg/Kg/min, the plasma half-life is approximately 3 to 5 minutes and platelet function is fully restored within 1 hour after cessation of infusion (20). Both European Medicines Agency and Food and Drug Administration recently (2015) approved its use in P2Y12 inhibitor-naive patients undergoing PCI, including primary PCI. Oral thienopyridines can be administrated at the end of cangrelor infusion (21).

Prasugrel is a third-generation oral thienopyridine that allows a consistent, more efficient (than clopidogrel) conversion to the active metabolite that irreversibly inhibits P2Y12 platelet receptor (22); in a study with STEMI patients treated with bivalirudin during primary PCI the mean delay from loading dose of 60 mg and reduction of platelet activity (assessed as Platelet Reactive Units with VerifyNow system) was 3 hours, with high residual platelet reactivity found in 44% patients after 2 hours (12); when a reversal of platelet inhibition is required in patients on maintenance dose, a 7-days interruption is needed (18). Prasugrel is recommended in patients with STEMI undergoing primary PCI (loading dose of 60 mg, followed by 10 mg daily; class of recommendation I, level of evidence B according to both ACCF/AHA 2013 Guidelines on STEMI and ESC/EACTS 2014 Guidelines on myocardial revascularization). It is contraindicated in patients with prior stroke or transient ischemic attack; in patients older than 75 years or with body weight less than 60 Kg can be used with a maintenance dose of 5 mg daily (18,19).

3.3 Preclinical Evidence

Not applicable, all the drugs used in this study have been previously approved for use in humans in the context of STEMI.

3.4 Clinical Evidence to Date

Dual antiplatelet therapy (DAPT) with aspirin and a last generation oral P2Y12 inhibitor is to date the gold standard for patients with STEMI undergoing primary PCI (10). In the pre-specified STEMI-sub-study of TRITON TIMI 38 trial, prasugrel, compared to clopidogrel, showed reduction of the primary end-point (composite of cardiovascular death, non-fatal myocardial infarction or stroke) as well as cardiovascular mortality alone and also stent thrombosis; differently from the main study, there was no significant increase in terms of non-CABG related bleeding eventss with prasugrel (23).

Tirofiban, along with other GPI, was already extensively used with clinical benefit in patients undergoing primary PCI before the routine use of DAPT (24). More recently, in the On-TIME 2 trial a strategy of routine upstream use of tirofiban, compared to placebo (blinded bail-out possibility), improved the primary end-point of ST resolution and reduced the rate of thrombotic bail-out, without a significant increase in bleeding events (25). In association with prasugrel or clopidogrel, tirofiban was directly compared with prasugrel only in the FABOLUS PRO trial, showing a more than doubled platelet inhibition after 30 minutes from drug administration (26).

Cangrelor as compared with clopidogrel showed in the large CHAMPION PHOENIX trial a reduction in adverse ischemic events at 48 hours after PCI, mainly driven by a reduction in non-fatal myocardial infarction and stent thrombosis (no significant difference in death nor in ischemia driven revascularization), without significant increase in GUSTO and TIMI bleeding events. Importantly, the results were consistent in the STEMI cohort,

without significant interaction with the clinical presentation (21).

3.5 Dose Rationale

Prasugrel and cangrelor will be administrated at the dosage regimen and duration as indicated in international guidelines (18,19) and as approved by international associations of drug monitoring (EMA, FDA).

Tirofiban will be administrated with the "high bolus (25 μg/Kg) and infusion (0.15 μg/Kg/min) dose", that is the dosage regimen at which tirofiban has been showed to be non-inferior compared with abciximab (this regimen is also recommended by international guidelines). In case of creatinine clearance ≤ 60 ml/min, a reduced rate of infusion at 0.075 μg/Kg/min will be used (10). The duration of infusion will be 2 hours (or up to the end of primary PCI, if longer), as in FABOLUS PRO trial, where the 2-h infusion followed by prasugrel administration showed high platelet inhibition up to 24 hours (26).

3.6 Explanation for choice of comparator

The main comparison will be aimed to show non-inferiority of cangrelor compared with tirofiban. Currently, therapy with cangrelor is to be considered in patients not receiving pre-treatment with a P2Y12 inhibitor undergoing PCI, in order to reduce the risk of subsequent periprocedural myocardial infarction and stent thrombosis. Both cangrelor and tirofiban have a fast onset and offset of action. In a third arm patients will receive only prasugrel which is the current standard of care. The aim of this further comparison is to show that both tirofiban and cangrelor might be superior in terms of platelet inhibition, without an excess of adverse clinical events. The last comparison will be within the prasugrel group, in which standard way of administration of loading dose (oral integer tablet) will be compared with oral chewed tablet loading dose administration, which is hypothesized to offer a faster platelet inhibition.

3.7 Risks / Benefits

The main risk after antiplatelet drug administration is related to bleeding events. Common measure of good clinical practice will be adopted to minimize this risk, including the limitation to use heparin after procedure, and discouraging drug cross-over. However, patients with recent or current bleeding are excluded. If necessary, in case of severe bleeding, early discontinuation of tirofiban or cangrelor infusion will be allowed.

No clinical sequelae have been noted in patients who accidentally received cangrelor overdosage in the trials.

Tirofiban has been previously reported to be associated with a slightly increased risk of thrombocytopenia (17); use of short infusion (2 hours) and exclusion of patients with previous thrombocytopenia following GPI administration should minimize this risk. However, platelet count will be monitored accordingly to clinical practice in case of GPI administration (platelet count after 6 hours from the start of treatment) and drug infusion will be immediately stopped in case of uncontrolled severe bleeding.

For patient participating to the imaging substudy with the cardiac MRI, the risks associated with the injection of the contrast medium include: headache, nausea and dizziness for a brief time after the injection as well as a feeling of coldness at the injection site (1 in 100). Less often (1 in 1000), an itchy skin rash might appear and usually settle down within an hour or so. Very rarely (1 in 10'000) a severe allergic (anaphylactic) reaction might occur. Rarely, a nephrogenic systemic fibrosis could occur (in patients with severe kidney disease). The potential benefit of an additional MRI investigation include the evaluation of the cardiac function in a more accurate way than using clinical observation only.

3.8 Justification of choice of study population

Patients with STEMI referred for primary PCI represent a particular situation of patients with emergency need for treatment. The more rapid is the treatment, the better is the outcome. For this reason, to study the rapidity of different pharmacologic regimens in reaching their antiplatelet effect is of paramount clinical relevance for these study population.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to compare the efficacy of cangrelor vs tirofiban, the efficacy of both to standard therapy (prasugrel at standard administration route) and the potential advantages of administrating a chewed loading dose of prasugrel as compared with standard integer tablet administration in patients undergoing primary PCI for STEMI.

4.2 Primary Objective

The main objective is to evaluate the clinical effect of 3 different regimens on platelet inhibition: tirofiban bolus +

infusion, cangrelor bolus + infusion, prasugrel chewed loading dose, prasugrel integer loading dose by assessing the inhibition of platelet aggregation in the early phase of primary PCI (i.e. 30 minutes after start of treatment as primary study endpoint) and up to 6 hours (secondary endpoints).

4.3 Secondary Objectives

Other secondary objectives will include the assessment of pharmacokinetic in prasugrel arms (chewed versus integer), the assessment of adverse clinical events in the overall patient population, the assessment of microvascular reperfusion with angiography and ECG, and assessment of infarct size and microvascular damage by using cardiac magnetic resonance in a subset of patients who will consent to participate into this sub-study.

4.4 Safety Objectives

Safety objective is to show that there is no significant difference in terms of bleeding up to 48 hours from randomization across the three regimens.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary end-point of the study is the percentage of inhibition of platelet activity (IPA) at light transmission aggregometry (LTA) in a platelet-rich plasma stimulated with ADP 20 μmol/l after 30±5 minutes from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose (at the beginning of the primary PCI) in the prasugrel only arm.

5.2 Secondary Outcomes

Secondary end-points include:

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 20 μmol/l at time 0 (before any drug administration, as baseline), at 15±5 minutes, at 1 hour ±5 minutes, at 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose in the prasugrel only arm (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 5 μmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with thrombin receptor agonist peptide (TRAP) 5 μmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with TRAP 15 μmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%));

area under the curve (AUC) at impedance aggregometry (Multiplate® Electrode Aggregometry) in whole blood with ADPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (AUC unit >46, that is the threshold for high platelet reactivity in patients undergoing PCI);

AUC at impedance aggregometry in whole blood with TRAPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours.

Time for the maximum plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}), and the area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC_{0-t}) will be calculated. Moreover, to explore early exposure to P-AM, AUC from time 0 to 2 h (AUC_{0-2}) will be also calculated.

5.3 Other Outcomes of Interest

Effect of drugs on microvascular reperfusion will be evaluated with:

- Corrected TIMI frame count at the end of PCI
- Proportion of patients with TIMI flow <3 at the end of PCI
- ST resolution and residual ST-elevation at the ECG recorded soon after PCI and at 90±30 minutes from

the end of PCI (pre-PCI, end-PCI, and 90 min after PCI)

- In patients participating to the imaging sub-study also:

  A) Infarct size at cardiac MRI at 3±1 days from primary PCI and at 5±1 months from primary PCI

  B) Intramyocardial haemorrhage at cardiac MRI at 3±1 days from primary PCI and at 5±1 months from primary PCI

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis. Cost-effectiveness analysis will be also carried out by inputting direct and indirect costs in relation to outcomes assessed both in terms of clinical events, surrogate markers of outcomes, such as ST segment elevation resolution or infarct size at MRI as well with respect to degree of platelet inhibition.

5.4 Safety Outcomes

Main safety outcomes are:

- Bleeding Academic Research Consortium (BARC) bleeding grade 2, 3 and 5 at 48 hours and 30 days
- Thrombolysis in Myocardial Infarction (TIMI) bleeding scale at 48 hours and 30 days
- Global Use of Strategies To Open occluded arteries (GUSTO) bleeding scale at 48 hours and 30 days
- Net adverse clinical events (NACE) defined as the composite of death, non-fatal myocardial infarction, definite/probable stent thrombosis, non-fatal stroke, and BARC 2, 3, or 5 at 48 hours and 30 days.

6. STUDY DESIGN

6.1 General study design and justification of design

This will be a multicenter, open-label, prospective, randomized study in patients with STEMI undergoing primary PCI with the aim to show, on top of aspirin, the non-inferiority of cangrelor compared with tirofiban in terms of early platelet inhibition and the superiority of both drugs compared with chewed prasugrel at the beginning of PCI; finally platelet inhibition of oral chewed prasugrel loading dose will be compared with integer oral loading dose.

Once the patient is judged eligible and the informed consent has been signed, the patient will be randomly assigned in a 1:1:1 fashion to tirofiban (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel), cangrelor (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel) or prasugrel 60 mg (40 patients, at the beginning of the PCI). The first randomization will be stratified according to center and to time of symptoms-PCI (<3 hours, 3-6 hours, >6 hours). Patients in the prasugrel arm will undergo a second 1:1 randomization to chewed oral loading dose of prasugrel or integer oral loading dose.

Treatment will be administrated as open-label for patients and treating physician, however results of laboratory tests, ECG, coronary angiography, cardiac MRI and clinical events will be managed by investigators unaware of actual treatment.

Blood samples for platelet inhibition assessment will be collected from the randomization up to 6 hours. Blood samples will be anticoagulated with 0.129 mol/l sodium citrate collected for platelet reactivity. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 70 g, will be stimulated with 5 and 20 mol/l ADP and 5 and 15 mol/l thrombin receptor agonist peptide (TRAP), and aggregation will be assessed using light transmittance aggregometry (LTA). The 100% line will be set using platelet poor plasma and the 0 baseline established with platelet rich plasma (adjusted from 18 x 109/l up to 30 x 109/l).

Blood samples for pharmacokinetic assessment (determination of plasma concentration of prasugrel's active metabolite (PAM)) will be collected from the randomization up to 6 hours. Specifically, 4 ml blood samples will be collected into pre-cooled EDTA tubes at the established time points (baseline, 15 min, 30 min, 1h, 2h, 3h and 4-6h) and will be treated with 25 μl of 500 mM 3′-methoxyphenacyl bromide in acetonitrile within 30 s of collection to derivatize and stabilize the PAM. Centrifugation of the sample will be performed within 30 minutes (2800 rpm for 15 min at 4°C), and plasma samples prepared from these blood samples will be stored at -20/-80°C in polypropylene tubes until they will be shipped to a central laboratory for analysis as previously performed (15). Plasma concentrations of PAM will be determined using validated liquid chromatography methods and tandem mass spectrometric detection

For patients participating at the imaging sub-study, a cardiac magnetic resonance imaging is planned at day 3±1 and at 5±1 months. A dedicated visit to assess vital signs and status is scheduled at 30 days after primary PCI.

6.2 Methods of minimising bias

Randomization will be performed via a web-based interactive randomization system, based on a computer-generated random sequence with a random block size stratified according to center and to the time from symptoms onset-PCI time (< 3 hours, 3-6 hours, > 6 hours).

Site investigator will report anonymized results of aggregation test, ECG, coronary angiography, cardiac MRI and

clinical visit to the CoreLab, for blinded adjudication of end-points.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all the following inclusion criteria are eligible for the study:

- Signed Informed Consent
- Age greater than 18 years old
- Have symptoms of acute myocardial ischemia (i.e. new persistent anginal pain) that were lasting at least 20 min with an electrocardiographic ST-segment elevation > 1 mm in 2 or more contiguous ECG leads, or with a new (or presumably new) left bundle branch block or ST segment depression of ≥1 mm in ≥2 of leads V1-3 with a positive terminal T wave
- Referred for primary PCI either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia

The presence of anyone of the following exclusion criteria will lead to exclusion of the participant:

- Unconsciousness
- Other conditions that make the patient incapable receiving integer loading dose of prasugrel
- Any contraindication and/or known hypersensitivity or allergy to aspirin, prasugrel, intravenous unfractionated heparin, cangrelor, tirofiban
- Any contraindication to primary PCI
- Administration of GPI or P2Y12-inhibitors or cangrelor < 7 days
- Chronic dialysis
- Recent (< 15 days) or current major bleeding
- Recent (< 15 days) major surgery
- Administration of fibrinolytics < 30 days
- Current use or indication to oral anticoagulant
- Previous stroke or TIA
- Inability to follow the procedures of the study (language problems, psychological disorders, dementia) or comorbidities associated with less than 6 months survival (active malignancies drug or alcohol abuse, etc.)
- Women who are pregnant or breast feeding or with potential to become pregnant during the course of the study (age < 55 years and last menstruation within the last 12 months) and did not undergo tubal ligation, ovariectomy or hysterectomy
- Participation in another study with investigational drug within the 30 days preceding and during the present study
- Enrolment of the investigator, his/her family members, employees and other dependent persons

7.2 Recruitment and screening

Patients will be screened at the admission. After adequate explanation, patients accepting to participate will sign the informed consent form and will be enrolled in the study by dedicated staff previously identified at each center. See 9.1 for additional details.

Study participants will not receive any payment or compensation for participation in the study.

7.3 Assignment to study groups

Randomization will be performed with a web-based interactive randomization system.

7.4 Criteria for withdrawal / discontinuation of participants

Patients can be withdrawn from the study at every time from the enrolment if any of the following criteria occurs: withdrawal of informed consent, non-compliance, safety issue (i.e. unexpected risk related to study procedure), premature interruption of the study, presence of any exclusion criteria that was not known at the time of enrolment.

8. STUDY INTERVENTION

8.1 Identity of Investigational Medicinal Products

8.1.1 Experimental Intervention

Cangrelor (Kengrexal®) is available as 50 mg powder concentrate vials for solution for infusion. For reconstitution, to each 50 mg/vial, 5 ml of sterile water for injection are added, then the so reconstituted solution is diluted with 250 ml sodium chloride 0.9% solution for injection or glucose 5% solution for injection (this dilution will generate a concentration of 200 μg/ml and should be sufficient for at least two hours of dosing as required). The solution is then visually inspected for particulate matter after reconstitution. Cangrelor is administrated via an intravenous line, the bolus is administered rapidly (<1 minute), from the diluted bag via manual intravenous push or pump, the infusion starts immediately after administration of the bolus.

8.1.2 Control Intervention

Tirofiban (Aggrastat®) concentrate is available in 50 ml vials of a clear, colourless concentrated solution; 1 ml of concentrate for infusion solution contains 281 μg of tirofiban hydrochloride monohydrate which is equivalent to 250 μg tirofiban. Aggrastat® concentrate must be diluted to the same strength of Aggrastat® solution: 50 ml are drawn from a 250 ml container of sterile 0.9% saline or 5% glucose in water and replaced with 50 ml Aggrastat® (from one 50 ml puncture vial) to make up a concentration of 50 μg/ml; before use the created solution is well mixed and visually inspected for visible particles or discolouration; then it is administrated intravenously with a calibrated infusion set.

Prasugrel (Efient®) is available as film-coated tablet of 5 mg (yellow and double-arrow shaped tablets, debossed with “5 MG” on one side and “4760” on the other) or 10 mg (beige and double-arrow shaped tablets, debossed with “10 MG” on one side and “4759” on the other). Prasugrel is intended for oral use, may be administrated with or without food. In the “chewed prasugrel” arm, the patient will be instructed to chew 60 mg prasugrel pill for at least 10–15 s followed by oral administration of 150 mL of water as previously described (16).

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

Cangrelor is administrated intravenously as a bolus of 30 μg/Kg (in 1 minute) followed by a 2-hours (or up to the end of primary PCI, if longer) infusion at a 4 μg/Kg/min rate, as in CHAMPION PHOENIX trial (21). At the end of the infusion a loading dose of 60 mg Prasugrel will be administrated orally, followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

8.2.2 Control Intervention

Tirofiban is administrated intravenously as a bolus of 25 μg/Kg (in 3 minutes) followed by a 2-hours (or up to the end of primary PCI, if longer) infusion at a 0.15 μg/Kg/min rate (0.075 μg/Kg/min in case of creatinine clearance < 60 ml/min), as in FABOLUS PRO trial (26). At the end of the infusion a loading dose of 60 mg Prasugrel will be administrated orally, followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

In the prasugrel-only arm, a loading dose of 60 mg Prasugrel is administrated orally (chewed or integer, accordingly to the second randomization) as soon as possible after randomization, as in TRITON-TIMI 38 trial (for STEMI) (23), followed by 10 mg daily (5 mg daily in patients > 75 years old or < 60 kg).

8.3 Dose modifications

Tirofiban, cangrelor and prasugrel administration can be discontinued in advance if an unexpected risk related to drugs rises up or in case of overt unmanageable bleeding, according to the responsible physician or investigator judgement.

8.4 Concomitant Interventions

As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg for Cangrelor and Tirofiban groups or 70-100 UI/Kg for Prasugrel group, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

Any urgent treatment that is needed (physician judgement) is allowed. Interventions that can increase bleeding risk (including minor surgery) that are not urgent will be postponed for at least 6 months after primary PCI, if possible.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Screening will be performed immediately before primary PCI. Potential patients will be informed about the study and asked for participation. Subjects are considered provisionally enrolled with the signature on the written informed consent form, however a subject will only proceed to the baseline evaluations and index procedure if all initial and applicable procedure related to eligibility criteria are met. A copy of the informed consent form with the patient's information document will be given to the patient.

Patients who have signed the informed consent form and meeting all inclusion and exclusion criteria will be included in the study and randomized before primary PCI. Patients will be followed-up at 30 days. A detailed summary of the study time schedule is provided in the Table of the "STUDY SCHEDULE" section.

The following evaluations will be performed at baseline:

- Demographics;
- Relevant medical history (general medical, cardiac, neurologic and renal history; cardiovascular history; risk factors (e.g. dyslipidemia, hypertension, diabetes mellitus, tobacco use); history of peripheral vascular disease, stroke, transient ischemic attack)
- Ischemic/anginal status assessment (according to the Canadian Cardiovascular Society (CCS) classification;
- Current cardiovascular and diabetic medications, including antiplatelet/anticoagulant medications;
- Physical examination, including weight, height, arterial blood pressure and heart rate;
- Routine laboratory tests within 24 hours prior to or immediately after the index procedure, including complete blood count, blood chemistry (Na, K, creatinine, urea), glucose (HbA1c if patient with known diabetes), lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), CK, CK-MB and troponin (T/I, or high sensitive, according to local practice).

After randomization, patients will receive the randomized treatment and will undergo primary PCI (see Figure 1).
Before, during and after primary PCI several blood samples will be drawn at specific time points for platelet aggregation and pharmacokinetic analyses (7 blood samples, see Figure 2).
12-lead ECGs will be recorded and encoded for adjudication at baseline, immediately after PCI and at 90 minutes after PCI and during hospitalization.

Coronary angiograms will be digitalized and encoded for adjudication.

Vital status and adverse clinical events will be assessed at 48 hours.

Patients will be asked to come back for a visit after 30days. A physical examination including a measurement of the vital signs will be performed. Information regarding AE/SAE and the current medication will be collected.

Patients providing consent to participate at the imaging substudy, will undergo a cardiac MRI with injection of contrast medium (Gadolinium) at 3±1 days and 5±1 months.

Figure 1.

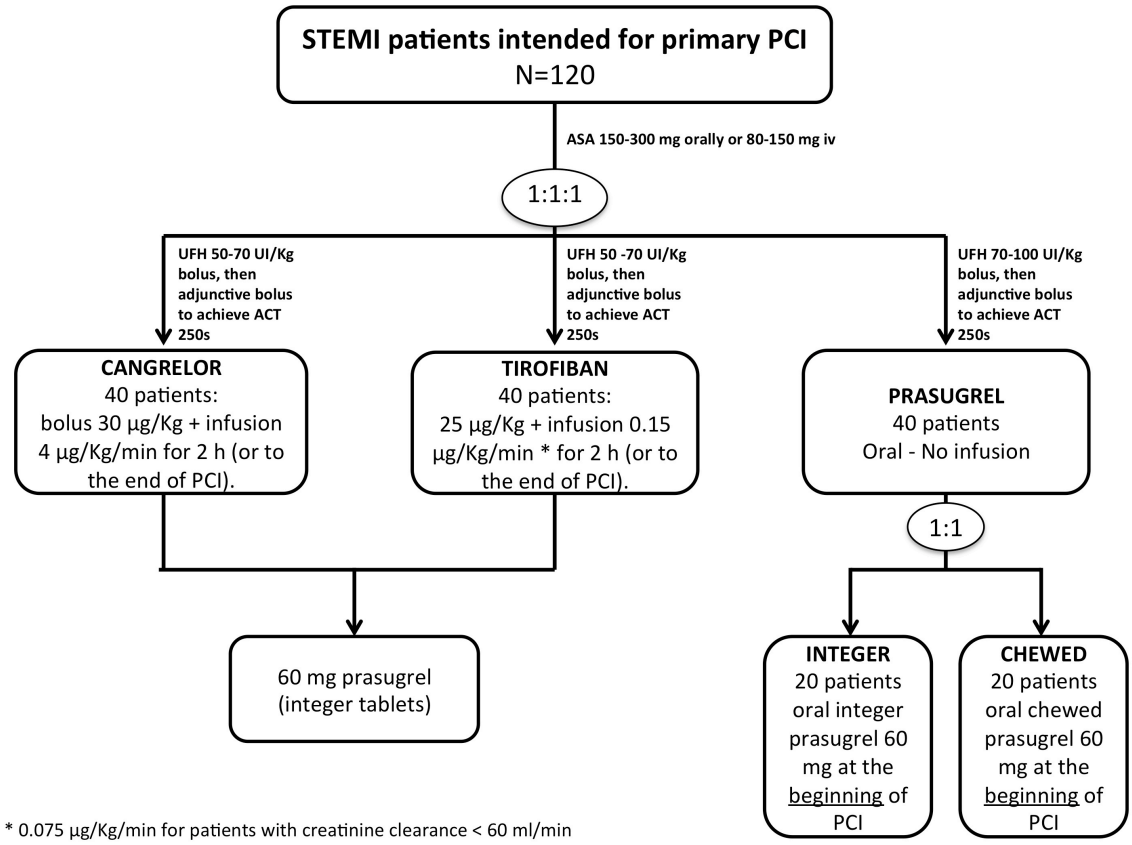
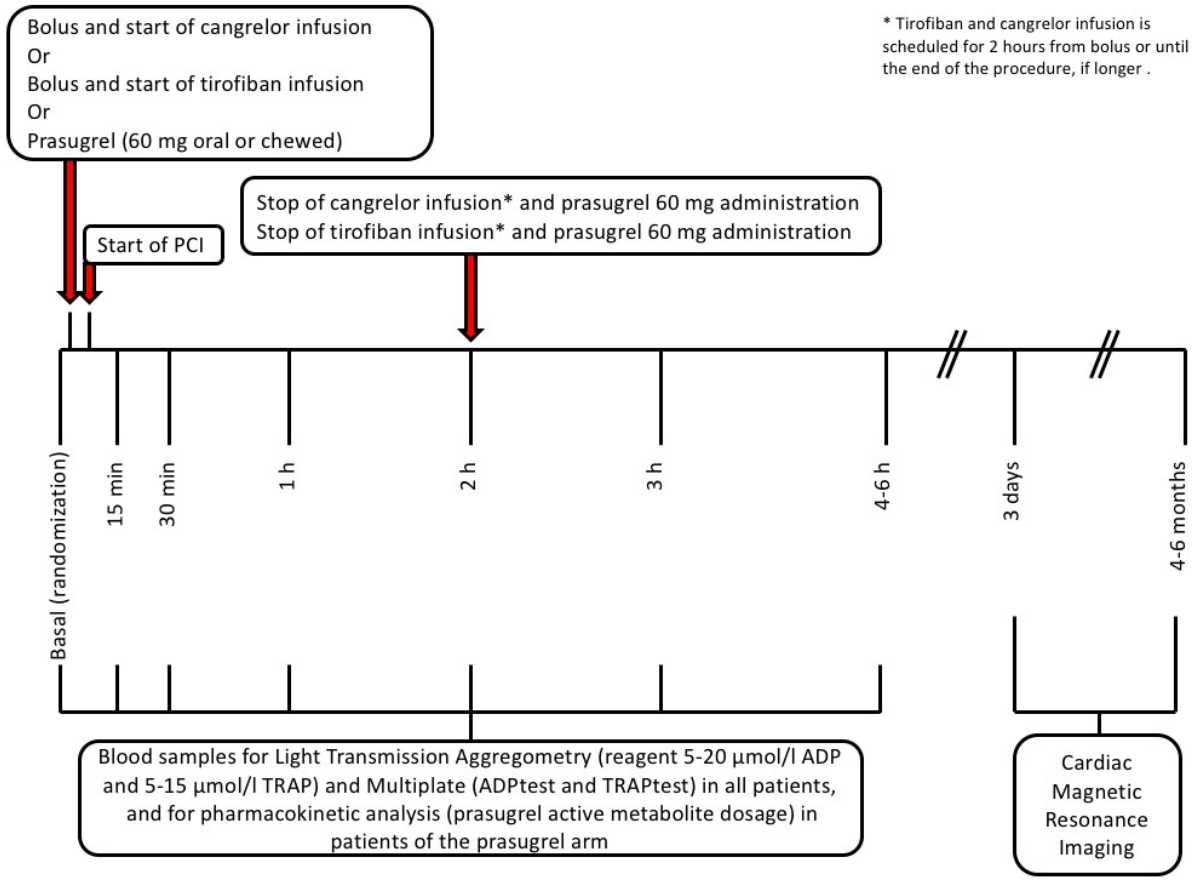

STEMI patients intended for primary PCI
N=120
ASA 150-300 mg orally or 80-150 mg iv
1:1:1
UFH 50-70 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
UFH 50 -70 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
UFH 70-100 UI/Kg bolus, then adjunctive bolus to achieve ACT 250s
CANGRELOR
40 patients:
bolus 30 µg/Kg + infusion 4 µg/Kg/min for 2 h (or to the end of PCI).
TIROFIBAN
40 patients:
25 µg/Kg + infusion 0.15 µg/Kg/min * for 2 h (or to the end of PCI).
PRASUGREL
40 patients
Oral - No infusion
1:1
60 mg prasugrel (integer tablets)
INTEGER
20 patients oral integer prasugrel 60 mg at the beginning of PCI
CHEWED
20 patients oral chewed prasugrel 60 mg at the beginning of PCI
* 0.075 µg/Kg/min for patients with creatinine clearance < 60 ml/min

Figure 2.



9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome is the percentage of inhibition of platelet aggregation in a sample of platelet-rich plasma stimulated with 20 μmol/l ADP assessed with Light Transmission Aggregometry after 30 minutes of termination of tirofiban bolus or cangrelor bolus or administration of oral 60 mg of prasugrel.

9.2.2 Assessment of secondary outcomes

At the following time point percentage of platelet inhibition will be assessed with ADP 5 and 20 μmol/l, with TRAP 5 and 15 μmol/l: time 0 (baseline), 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, 3 hours ±5 minutes, 4-6 hours.

At the same time points platelet inhibition will compared between the three arms using AUC at impedance aggregometry (Multiplate® Electrode Aggregometry) in whole blood stimulated with ADP test and TRAP test.

At the same time points levels of prasugrel active metabolite (PAM) will be assessed and compared between chewed and integer prasugrel arms.

9.2.3 Assessment of other outcomes of interest

12-lead ECG will be recorded at baseline, soon after PCI and 90±30 minutes from the end of PCI, to assess ST resolution (Δ% variation of the sum of ST elevation) and residual ST elevation (sum of the absolute values of the 12-lead elevation/depression).

Corrected TIMI frame count and proportion of patients with TIMI flow < 3 at the end of PCI will be derived by two independent expert interventional cardiologists.

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days (dedicated outpatient visit or at least telephone contact). They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis.

For patients participating at the imaging sub-study, cardiac MRI will be performed at 3±1 days from primary PCI and at 5±1 months from primary PCI in order to assess infarct size and intramyocardial haemorrhage.

9.2.4 Assessment of safety outcomes

BARC bleeding grade 2, 3 and 5, TIMI scale and GUSTO scale bleeding at 48 hours and 30 days (blinded adjudication)

Net adverse clinical events defined as the composite of death, definite/probable stent thrombosis and BARC 2-3-5 (blinded adjudication) at 48 hours and 30 days

9.2.4.1 Adverse events

For every suspected adverse event, investigator will be asked to collect time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment.

9.2.4.2 Laboratory parameters

Platelet count reduction under 90,000/mm^3 after 2-6 hour will be considered suggestive for drug-induced thrombocytopenia. Further therapeutic measures will be taken at the physician's discretion.

Hemoglobin and other parameters will be assessed as per local policy.

9.2.4.3 Vital signs

Heart rate, blood pressure, body temperature, respiratory rate, glycemia, invasive hemodynamic measures will be collected at the physician discretion.

ECG will be recorded at the beginning of the procedure, soon after PCI and 90±30 minutes after the end of PCI.

9.2.5 Assessments in participants who prematurely stop the study

Data of withdrawn participants will be collected up to the time of withdrawn. After analysis, the data will be anonymized. The blood specimen collected up to the time of withdrawn will be analysed and destroyed afterwards. After the procedure, all patients will be prescribed the same pharmacologic treatment (irrespective of the study and irrespective of withdraw) corresponding to the standard of care for patients with STEMI treated with primary PCI.

9.3 Procedures at each visit

Vital status and adverse clinical events will be assessed at 30 days, with a dedicated outpatient visit (follow up visit) or at least a telephone contact.

Cardiac MRI at 5±1 months (for patients consenting to participate to the specific substudy).

10. SAFETY REPORTING

During the entire duration of the study, all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and electronic case report forms (eCRF).

Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. [ICH E2A]

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

The “Common Terminology Criteria for Adverse Events CTCAE Version 4.0” terminology will be used.

10.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAE

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The SAE report is contained in the eCRF system and must be completed within 24 hours.

Safety contact:

Dr Marco Valgimigli, Tel: +41 31 6324714, Fax: +41 31 3821069

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days.

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator within 7 days.

Reporting of SUSAR

In order to identify possible SUSAR, the Sponsor-Investigator will re-evaluate SAE with the Investigator:

- the causality to the Investigational Medicinal Products
- the expectedness of the occurrence

The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. A SUSAR needs to be reported to the Ethics Committee within 7 days, if the event is fatal or within 15 days (all other events).

All SUSAR and SAE will be reported to the Ethics Committee by the Sponsor-Investigator in the Annual Safety

report.

10.3 Follow up of (Serious) Adverse Events

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

11. STATISTICAL METHODS

Statistical considerations

11.1 Hypothesis

Null hypothesis A (H_{0A}): cangrelor (bolus followed by infusion) induces a weaker platelet inhibition compared with tirofiban (bolus followed by infusion) after 30 minutes from bolus termination.

Null hypothesis B (H_{0B}): there is no differences between the platelet inhibition induced by both cangrelor and tirofiban (analysed as pooled effect if non-inferiority will be met or analysed for tirofiban only if non-inferiority of cangrelor vs tirofiban will not be met) compared with that induced by chewed prasugrel 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (prasugrel).

Null hypothesis C (H_{0C}): there is no difference between platelet inhibition induced by chewed prasugrel 60 mg compared with integer prasugrel 60 mg after 30 minutes from prasugrel administration.

Alternative hypothesis A (H_{1A}): cangrelor (bolus followed by infusion) induces a platelet inhibition after 30 minutes from bolus termination that is non-inferior to that induced by tirofiban (bolus followed by infusion).

Alternative hypothesis B (H_{1B}): both cangrelor and tirofiban (analysed together if non-inferiority will be met or analysed for tirofiban only group if non-inferiority of cangrelor vs tirofiban will not be met) induces a stronger platelet inhibition compared with chewed prasugrel 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (prasugrel).

Alternative hypothesis C (H_{1C}): chewed prasugrel 60 mg induces a stronger platelet inhibition compared with integer prasugrel 60 mg after 30 minutes from oral administration.

11.2 Determination of Sample Size

Assuming %IPA with 20 μmol/l ADP at 30 minutes from randomization of at least 94% with i.v. antiplatelet therapy, with a standard deviation of 8%, a non-inferiority margin of 9%, with an alpha of 0.016, 40 patients per group will give 99% of power to show non-inferiority of cangrelor compared to tirofiban. If non-inferiority of cangrelor will not be met, then the superiority of tirofiban over cangrelor will be tested (pre-specified secondary endpoint).

Assuming %IPA with 20 μmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, this study will have 100% of power to show both superiority of tirofiban (n=40) compared to chewed prasugrel (n=20) and superiority of cangrelor (n=40) compared to chewed prasugrel (n=20).

Assuming %IPA with 20 μmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, 20 patients per group will give 82% of power to show superiority of chewed prasugrel compared with integer prasugrel.

The sample size was calculated using the software Stata Release 14 (StataCorp, Txas, USA).

11.3 Statistical criteria of termination of trial

No statistical interim analyses are planned.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The analysis will be performed according to the intention to treat principle. In patients in the Prasugrel arm in whom bailout intravenous antiplatelet (Tirofiban) is deemed necessary, these patients will be excluded from the analysis which will be performed as modified intention to treat (mITT) considering patients receiving only the randomized treatment. For the primary end-point only patients with a valid value of 30 minutes inhibition of platelet activity will be considered; for the other end-points all the patients randomized will be included.

11.4.2 Primary Analysis

Inhibition of platelet activity (% of IPA at LTA or AUC unit at Multiplate, as continuous variables) will be compared

between the groups with ANOVA with Bonferroni post-hoc test.

The proportion of patients with >80% of IPA and >90% of IPA in the three groups will be compared with χ^2 test.

11.4.3 Secondary Analyses

Extent of infarct size at cardiac MRI will be compared between treatment groups with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with multivariable linear regression.

Rate of intramyocardial haemorrhage at cardiac MRI will be compared with χ^2 test and hazard ratios calculated with multivariable logistic regression

Corrected TIMI frame count at the end of PCI will be compared with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with multivariable linear regression

Proportion of patients with TIMI flow < 3 at the end of PCI will be compared with χ^2 test and hazard ratios calculated with multivariable logistic regression

Rate of ST resolution ≥70% at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be compared to baseline ECG with χ^2 test and hazard ratios calculated with multivariable logistic regression

Residual ST elevation at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be calculated by the sum of the absolute values of the 12-lead elevation/depression data and then differences between treatments will be tested with both the nonparametric Wilcoxon rank sum test and a t-test.

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis, bleeding events, net adverse clinical event. Rate of events will be compared with χ^2 test and hazard ratios calculated with multivariable logistic Cox-proportional-hazard model.

11.4.4 Deviation(s) from the original statistical plan

Any deviation from the planned analyses will be reported in the final trial report.

11.5 Handling of missing data and drop-outs

Patients with missing data for the primary end-point will be excluded from the primary analysis.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

The Local Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual enrolled in the study.

An web-based electronic data capture (EDC) system will be used for the study (database technology Oracle Mysql), that fulfils the legal requirements and guidelines. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff. eCRFs documenting SAEs should be submitted via the EDC system within 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment or follow-up visit.

The subject's anonymity will be maintained and the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable legal requirements. Patients data will be encoded:

- Subjects will be identified only by their assigned study number, initials and year of birth on all CRFs
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
- The investigator will maintain all study documents in strict confidence.
- CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified. Copy of coronary angiogram, cardiac MRI and ECG will be stored at the main site in Bern.

All data will be cleared of any sensible personal information, patients will be identified by their assigned study number. For end-point adjudication data will be examined without any form of identification (blinded).

12.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent

Forms, randomisation number, SAEs, AEs and concomitant medication, and results of relevant examinations. The investigator assures that source documents are appropriately stored and completed. The patient's file will reveal that this patient is a study participant by entering the following details: study name, protocol number, date of enrolment, informed consent obtained prior to any study specific procedure. Each follow up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that medical files and Case Record Forms are accessible for inspection by authorities and monitoring visits.

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. All data will be stored at the main site in Bern.

12.3 Data management

Clinical Trial Unit (CTU) – Bern University, will be in charge for data management and analysis.

Every investigator has access to data of patients enrolled in the own site. CTU in Bern has access to all patient data and can lock patient's data at the end of the trial. Once locked, data can no longer be modified by site investigator.

12.4 Monitoring

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and that the protocol is followed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Informed Consent Forms for each study participant;
- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.
- Periodic on-site visits and, if necessary, remote monitoring of data.

12.5 Audits and Inspections

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP), and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also CEC) and questions should be answered during inspections. All involved parties must keep the participant data strictly confidential.

12.6 Confidentiality, Data Protection

Direct access to source documents will be permitted for monitoring, audits and inspections. Clinical Trial Unit – Bern has full access to protocol, dataset and statistical codes, during and after the study.

12.7 Storage of biological material and related health data

Biological samples for main endpoints of platelet aggregation will be analysed within few hours from collection. Each participating centre will perform its own platelet aggregation analysis. In addition, 3 samples (plasma, serum and DNA) for each patient will be stored in each centre at -80°C up to one year after study end for future researches. Patients will be adequately informed and will provide consent to this storage of biological material.

13. PUBLICATION AND DISSEMINATION POLICY

After the database has been closed, findings will be shared and discussed with all of the investigators for the study. An estimated timeline for creation of an abstract will be defined at that time. An abstract of the completed study, after input from all the authors, will be submitted to the most important and representative international meetings. A manuscript of the study, having received input from all of the authors, is tentatively scheduled for submission in a renowned international medical journal. Authorship will be selected according to the requirements of the New England Journal of Medicine (http://www.icmje.org/). These indicate that every author provided such contribution to the clinical trial and the subsequent publication that he can take public responsibility for the integrity of the entire work. Therefore the credit for authorship requires substantial contributions to:

1. The conception and design or analysis and interpretation of the data.

2. The drafting of the article or critical revision for important intellectual content.

3. Final approval of the version to be published.

Authors must have fundamentally taken part in all of the 3 aspects.

For the main publication each of the 5 main centers will obtain at least 1 authorship, if the above mentioned requirements 1-3 are met. Prior to sub-publication consultation and agreement of the coordinating investigator and the steering committee are mandatory.

14. FUNDING AND SUPPORT

This study is an Investigator Initiated Trial supported by a grant from Medicure Inc, 2-1250 Waverley Street, Winnipeg, Manitoba, CANADA R3T 6C6.

15. INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

16. REFERENCES

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Faculty of Medicine

Department of Clinical
Research (DCR)

CTU Bern

Statistical Analysis Plan

Study: **FABOLUS FASTER**

Facilitation through Aggrastat or cangrelor Bolus and infusion Over prasugreL: a mUlticenter randomized open-label trial in patientS with ST-elevation myocardial inFarction referred for primAry percutaneouS inTERvention. FABOLUS FASTER trial

CTU project number: **633**

Protocol: Version 2, 06.12.2016

Authored by: Dik Heg

Date: 23.08.2019

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Change history:

Version	Date	Major changes

UNIVERSITÄT BERN

Contents

1. Study synopsis

Primary PCI is the main reperfusion therapy in patients with ST-elevation myocardial infarction. Ancillary pharmacological therapy includes dual antiplatelet therapy with aspirin and an inhibitor of P2Y12 receptor, responsible of ADP-mediated platelet activation. Ticagrelor and prasugrel are the most recent and efficient oral P2Y12 inhibitors available to date. However, in STEMI even prasugrel and ticagrelor could have a significant delay of onset of action. Early in-ambulance administration can increase the inhibition of P2Y12 receptor, however, the benefits versus risks balance remain uncertain. Recently, small-scale independent studies suggested that chewed or crushed loading dose of ticagrelor or prasugrel can achieve more pronounced platelet inhibition compared with standard whole tablets soon after drug administration. Yet, the delay in platelet inhibition remains considerable even after chewed or crushed loading dose of newer oral P2Y12 inhibitors and suboptimal modulation of platelet reactivity at the time of primary intervention may persist. Tirofiban and cangrelor are intravenous drugs with a more rapid onset and offset of action (compared with oral agents). Both agents have been extensively tested in clinical trials including patients with STEMI. However, the comparative speed of action of cangrelor as opposed to tirofiban and to chewed or integer loading dose of prasugrel is unknown.

In the **FABOLUS FASTER** randomized clinical trial patients are randomized to **Cangrelor** vs **Tirofiban** vs **Prasugrel** (1:1:1 randomization) and then within the Prasugrel group again randomized (sub-randomization) to **integer Prasugrel** (the standard reference treatment) vs. **chewed Prasugrel** (the novel treatment in which the pills are chewed to obtain faster resorption and thus a faster pharmacological effect compared to whole integer pills).

2. Study objectives

2.1. Primary objective

To assess the inhibition of platelet aggregation in the early phase of primary PCI (i.e. 30 minutes after start of treatment as primary study endpoint) and up to 6 hours (secondary endpoints). To evaluate the clinical effect of different regimens on platelet inhibition: tirofiban bolus + infusion, cangrelor bolus + infusion, prasugrel chewed loading dose, prasugrel integer loading dose.

2.2. Secondary objectives

Other secondary objectives will include adverse clinical events in the overall patient population and the assessment of infarct size and micro-vascular damage by using cardiac magnetic resonance in a subset of patients who will consent to participate into this sub-study.

2.3. Assessment of objectives

All patients will receive aspirin before primary PCI (150-300 mg orally or 80-150 mg i.v., then 81-325 mg daily) and then will be randomized to **3 different treatment regimens**: ***tirofiban***, ***cangrelor*** or ***prasugrel***; patients in the prasugrel group will be subsequently randomized to ***integer oral tablets*** or ***chewed oral tablets*** loading dose at the beginning of primary PCI. In each patient, 7 blood samples will be obtained at different time points (the first before starting of the procedure (baseline), then, counting from drug bolus termination (tirofiban and cangrelor arms) or oral loading dose of prasugrel, at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and between 4 to 6 hours thereafter). ECG will be recorded before and soon after PCI and 90 minutes thereafter. Patients providing consent to participate at the ***imaging sub-study***, will perform cardiac magnetic resonance at 3±1 days (within hospitalization) and 5±1 months. Clinical data collection (vital signs, therapy, clinical events and other data) is scheduled at 30 days.

Cangrelor will be administered according to current European label as follows: as bolus of 30 µg/Kg followed by infusion at 4 µg/Kg/min for 2 h (or to the end of PCI); at the end of infusion, oral prasugrel at loading dose of 60 mg will be administrated, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines. As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

Tirofiban will be administrated according to current European guidelines as follows: as 25 µg/Kg bolus followed by infusion at 0.15 µg/Kg/min for 2 h (or to the end of PCI) (infusion rate of 0.075 µg/Kg/min for patients with creatinine clearance < 60 ml/min); at the end of infusion, oral prasugrel at loading dose of 60 mg will be administrated, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines. As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 50-70 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

In the ***Prasugrel*** arm no intravenous anti-platelet drug will be administered. Patients will be randomized to oral integer prasugrel or chewed oral prasugrel at an identical loading dose of 60 mg, then 10 mg daily (5 mg daily if body weight < 60 kg or age > 75 years old) in accordance to the instructions for use and international guidelines; As anticoagulant therapy, only concomitant unfractionated heparin (UFH) will be allowed (the use of bivalirudin is not allowed) to avoid potential confounding effects. UFH will be administrated as bolus of 70-100 UI/Kg, then adjunctive boluses to achieve Activated Clotting Time of at least 250s during the procedure. UFH administration after the end of procedure is discouraged unless clinically indicated.

2.4. Changes of the primary objective during the conduct of the study

Changes of the primary objective during the conduct of the study are not planned and need to be covered using a protocol amendment.

3. Study design

3.1. General design and plan

Open-label four-arm (***Cangrelor*** vs ***Tirofiban*** vs ***integer Prasugrel*** vs ***chewed Prasugrel***), parallel, randomized multicenter clinical trial (1:1:1:1 randomized allocation); first randomization to ***Cangrelor*** vs ***Tirofiban*** vs ***Prasugrel***), with a second randomization within the Prasugrel arm to ***integer oral Prasugrel tablets*** or ***chewed oral Prasugrel tablets*** loading dose at the beginning of primary PCI. After first randomization (***Cangrelor*** vs ***Tirofiban*** vs ***Prasugrel***) and again after the second randomization (***integer oral tablets*** or ***chewed oral tablets***) the study personnel is not blinded to the treatment allocations. Due to the second randomization the patients will not be throughout blinded to the treatment allocation ***Cangrelor*** vs ***Tirofiban*** vs ***Prasugrel***, although they will not know whether they are randomized to Cangrelor or Tirofiban, as these randomized arms do not have a second randomization.

This will be a multicenter, open-label, prospective, randomized study in patients with STEMI undergoing primary PCI with the aim to show, on top of aspirin, the non-inferiority of cangrelor compared with tirofiban in terms of early platelet inhibition and the superiority of both drugs compared with chewed prasugrel at the beginning of PCI; finally platelet inhibition of oral chewed prasugrel loading dose will be compared with integer oral loading dose.

Once the patient is judged eligible and the informed consent has been signed, the patient will be randomly assigned in a 1:1:1 fashion to tirofiban (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel), cangrelor (40 patients, bolus + 2 hours infusion, then 60 mg of prasugrel) or prasugrel 60 mg (40 patients, at the beginning of the PCI). The first randomization will be stratified according to center and to time of symptoms-PCI (<3 hours, 3-6 hours, >6 hours). Patients in the prasugrel arm will undergo a second 1:1 randomization to chewed oral loading dose of prasugrel or integer oral loading dose.

Treatment will be administrated as open-label for patients and treating physician, however results of laboratory tests, ECG, coronary angiography, cardiac MRI and clinical events will be managed by investigators unaware of actual treatment.

Blood samples for platelet inhibition assessment will be collected from the randomization up to 6 hours. Blood samples will be anticoagulated with 0.129 mol/l sodium citrate collected for platelet reactivity. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 70 g, will be stimulated with 5 and 20 mol/l ADP and 5 and 15 mol/l thrombin receptor agonist peptide (TRAP), and aggregation will be assessed using light transmittance aggregometry (LTA). The 100% line will be set using platelet poor plasma and the 0 baseline established with platelet rich plasma (adjusted from 18 x 10^9/l up to 30 x 10^9/l)

For patients participating at the imaging sub-study, a cardiac magnetic resonance imaging is planned at day 3±1 and at 5±1 months. A dedicated visit or telephone call to assess vital signs and status is scheduled at 30 days after primary PCI.

3.2. Sample size

Total number of patients with primary endpoint assessment: 120

40 patients in the tirofiban group

40 patients in the cangrelor group

40 patients in the prasugrel group (20 integer, 20 chewed)

Sample size is calculated to state non-inferiority of cangrelor compared with tirofoban, superiority of both tirofiban and cangrelor compared with chewed prasugrel and to show superiority of chewed prasugrel compared to integer prasugrel.

The sample sizes were determined following these considerations, three primary non-inferiority tests each with alpha of 0.05/3 tests = 0.016 and one additional test also with alpha of 0.016 for consistency (chewed prasugrel vs integer prasugrel):

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of at least 94% with i.v. antiplatelet therapy, with a standard deviation of 8%, a *non-inferiority* margin of 9%, with an alpha of 0.016, 40 patients per group will give 99% of power to show non-inferiority of ***Cangrelor*** compared to ***Tirofiban***. If non-inferiority of cangrelor will not be met, then the superiority of tirofiban over cangrelor will be tested (pre-specified secondary endpoint).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, this study will have 100% of power to show both *superiority* of ***Tirofiban*** (n=40) compared to ***chewed Prasugrel*** (n=20) and superiority of ***Cangrelor*** (n=40) compared to ***chewed Prasugrel*** (n=20).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, 20 patients per group will give 82% of power to show *superiority* of ***chewed Prasugrel*** compared with ***integer Prasugrel***.

3.3. Randomization

The first randomization will be stratified according to center and to time of symptoms-PCI (<3 hours, 3-6 hours, >6 hours) within the electronic data capture EDC system of Advice Pharma. Patients in the prasugrel arm will undergo a second 1:1 randomization to chewed oral loading dose of prasugrel or integer oral loading dose, again randomization will be performed with the EDC system of Advice Pharma. The treatment allocation is therefore concealed.

3.4. Blinding

Treatment will be administrated as open-label, unblinded, for patients and treating physician and study nurses, however results of laboratory tests, ECG, coronary angiography, cardiac

MRI and clinical events will be managed by investigators unaware of actual treatment and allocated treatment.

The first biostatistician will remain blinded to the actual treatment allocation until the primary endpoint (%IPA) has been summarized on the total patient population for each time-point (15 min, 30 min, 1h, 2h, 3h, 4-6h), has been cleaned for potential mistakes in data entry including an outlier analysis with outliers confirmed as valid entries of %IPA. Afterwards, the %IPA entries per patient can no longer be changed and the biostatistician will perform the primary endpoint and secondary endpoints analyses and comparisons as described below.

A second independent biostatistician will remain blinded for the treatment allocation and will remain blinded to the actual treatment allocation until the primary endpoint of the imaging substudy has been summarized on the total patient population for each time-point (3 days and 5±1 month), has been cleaned for potential mistakes in data entry including an outlier analysis with outliers confirmed as valid entries. Afterwards, the imaging outcome entries per patient can no longer be changed and the biostatistician will perform the primary endpoint and secondary endpoints analyses and comparisons as described below for the imaging substudy.

3.5. Study assessments

The following assessments will be performed after written informed consent was obtained from the patients (including separate consent for MRI substudy): consenting & enrollment before the PCI with randomization, clinical & medical history, various assessments & examinations & concomitant therapies & interventions, administration of randomly allocated study drug (***Cangrelor*** vs ***Tirofiban*** vs ***chewed Prasugrel*** vs ***integer Prasugrel***) (Enrolment); ECG at the end of the PCI; assessments of the primary and secondary variables at the various time-points (Primary Variables and Secondary Variables at 15min, 30min, 1h, 2h, 3h and 4 to 6h; min=minutes and h=hours since randomization). After 2 hours, 48 hours and 30 days the patient will be checked for vital signs and Adverse Events will be collected throughout up to 30 days since randomization (with additional physical examination and re-evaluation of concomitant therapies & interventions at 30 days).

The MRI substudy will be conducted 3 days and 5 months after randomization.

Table of the visit plan from the Protocol version

Study Periods	*Enrol lment*	*Treatment, Intervention Period*					*In-Hospital course*				*Follow-up*	
Time point	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Time	*0*	*End of PCI*	*15 min*	*30 min*	*1 h*	*2 h*	*3 h*	*4-6 h*	*48 h*	*3 days*	*30 days*	*5±1 months*
Patient Information and Informed Consent	*x*											
Demographics	*x*											
Medical History	*x*											
In- /Exclusion Criteria	*x*											
Physical Examination	*x*										*x*	
Vital Signs	*x*					*x*			*x*		*x*	
Randomisation	*x*											
ECG	*x*	*x*				*x*						
Administer Study Medication	*x*		*x*	*x*	*x*	*x*						
*MRI**										*x**		*x**
*Primary Variables ** *	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
*Secondary Variables** *	*x*		*x*	*x*	*x*	*x*	*x*	*x*				
Concomitant Therapy, Intervention	*x*					*x*					*x*	
Adverse Events						*x*			*x*	*x**	*x*	

*This will be performed in patients providing consent to participate to the imaging sub-study.

**Blood samples will be collected and processed with Light Transmission Aggregometry and Multiplate; platelets will be stimulated with different agents and concentrations (ADP 5 and 20 micromol/l and TRAP 5 and 15 micromol/l for LTA; ADP test and TRAT test for Multiplate). In Prasugrel group, samples will be collected for pharmacokinetic analysis.

4. Data management

4.1. Data export

The electronic data capture EDC system is provided by Advice Pharma, see: https://www.advicepharma.com/?lang=en

Exports of data are provided using the current standard operating procedures of Advice Pharma, and should be in importable format, e.g. comma separated values files ({name}.csv).

4.2. Data validation

Data validation is performed by Advice Pharma according to the standard operating procedures of Advice Pharma within the electronic data capture EDC system.

The first biostatistician will perform a validation of the primary and secondary endpoints only, which includes assessment of missing endpoints at each time-point, assessment of outliers and improbable sequences of data across the various time-point (i.e. changes of each single endpoint from 15min to 4-6h per patient provided to the sponsor for plausibility checking).

The second biostatistician will perform a validation of the MRI endpoints only, which includes assessment of missing endpoints at each time-point, assessment of outliers and improbable sequences of data across the various time-point (i.e. changes of each single endpoint from 3 days to 5±1 month per patient provided to the sponsor for plausibility checking).

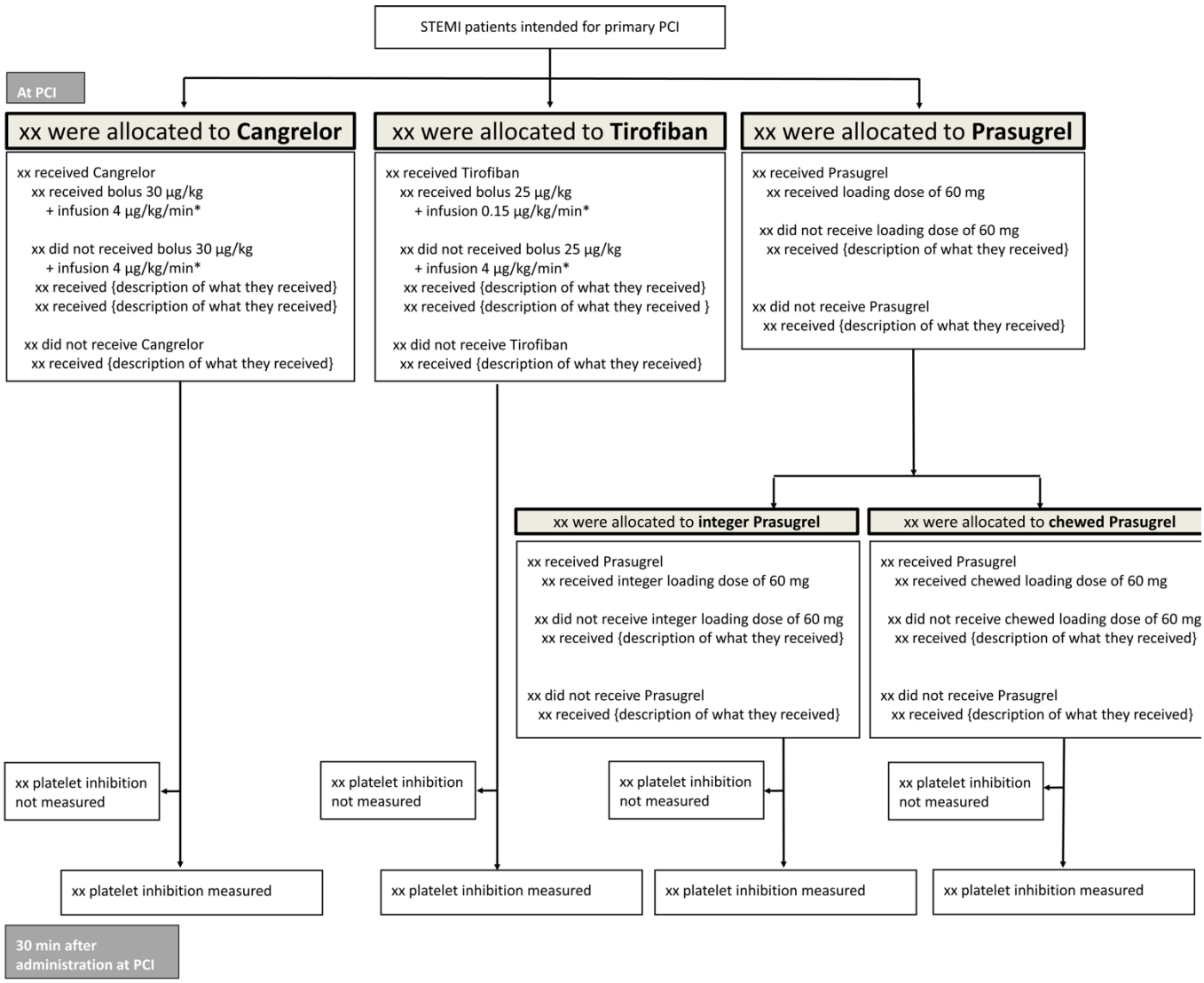
Any other support in validating the data will be conducted according to specific requests from the Sponsor, as far as they could not be covered by Advice Pharma.

5. Study populations

5.1. Patient flow

Patients will be screened at the admission. After adequate explanation, patients accepting to participate will sign the informed consent form and will be enrolled in the study by dedicated staff previously identified at each center. No screening log is entered for this study and only randomized patients with written consent will be reported.

The following flowchart of the patients will be provided (platelet inhibition is measured as %IPA):



Note that patients who did *not* receive the randomized medication (Cangrelor or Tirofiban or Prasugrel; within Prasugrel integer or chewed) will be listed according to what they received, generic in the flowchart. More elaborate descriptive text in the manuscript or supporting

material of the manuscript will be provided if the generic text inside the flowchart is not informative enough. Secondary endpoints are measured at other time-points since the study drug administration at PCI: 15 minutes, 30 minutes, 1h, 2h, 3h and 4-6h after administration of the study drug. Clinical outcomes are reported at 48h and 30 days since drug administration.

Patients can be withdrawn from the study at every time from the enrolment if any of the following criteria occurs: withdrawal of informed consent, non-compliance, safety issue (i.e. unexpected risk related to study procedure), premature interruption of the study, presence of any exclusion criteria that was not known at the time of enrolment.

5.2. Definition of populations for analysis

The analysis will be performed according to the intention to treat principle. In patients in the Prasugrel or Cangrelor arms in whom bailout intravenous antiplatelet (Tirofiban) is deemed necessary, these patients will be excluded from the analysis which will be performed as modified intention to treat (mITT) considering patients receiving only the randomized treatment. However, if the bailout occurs *after* the 30 minute time point which is the primary endpoint, this patient will be analyzed for the primary endpoint. For the primary endpoint only patients with a valid value of 30 minutes inhibition of platelet activity will be considered; for the other end-points all the patients randomized will be included.

5.3. Full analysis set (FAS)

The Full analysis set (FAS) will include all randomized subjects and following the intent-to-treat principle, subjects will be analyzed according to the drug they were assigned to at randomization. In patients in the Prasugrel arm or Cangrelor arm in whom bailout intravenous antiplatelet (Tirofiban) is deemed necessary before 30 minutes, these patients will be excluded from the analysis which will be performed as modified intention to treat (mITT) considering patients receiving only the randomized treatment.

5.4. Per-protocol (PP)

The PP analyses includes patients who received the randomized drug administration at the PCI and excludes patients in the Prasugrel arm or Cangrelor arm in whom bailout intravenous antiplatelet (Tirofiban) is deemed necessary before 30 minutes.

5.5. Safety population

The safety population consists of all subjects in the FAS who take at least one dose of study medication. Subjects will be analyzed according to the treatment they are assigned to at randomization unless a subject takes non-randomized study medications and does not take any study medication as randomized, in that case the subject will be analyzed according to the treatment actually taken.

5.6. Definition of sub-group populations in different analyses

Patients providing consent to participate at the imaging substudy, will undergo a cardiac MRI with injection of contrast medium (Gadolinium) at 3±1 days and 5±1 months.

6. Statistical analysis

6.1. General

Null hypothesis A (H0A): **Cangrelor** (bolus followed by infusion) induces a weaker platelet inhibition compared with **Tirofiban** (bolus followed by infusion) after 30 minutes from bolus termination.

Null hypothesis B (H0B): there is no differences between the platelet inhibition induced by both **Cangrelor** and **Tirofiban** (analysed as pooled effect if non-inferiority will be met or analysed for tirofiban only if non-inferiority of cangrelor vs tirofiban will not be met) compared with that induced by **chewed Prasugrel** 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (prasugrel).

Null hypothesis C (H0C): there is no difference between platelet inhibition induced by **chewed Prasugrel** 60 mg compared with **integer Prasugrel** 60 mg after 30 minutes from prasugrel administration.

Alternative hypothesis A (H1A): **Cangrelor** (bolus followed by infusion) induces a platelet inhibition after 30 minutes from bolus termination that is non-inferior to that induced by **Tirofiban** (bolus followed by infusion).

Alternative hypothesis B (H1B): both **Cangrelor** and **Tirofiban** (analysed together if non-inferiority will be met or analysed for tirofiban only group if non-inferiority of cangrelor vs tirofiban will not be met) induces a stronger platelet inhibition compared with **chewed Prasugrel** 60 mg after 30 minutes from bolus termination (cangrelor/tirofiban) or oral administration (**integer Prasugrel**).

Alternative hypothesis C (H1C): **chewed Prasugrel** 60 mg induces a stronger platelet inhibition compared with **integer Prasugrel** 60 mg after 30 minutes from oral administration.

The alpha for the below three tests are divided 5%/3 is approximately 1.6%:

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of at least 94% with i.v. antiplatelet therapy, with a standard deviation of 8%, a non-inferiority margin of 9%, with an alpha of 0.016, 40 patients per group will give 99% of power to show non-inferiority of cangrelor compared to tirofiban. If non-inferiority of cangrelor will not be met, then the superiority of tirofiban over cangrelor will be tested (pre-specified secondary endpoint).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, this study will have 100% of power to show both superiority of tirofiban (n=40) compared to chewed prasugrel (n=20) and superiority of cangrelor (n=40) compared to chewed prasugrel (n=20).

Assuming %IPA with 20 µmol/l ADP at 30 minutes from randomization of 55% with chewed prasugrel, with a standard deviation of 24% and an alpha of 0.016, 20 patients per group will give 82% of power to show superiority of chewed prasugrel compared with integer prasugrel.

Otherwise and if not otherwise explicitly stated, the alpha used to claim statistical significance is 5%. The alpha for the above three tests were divided, otherwise, no adjustment for multiple testing will be performed, i.e. all other tests are secondary or are on secondary endpoints, and thus will be interpreted as supportive evidence only with the nominal alpha of 5% throughout.

Statistical analyses will be performed with Stata version 14.2 or higher, or R version 3.4 or higher.

6.2. Pooling of sites

All the sites are pooled before the analyses, adding a random effect for the site identifier in case each site has at least one patient randomized to each arm.

6.3. Interim analyses

No interim analyses are planned.

6.4. Time-points for analysis

The primary endpoint of platelet inhibition %IPA using LTA in a platelet-rich plasma stimulated with ADP 20 µmol/l after **30±5 minutes** from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose (at the beginning of the primary PCI) in the prasugrel only arm – adding a random effect of the site (hospital identifier) on the primary endpoint in case each site has at least one patient randomized to each arm, and adding a random effect of the patient identifier. Estimates will be based on mixed models using the data of all timepoints.

All primary endpoints reported at other timepoints are considered secondary or other outcomes.

6.5. Methods for handling missing data

A low drop-out rate is expected:

6.5.1. Handling of dropouts

Considering the primary endpoint is collected 30 min after the first drug administration (which is directly after randomization), we expect a very low or zero drop-out rate. Patients with missing data for the primary end-point will be excluded from the primary analysis.

In case of drop-outs a sensitivity analysis will be performed on the primary endpoint platelet inhibition %IPA at 30 minutes since randomization using multiple imputation with chained equations (MICE). The MICE model will include Medical History parameters (age, gender, BMI, diabetes, hypertension, dyslipidemia, family history of CAD, current smoking, carotid artery disease, chronic kidney disease, heart failure; previous myocardial infarction, PCI, CABG, and bleeding requiring medical attention, COPD, LVEF, cardiac arrest, sinus rhythm, intraventricular conduction defects, radial access, any hemodynamic support; time-points and all valid %IPA measurement as predictor variables.

If requested, similar multiple imputed general or generalized mixed models can be executed on the other endpoints, including a random effect of the site if at least one measurement per arm per site available (sensitivity analyses) and adding a random effect of patient identifier.

6.6. Statistical analytical issues

6.6.1. Assessment of statistical assumptions and statistical tests

The pairwise mean difference in platelet inhibition (difference in %IPA) will be estimated and reported with the 95% confidence intervals (Cangrelor vs Tirofiban, Cangrelor vs chewed Prasugrel, Tirofiban vs chewed Prasugrel; based on using mixed models - including data on

all time-points since PCI, random effects of site and patient as appropriate), non-inferiority will be tested using a z-test.

Superiority tests will be conducted on platelet activity (% of IPA at LTA or AUC unit at Multiplate, as continuous variables, random effects of site and patient as appropriate) using mixed models (including data on all time-points since PCI) with Bonferroni post-hoc test.

The proportion of patients with >80% of IPA and >90% of IPA in the three groups will be compared with mixed models (including data on all time-points since PCI, random effects of site and patient as appropriate) with Bonferroni post-hoc test.

Mixed models will use the appropriate link function according to the type of primary or secondary endpoints measured (continuous, binary etc.) and adjust for time-point (minutes to hours since PCI) and the interaction between randomized arm and time-point, random effects added of site and patient as appropriate.

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, transient ischemic attack, urgent target vessel revascularization, unplanned revascularization, definite/probable stent thrombosis, bleeding events, net adverse clinical event. Rate of events will be compared with $\chi 2$ test and hazard ratios calculated with Cox-proportional-hazard model.

Corrected TIMI frame count at the end of PCI will be compared with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with linear regression.

Proportion of patients with TIMI flow < 3 at the end of PCI will be compared with $\chi 2$ test and odds ratios calculated with logistic regression.

Rate of ST resolution ≥70% at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be compared to baseline ECG with $\chi 2$ test and odds ratios calculated with logistic regression.

Residual ST elevation at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be calculated by the sum of the absolute values of the 12-lead elevation/depression data and then differences between treatments will be tested with both the nonparametric Wilcoxon rank sum test and a t-test.

Extent of infarct size at cardiac MRI will be compared between treatment groups with ANOVA with Bonferroni post-hoc test and coefficients of correlation and determination will be calculated with multivariable linear regression. Mixed models will be used random effects of site and patient as appropriate

Rate of intramyocardial haemorrhage at cardiac MRI will be compared with $\chi 2$ test and odds ratios calculated with logistic regression

In case of any additional endpoints measured at multiple time points: all tests will be conducted with their equivalent mixed model (general or generalized mixed model) accounting for repeated measures per patient, time since PCI and the interaction between time since PCI vs randomized arm, and the estimates from those models will be used for testing.

6.6.2. Adjustments for covariates

No adjustment of covariates for the primary endpoint analyses.

6.6.3. Multiple comparisons

No multiple comparisons are planned beyond those already specified above (Bonferroni corrections to compare pairwise within the 5 randomized arms).

6.6.4. Use of efficacy subset

All patients are included by intention-to-treat and no efficacy subset is defined.

6.6.5. Active-control studies intended to show equivalence

The initial testing is non-inferiority of cangrelor compared to tirofiban (so equivalence testing is not applicable), afterwards only superiority tests are planned.

6.6.6. Examination of subgroups

No subgroups are predefined, but subgroup testing is allowed for exploratory purposes only (considering the overall low sample size subgroup testing will have a low power).

7. Evaluation of demographics and baseline characteristics

7.1. Baseline and treatment characteristics

The following Tables will be produced to describe the population included, the PCI procedure performed and concomitant medications or treatments. Note that additional tables, e.g. additional comparisons of, e.g. Cangrelor vs Prasugrel, Tirofiban vs Prasugrel will be provided in supplementary Tables on request, using the same templates as shown below.

7.1.1. Baseline Table

No p-values will be reported for this table.

Table 1

7.1.2. Presentation and catheterization Table

Table 2

7.1.3. Medications before and during index PCI Table

Table 3

7.1.4. Angiography and index PCI Table

Table 4

7.1.5. Follow-up Table

Table 6

8. Evaluation of treatment compliance and exposure

8.1. Compliance to study drug and treatment

8.1.1. Compliance to study drug

The patients randomized to the **Cangrelor** infusion should get this infusion immediately after the randomization result and the index PCI is started, the patients randomized to the **Tirofiban** infusion should get this infusion immediately after the randomization result and the index PCI is started (both arms will get a loading dosage of prasugrel at the end of their infusion), the non-compliance will be shown in the flowchart. The patients randomized to **Prasugrel** arm will immediately get the loading dosage of prasugrel, either as sub-randomized **chewed** or **integer**. Again, the non-compliance is shown in the flowchart. Note that the loading of Prasugrel (before PCI or after infusion) and whether it is chewed or integer is captured inside the eCRF.

8.2. Exposure to study drug

8.2.1. Extent of exposure

Cangrelor will be administered according to current European label as follows: as bolus of 30 µg/Kg followed by infusion at 4 µg/Kg/min for 2 h (or to the end of the percutaneous coronary intervention PCI).

Tirofiban will be administrated according to current European guidelines as follows: as 25 µg/Kg bolus followed by infusion at 0.15 µg/Kg/min for 2 h (or to the end of PCI) (infusion rate of 0.075 µg/Kg/min for patients with creatinine clearance < 60 ml/min).

8.2.2. Duration of exposure

Cangrelor the duration of exposure will be for 2 hours, or if the PCI is finished before 2 hours: to the end of the PCI.

Tirofiban the duration of exposure will be for 2 hours, or if the PCI is finished before 2 hours: to the end of the PCI.

8.2.3. Dose of exposure

Cangrelor the initial bolus is 30 µg/Kg followed by an infusion of 4 µg/Kg/min for 2 h (or to the end of the percutaneous coronary intervention PCI).

Tirofiban the initial bolus is 25 µg/Kg followed by an infusion of 0.15 µg/Kg/min for 2 h (or to the end of PCI). In patients with a creatinine clearance < 60 ml/min (eGFR) a lower infusion rate of 0.075 µg/Kg/min will be used.

8.2.4. Drug concentrations

Cangrelor the drug concentrations are bolus: 30 µg/Kg; and infusion at 4 µg/Kg/min.

Tirofiban the drug concentrations are bolus: 25 µg/Kg; and infusion at 0.15 µg/Kg/min.

9. Evaluation of pharmacokinetics

A pharmacokinetic analysis will be performed in the Prasugrel randomized arm, comparing the patients actually receiving the chewed Prasugrel treatment correctly vs the patients actually receiving the integer Prasugrel. The collection started after enrollment of some patients and it is anticipated to have data in approximately 30 of the 40 randomized patients in the Prasugrel arm.

The samples will be safely stored at University Hospital of Verona (LURM) at -80°C for a duration of 5/10 years from the date of collection.

9.1. Evaluation of pharmacokinetics

Prasugrel Active Metabolites (PAM) will be measured at each time point will be compared between chewed vs integer with the hypothesis that chewed is superior to integer at 30 minutes (and other time points: 15min to 4-6h hours).

Blood samples for pharmacokinetic assessment (determination of plasma concentration of prasugrel's active metabolite (PAM)) will be collected from the randomization up to 6 hours at the same time points of the pharmacodynamics evaluation: 4 ml blood samples will be collected into pre-cooled EDTA tubes at the established time points (baseline, 15 min, 30 min, 1h, 2h, 3h and 4-6h) and will be treated with 25 μl of 500 mM 3′-methoxyphenacyl bromide in acetonitrile within 30 s of collection to derivatize and stabilize the PAM. Centrifugation of the sample will be performed within 30 minutes (2800 rpm for 15 min at 4°C), and plasma samples prepared from these blood samples will be stored at -20/-80°C in polypropylene tubes until they will be shipped to a central laboratory for analysis as previously performed. Plasma concentrations of PAM will be determined using validated liquid chromatography methods and tandem mass spectrometric detection.

9.2. Pharmacokinetic parameters

Time for the maximum plasma concentration (Tmax), maximum observed plasma concentration (Cmax), and the area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC0–t) will be calculated. Moreover, to explore early exposure to PAM, AUC from time 0 to 2 h (AUC0–2) will be also calculated.

Parallel analysis of the parental compound (prasugrel) and its main intermediate and active metabolites should allow to identify the contribution of drug metabolism to pharmacokinetics and pharmacodynamics.

9.3. Bioequivalent

N/A

10. Evaluation of efficacy parameters

10.1. Analysis of primary, secondary, and other efficacy endpoints

10.1.1. Analysis of primary endpoint

The primary end-point of the study is the percentage of inhibition of platelet activity (IPA) at light transmission aggregometry (LTA) in a platelet-rich plasma stimulated with ADP 20 µmol/l after 30±5 minutes from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose (at the beginning of the primary PCI) in the prasugrel only arm. Percentage IPA is defined as 100%*(baseline platelet aggregration minus at time t platelet aggregation) / baseline platelet aggregration. Baseline is at time 0 minutes just before drug administration, follow-up measurements are at time 15 minutes, 30 minutes, 1 hours, 2 hours, 3 hours and 4 to 6 hours since drug administration.

10.1.2. Analysis of secondary efficacy endpoints

Secondary end-points include:

Percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 20 µmol/l at time 0 (before any drug administration, as baseline), at 15±5 minutes, at 1 hour ±5 minutes, at 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours from the bolus of tirofiban or cangrelor or from the administration of prasugrel oral loading dose in the prasugrel only arm (the variable will be considered as continuous and also as categorical (%>80% and %>90%)).

Percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with ADP 5 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%)).

Percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with thrombin receptor agonist peptide (TRAP) 5 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%)).

Percentage of inhibition of platelet activity at light transmission aggregometry in a platelet-rich plasma stimulated with TRAP 15 µmol/l at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (%>80% and %>90%)).

Area under the curve (AUC) at impedance aggregometry (Multiplate® Electrode Aggregometry) in whole blood with ADPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5

minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours (the variable will be considered as continuous and also as categorical (AUC unit >46, that is the threshold for high platelet reactivity in patients undergoing PCI).

AUC at impedance aggregometry in whole blood with TRAPtest at time 0, 15±5 minutes, 30±5 minutes, 1 hour ±5 minutes, 2 hours ±5 minutes, at 3 hours ±5 minutes, at 4-6 hours.

High Platelet Reactivity» and «Low platelet reactivity» based on the % values of platelet aggregation (not IPA). For “High platelet reactivity” the common definition of platelet aggregation >59% at LTA ADP 20 microM or >46% at LTA ADP 5 microM, and by Multiplate ADP >46 U while Low Platelet Reactivity is defined by Multiplate ADP <19 U. There are no literature cutoffs for TRAP (both LTA and multiplate tests) so we will use tertiles (1st tertile to define LPR and 3rd tertile to define HPR).

The same LTA parameters listed above (primary and secondary endpoints) will be also calculated by using the “Late Aggregation (%)” instead of “Max Aggregation (%)”.

Time for the maximum plasma concentration (Tmax), maximum observed plasma concentration (Cmax), and the area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC0–t) will be calculated. Moreover, to explore early exposure to P-AM, AUC from time 0 to 2 h (AUC0–2) will be also calculated.

10.1.3. Analysis of other endpoints of interest

Adverse clinical events will be assessed at 48 hours from PCI and at 30 days. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, transient ischemic attack, urgent target vessel revascularization, unplanned revascularization, definite/probable stent thrombosis, bleeding events, net adverse clinical event. These endpoints will be reported as total number of events per randomized arm per time point (48h or 30 days - counting each event type per patient once, % of all patients) and compared using Fisher’s exact tests (Cangrelor or Tirofiban vs. the reference arm Prasugrel; chewed Prasugrel vs the reference arm integer Prasugrel)..

10.2. Method for analysis

10.2.1. Binary data

Binary data will be tested in the pairwise comparisons using Fisher’s exact test. Lesion-level binary data will be tested using nested logistic regressions with robust standard errors accounting for lesions nested within patients (in case of failing model fits with simple Fisher’s tests on the lesion-level data). Mixed models accounting for random effects of patients and sites will be used as appropriate, if there are multiple measurements per patient to be compared (e.g. at each time point) and if there are enough patients per site (e.g. at least one patient per randomized arm per site).

10.2.2. Count data

Counts per category will be tested in the pairwise comparisons using chisquare tests. Lesion-level counts per category will be tested using nested multinomial regressions with robust standard errors accounting for lesions nested within patients (in case of failing model fits with simple chisquare tests on the lesion-level data). Mixed models accounting for random effects of patients and sites will be used as appropriate, if there are multiple measurements per patient to be compared (e.g. at each time point) and if there are enough patients per site (e.g. at least one patient per randomized arm per site).

10.2.3. Continuous scale data

Means will be tested in the pairwise comparisons using t-tests. Lesion-level means per category will be tested using mixed models with robust standard errors accounting for lesions nested within patients (in case of failing model fits with simple t-tests on the lesion-level data).

Means of Inhibition of platelet activity (% of IPA at LTA or AUC unit at Multiplate, as continuous variables) will be compared between the groups using Mixed models accounting for random effects of patients and sites will be - as appropriate, if there are multiple measurements per patient to be compared (e.g. at each time point) and if there are enough patients per site (e.g. at least one patient per randomized arm per site) with Bonferroni post-hoc test used to interpret the resulting p-values.

10.2.4. Time-to-event data

The safety events will be reported descriptively at 48 hours, as considering the low number of patients only a few events are expected. At 30 days the safety events will be reported as first event of each type per patient only per randomized arm (cumulative incidence rate %, starting with the total number of patients randomized to that arm at risk at time of randomization) with Fisher's exact test. Hazard ratios in the pairwise comparisons will be reported, replaced with continuity corrected Risk ratios in case of zero events in one arm.

10.2.5. Ordinal scales and non-ordered scales data

No ordinal scale tests are planned.

10.3. Platelet aggregation (primary outcome) Table

The table contains the primary outcome at 30 minutes.

Table 5

The supplementary table shows all secondary outcomes:

Supplementary Table 1

11. Evaluation of safety parameters

11.1. Safety events

11.1.1. Brief summary of safety events

Main safety outcomes are:

- Bleeding Academic Research Consortium (BARC) bleeding grade 2, 3 and 5 at 48 hours and 30 days
- Thrombolysis in Myocardial Infarction (TIMI) bleeding scale at 48 hours and 30 days
- Global Use of Strategies To Open occluded arteries (GUSTO) bleeding scale at 48 hours and 30 days
- Net adverse clinical events (NACE) defined as the composite of death, non-fatal myocardial infarction, definite/probable stent thrombosis, non-fatal stroke, and BARC 2, 3, or 5 at 48 hours and 30 days.

11.1.2. Analysis of safety events

Safety outcomes will be assessed at 48 hours from PCI and at 30 days from PCI. They include: death, cardiac death, non-fatal myocardial infarction, non-fatal stroke, urgent target vessel revascularization, definite/probable stent thrombosis. These endpoints will be reported as total number of events per randomized arm per time point (48h or 30 days - counting each event type per patient once, % of all patients) and compared descriptively without p-values for 48h, and compared statistically wuth p-values for the 30 days period using Fisher's exact tests (Cangrelor or Tirofiban vs. the reference arm Prasugrel; chewed Prasugrel vs the reference arm integer Prasugrel).

11.1.3. Analysis of serious adverse events

Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

SAEs will be will be assessed at 48 hours from PCI and at 30 days. These endpoints will be reported as total number of events per patient per randomized arm per time point (48h or 30 days - % of all patients) and compared using Poisson regression (Cangrelor or Tirofiban vs. the reference arm Prasugrel; chewed Prasugrel vs the reference arm integer Prasugrel). Reporting in the main publication is on request.

11.1.4. Clinical outcomes Table

The following table is produced to show the clinical outcomes at 30 days (the 48 hours outcomes will be reported descriptively in the text):

Supplementary Table 2

12. Substudies

12.1 Cardiac Magnetic Resonance Imaging substudy

Cardiac MRI is performed, in patients providing consent, at 3±1 days and at 5±1 months from primary PCI.

A dedicated core-lab will collect anonymized cMRI scans and perform the qualitative/quantitative analysis blinded to treatment.

The protocol applied is as follows:

- Acquisition of a contiguous stack of short axis retrogated steady state free precession cines. We would suggest a slice thickness of 8mm and no gap between the slices. According to the size of the heart we will need 10-14 slices for complete coverage of the LV, which according to the scanner used will take between 5-14 breathholds.
- Area at risk: acquisition of a contiguous stack of short axis T2 maps with the same slice position/slice thickness/field of view as for cine imaging. This will require around 10 breathholds.
- Intramyocardial hemorrhage: same as above, but using T2* maps
- Delayed enhancement: we suggest to give 0.15mmmol/kg/body weight of MR contrast (gadolinium) and to wait at least 10 minutes before the acquisition of the delayed enhancement short axis slices, again with the same slice position/slice thickness/field of view as for cine imaging. This will take around 10-12 breathholds.

The aim of this substudy is to compare randomized treatment groups by accounting for the time from symptom onset (for which randomization was stratified).

The relationship with all MRI parameters and platelet inhibition at each time point will be also explored. Main MRI endpoints are myocardial salvage, MVO, infarct size, and intramyocardial haemorrhage. Among the pre-specified sub-analyses, we will explore the relationship between presence and extent of intramyocardial haemorrhage and allocated treatment, degree of platelet inhibition and time to presentation. We hypothesize that mainly in late comers, high degree of platelet inhibition or use of more potent anti-platelet agents increases the chance to detect the presence of any or large intramyocardial haemorrhage at acute MRI examination.

The improvement/worsening of quantitative parameters will be assessed by comparing the 2 MRI exams (3 days and 5 months) in each patient and randomized group. This analysis will be conducted in all patients presenting both MRI exams.

Specifically, we will compare infarct size and LV (and RV) volumes and systolic function between baseline and follow up exams. We expect to find a small decrease in infarct size and an increase in the mean LV enddiastolic volume for the whole group, driven by negative remodeling in patients with large infarcts. Negative remodeling is classically defined as an increase in normalized LV enddiastolic volume LVEDVI of 10-20% between baseline and follow-up.

The primary endpoint will be the Myocardial salvage Index (MSI) which is defined as Myocardial Salvage/Area at risk (MS/AAR). Many other secondary endpoints will be analyzed. The list of parameters analyzed is as follows:

Fabolous Faster CMR Sub-study baseline

- LV enddiastolic volume absolute (ml) and indexed to BSA (ml/m2)
- LV endsystolic volume absolute (ml) and indexed to BSA (ml/m2)
- LVEF (%)
- LV mass absolute (g) and indexed to BSA (g/m2)
- Regional wall motion abnormalities, per segment and severity, using the AHA 16 segments model and a wall motion score (1=normal; 2=hypokinetic; 3=akinetic; 4=dyskinetic). Wall motion score index obtained by summation of the wall motion score of all segments.
- Segmental wall thickness (mm), 16 AHA segments
- Aortic flow (phase contrast flow velocity mapping)
- Regurgitant fraction of mitral regurgitation (%), if any: (LV stroke volume – aortic forward flow) / LV stroke volume
- Infarct size absolute (g) and indexed to total LV mass (%)
- Transmural extent of necrosis per segment, in quartiles (none; 1-25%, 26-50%; 51-75%; 76-100%)
- Area at risk (myocardial oedema on T2 SAX images) absolute (g) and indexed to total LV mass (%)
- Myocardial salvage index = (Area at risk – infarct size) / Area at risk
- IMH (on T2* SAX images) absence / presence / location / size in g and % of LV mass
- MVO absence / presence / location / size in g and % of LV mass
- LV thrombus, absence / presence
- Pericardial effusion, absence / presence
- Old remote infarct size
- RV enddiastolic volume absolute (ml) and indexed to BSA (ml/m2)
- R V endsystolic volume absolute (ml) and indexed to BSA (ml/m2)
- RVEF (%)
- Regional wall motion abnormalities
- Myocardial LGE, absence / presence / location
- Atrial compromission at LGE, absence / presence

Fabolous Faster CMR Sub-study follow-up

- LV enddiastolic volume absolute (ml) and indexed to BSA (ml/m2)

· LV endsystolic volume absolute (ml) and indexed to BSA (ml/m2)
· LVEF (%)
· LV mass absolute (g) and indexed to BSA (g/m2)
· Regional wall motion abnormalities, per segment and severity, using the AHA 16 segments model and a wall motion score (1=normal; 2=hypokinetic; 3=akinetic; 4=dyskinetic). Wall motion score index obtained by summation of the wall motion score of all segments.
· Segmental wall thickness (mm), 16 AHA segments
· Aortic flow (phase contrast flow velocity mapping)
· Regurgitant fraction of mitral regurgitation (%), if any: (LV stroke volume – aortic forward flow) / LV stroke volume
· Infarct size absolute (g) and indexed to total LV mass (%)
· Transmural extent of necrosis per segment, in quartiles (none; 1-25%, 26-50%; 51-75%; 76-100%)
· LV thrombus, absence / presence
· Pericardial effusion, absence / presence
· RV enddiastolic volume absolute (ml) and indexed to BSA (ml/m2)
· RV endsystolic volume absolute (ml) and indexed to BSA (ml/m2)
· RVEF (%)
· Regional wall motion abnormalities
· Myocardial LGE, absence / presence / location

Extent of infarct size at cardiac MRI will be compared between treatment groups with ANOVA with post-hoc test adjustment and coefficients of correlation and determination will be calculated with multivariable linear regression.

Rate of intramyocardial haemorrhage at cardiac MRI will be compared with $\chi 2$ test and odds ratios calculated with logistic regression

12.2 ECG and Angiography substudy

This substudy will investigate the impact of randomized treatment strategy on electrocardiographic and angiographic parameters.

Anonymized ECGs and angiographies will be collected and analyzed by a core-lab blinded to treatment strategy.

Multiple parameters will be extracted and compared among the groups. Yet, the associations of ECG and angio findings with platelet reactivity will be also evaluated.

All ECGs will be screened through computer software to conduct the digital analysis. Digital ECG measurements will be calculated with a professional software (EP Calipers) using manual electronic calipers to obtain highly sensitive measurements for both time and amplitude

variables (additional information available online at https://www.epstudiossoftware.com/about-ep-calipers/).

The following ECG variables will be analyzed and calculated for each ECG recording:

Heart rhythm	- Heart rate - Rhythm definition - Rhythm disturbance (supra-ventricular and ventricular arrhythmias) - Premature ectopic beats (atrial and ventricular)
Frontal plane QRS axis	- Normal axis orientation - Left or right axis deviation
Atrial depolarization	- P-wave voltage - P-wave duration - P-wave dispersion - P-wave time-to-peak (atrial intrinsicoid deflection) - P-peak to P-end interval - P-wave peak-to-end interval - P-wave morphology (i.e., irregular, M- / W-shaped) - P-wave terminal force in V1 - Left atrial enlargement - Right atrial enlargement - Interatrial block
Atrial repolarization	- PR-deviation at atrial J-point (elevation and/or depression) - Maximum PR-deviation (elevation and/or depression) - ∑ PR-deviation at atrial J-point (elevation and/or depression) - ∑ Maximum PR-deviation (elevation and/or depression) - PR-deviation resolution at atrial J-point (elevation and/or depression) - Maximum PR-deviation resolution (elevation and/or depression) - PR-segment deviation slope (flat, slightly/markedly down-sloping or up-sloping) - P-wave / PR-segment junction shape distinguishing a smooth-angled versus a sharp-angled - P-wave polarity / PR-deviation concordance (or discordance)
Atrioventricular conduction	- PR-interval duration - Time relation between P-wave / QRS complex - Atrioventricular block - Wolf-Parkinson-White pattern
Ventricular depolarization	- Q-, R-, S-, R'-, S'- (individual) waves voltage - Q-, R-, S-, R'-, S'- (individual) waves duration - R-wave time-to-peak (ventricular intrinsicoid deflection); - Peak-to-peak QRS complex amplitude - Net QRS complex deflection - QRS complex duration - QRS complex dispersion - Complete/incomplete right/left bundle branch block - Left anterior/posterior fascicular block - Bifascicular block
Ventricular repolarization	- ST-segment deviation at J-point (elevation and/or depression) - ST-segment deviation 60 ms after the J-point (elevation and/or depression) - ∑ ST-segment deviation at J-point (elevation and/or depression) - ∑ ST-segment deviation 60 ms after the J-point (elevation and/or depression) - ST-segment resolution at J-point (elevation and/or depression) - ST-segment resolution 60 ms after the J-point (elevation and/or depression)

	- Non-persistent ST-segment elevation - Dynamic ST-segment shifts - T-wave amplitude - Peak-to-peak T-wave amplitude - Net T-wave deflection - T-wave duration - T-wave morphology (i.e., biphasic, hyper-acute) - T-wave time-to-peak (T-wave intrinsicoid deflection) - Tp-e interval with tail method (with and without Bazett's correction) - Tp-e interval with tangent method (with and without Bazett's correction) - Tp-e interval dispersion - JT-interval with tail method (with and without Bazett's correction) - JT-interval with tangent method (with and without Bazett's correction) - JT-interval dispersion - JT-interval prolongation index - QT-interval with tail method (with and without Bazett's correction) - QT-interval with tangent method (with and without Bazett's correction) - QT-interval dispersion - QT-interval prolongation index
Additional metrics (including scores or patterns)	- Wellens' pattern - De Winter's pattern - Sgarbossa's criteria for left bundle branch block - Smiths' criteria for left bundle branch block - Anderson-Wilkins acuteness score - Left ventricular hypertrophy - Right ventricular hypertrophy - Index of Cardiac Electrophysiological Balance (iCEB) - ECG-based Regional Restitution Instability Index (R2I2) - Mechanical systole duration by Waller's formula

Each coronary angiography will be analyzed and the following variables will be extracted:

- Lesion length, mm
- Lesion diameter, %
- Minimal lumen diameter, mm
- Reference vessel diameter, mm
- Thrombus score pre-PCI
- TIMI flow pre-PCI in the culprit vessel
- TIMI flow post-PCI in the culprit vessel
- Corrected TIMI frame count post-PCI
- Myocardial blush grade (MBG) post-PCI
- SYNTAX score at baseline
- SYNTAX score post-PCI

Continuous variables (i.e. corrected TIMI frame count at the end of PCI, SYNTAX score, etc) will be compared with ANOVA with post-hoc test adjustment and coefficients of correlation and determination will be calculated with linear regression

Rates (i.e. proportion of patients with MBG flow <3 or TIMI flow <3 at the end of PCI, or with ST resolution ≥70% at the ECG recorded soon after PCI and at 90±30 minutes after PCI, etc.) will be compared with χ2 test and odds ratios calculated with logistic regression

Residual ST elevation at the ECG recorded soon after PCI and at 90±30 minutes from the end of PCI will be calculated by the sum of the absolute values of the 12-lead elevation/depression data and then differences between treatments will be tested with both the nonparametric Wilcoxon rank sum test and a t-test.

12.3 Pharmacokinetic methodology validation and Prasugrel PK/PD substudy

Sample preparation for mass spectrometric detection will be carried out using a liquid-liquid extraction (LLE) technique following the Lukram's protocol with some modifications (Lukram, O. et al.Electrospray ionization LC-MS/MS validated method for the determination of the active metabolite (R-138727) of prasugrel in human plasma and its application to a bioequivalence study. Drug Test. Anal.4, 158–166 (2012)). Briefly, 400 µl of plasma is aliquoted into 10 ml tubes, filled with 400 µl of 6% formic acid. After this, 4 ml of hexane:ethylacetate (9:1) is added to each acidified plasma solution and the samples are vortexed gently and then centrifuged at 2400g for 30 min. Finally the organic layer is transferred to evaporating tubes and the hexane:ethylacetate fase is dried under the stream of nitrogen gas.

Each of the dried extracts will be resuspended with 50µl of the mobile phase (5 mM aqueous ammonium formate added with 0.01% formic acid: methanol added with 10% acetonitrile and 0.01% formic acid 50:50) and then directly injected in the UHPLC–MS/MS system.

Calibration curves are prepared by adding standard solution of prasugrel (and/or prasugrel inactive metabolite R-95913) and its derivatized active metabolite (R-138727) to blank plasma to obtain the range 0.039-100 ng/ml for prasugrel and 0.310-800 ng/ml for prasugrel active/inactive metabolite.

LC-MS/MS analyses are performed using a model 1290 UHPLC coupled to a model 6440 triple quadruple mass spectrometer (Agilent Technologies, Waldbronn, Germany). The system hosted a Jetstream ESI source (Agilent) operating in positive ionization mode. Separations are carried out on Eclipse plus C18 RRHD column (2,1 x 100mm, 1.8µm)(Agilent Technologies, Waldbronn, Germany) with a flow rate of 500 µl/min and temperature is set at 40°C. The gradient elution is performed by mixing 5 mM aqueous ammonium formate added with 0.01% formic acid (eluent A) and methanol added with 10% acetonitrile and 0.01% formic acid (eluent B), the gradient A+B starting at 30%B for 1 min then increasing linearly to 95%B in 8 min and back to 30%B at 10 min.

Relationship between pharmacokinetic profile and pharmacodynamic response will be analysed by non-linear regression analysis assuming hysteresis and the irreversible bioactivity of prasugrel active metabolite as contributors to the pharmacodynamic profile.

According to the kinetics profile, the threshold exposure that is required to determine a meaningful pharmacodynamics response in platelets will be tentatively defined. To this aim separate and cumulative analysis of kinetics data deriving from each time point and any single patients will be considered along with the maximum platelet response in ADP-induced platelet aggregation, irrespectively of timing of blood sample collection. Time to response, threshold response and maximum response will be considered.

12.4 Cost-effectiveness substudy

Cost-effectiveness analysis will be also carried out by inputting direct and indirect costs in relation to outcomes assessed both in terms of clinical events, surrogate markers of outcomes, such as ST segment elevation resolution or infarct size at MRI as well with respect to degree of platelet inhibition.

Table 1. Baseline Clinical Characteristics

	Cangrelor (N=)	Tirofiban (N=)	chewed Prasugrel (N=)	integer Prasugrel (N=)
Age — years (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx
Male gender — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Body mass index — kg/m^2	xx ± xx	xx ± xx	xx ± xx	xx ± xx
Diabetes mellitus — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Diet	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Oral-treated	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Insulin-treated	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Hypertension — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Dyslipidemia — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Family history of CAD — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Current smoker — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Carotid artery disease — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Chronic kidney disease (eGFR<60 ml/min)— no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Heart failure — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Previous MI — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Previous PCI — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Previous CABG — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Previous bleeding requiring medical attention* — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
COPD — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Baseline Medications				
Aspirin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
daily dose ≤100mg	x (xx%)	x (xx%)	x (xx%)	x (xx%)
daily dose 101-200mg	x (xx%)	x (xx%)	x (xx%)	x (xx%)
daily dose >200mg	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Oral anticoagulants — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Novel oral anticoagulants — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Statins — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Other lipid lowering drug — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
ACE inhibitor — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
ATII antagonist — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Beta blocker — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Amiodarone — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Antiarrhythmic drug** — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Ca-antagonist — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Digoxin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Nitrates — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Diuretics — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Insulin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Oral antidiabetic — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
NSAID — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Antidepressant drug — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)
PPI — no. (%)	x (xx%)	x (xx%)	x (xx%)	x (xx%)

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

MI: Myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate or creatinine clearance; NSAID: non-steriodal anti-inflammatory drugs; PPI: proton-pump inhibitor.

*>15 days before randomization

**Other than Beta blocker or Amiodarone

Table 2. Presentation and catheterization

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-value	C vs cP p-value	T vs cP p-value	integer Prasugrel [iP] (N=)	iP vs cP p-values
Presentation								
Systolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Diastolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Heart rate - beats/min (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Killip class — no. (%)								
I	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
II	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
III	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
IV	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Left ventricular ejection fraction — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Cardiac arrest — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
≥2 episodes of chest pain in the last 24h — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Rhythm — no. (%)								
Sinus rhythm	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Atrial fibrillation	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Other rhythm	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Intraventricular conduction defects — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
LBBB	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
RBBB	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Other conduction defect	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Catheterization								
First arterial access — no. (%)								
Femoral	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Radial	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Shift to other access site — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
To femoral	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
To radial	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
To other access site	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
First access site closure — no. (%)								
Manual compression/elastic bandage	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Radial or femoral closure device	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Sheath or device in place*	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Second arterial access needed — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Femoral	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Radial	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Other access site	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Second access site closure — no. (%)								
Manual compression/elastic bandage	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Radial or femoral closure device	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Sheath or device in place*	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Hemodynamic support — no. (%)								
IABP	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Percutaneous left ventricular assist device	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Vasopressor (continuous infusion)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

LBBB: left-branch bundle block; RBBB: right-branch bundle block; IABP: intra-aortic balloon pump

*e.g. IABP

Table 3. Medications before and during the index PCI

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-value	C vs cP p-value	T vs cP p-value	integer Prasugrel [iP] (N=)	iP vs cP p-values
Unfractionated heparin	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x.xx**	**x.xx**	**x.xx**	**x (xx%)**	**x.xx**
Before catheterization — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Bolus dose — UI/Kg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Infusion rate — ml/h (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
ACT performed — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ACT value — seconds (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
ACT out of range — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
During catheterization and PCI — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
First Bolus dose — UI/Kg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Second bolus — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Second Bolus dose — UI/Kg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Based on ACT performed — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ACT value — seconds (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
ACT out of range — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Third bolus — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Third Bolus dose — UI/Kg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Based on ACT performed — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ACT value — seconds (±SD)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ACT out of range — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Aspirin — no. (%)	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x.xx**	**x.xx**	**x.xx**	**x (xx%)**	**x.xx**
Loading dose — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Route of administration — no. (%)								
Intravenous	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Oral	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Morphine — no. (%)	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x.xx**	**x.xx**	**x.xx**	**x (xx%)**	**x.xx**
Total dose — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Other opioids — no. (%)	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x.xx**	**x.xx**	**x.xx**	**x (xx%)**	**x.xx**
Total dose — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

ACT: activated clotting time.

Note that all patients received a loading dosage of Prasugrel, for the Cangrelor and the Tirofiban patients this loading was received after the infusion of either Cangrelor or Tirofiban was stopped.

Table 4. Angiography and index PCI

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-value	C vs cP p-value	T vs cP p-value	integer Prasugrel [iP] (N=)	iP vs cP p-values
Time of procedure — minutes (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Amount of contrast — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Culprit vessel — no. (%)				x.xx	x.xx	x.xx		x.xx
Left main artery	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Left anterior descending artery	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Left circumflex artery	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Right coronary artery	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Bypass graft — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
SVG	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
LIMA	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
RIMA	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Radial graft	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Culprit lesion type — no. (%)				x.xx	x.xx	x.xx		x.xx
De novo	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
ISR	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Stent thrombosis	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Graft	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Culprit lesion length — mm (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Culprit lesion diameter stenosis — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Thrombus aspiration performed — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Bifurcation — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Nr of lesions	N=xx	N=xx	N=xx				N=xx	
Number of stents per lesion – mean (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Type of stent per lesion – (%)				x.xx	x.xx	x.xx		x.xx
New generation DES	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Bioresorbable scaffold	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Bare-metal stent	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
Maximum stent diameter per lesion — mm (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Total stent length per lesion — mm (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Any p redilatation per lesion — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Any post dilatation per lesion — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Any overlapping stents per lesion — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Post-procedural stenosis — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
TIMI flow per PCI per lesion — no. (%)				x.xx	x.xx	x.xx		x.xx
0 or 1	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
2	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
3	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
TIMI Flow post PCI per lesion — no. (%)				x.xx	x.xx	x.xx		x.xx
0 or 1	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
2	x (xx%)	x (xx%)	x (xx%)				x (xx%)	
3	x (xx%)	x (xx%)	x (xx%)				x (xx%)	

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

SVG: saphenous vein graft; LIMA: left internal mammary artery; RIMA: right internal mammary artery; ISR: in-stent restenosis; TIMI: Thrombolysis In Myocardial

First generation DES are Cypher or Taxus will be reported separately if they are used.

Table 5. Platelet aggregation

	Cangrelor [C]	Tirofiban [T]	chewed Prasugrel [cP]	C vs T mean difference (95% CI)	C vs T p-value	C vs cP mean difference (95% CI)	C vs cP p-value	T vs cP mean difference (95% CI)	T vs cP p-value	integer Prasugrel [iP]	cP vs iP mean difference (95% CI)	cP vs iP p-values
	(N=)	(N=)	(N=)							(N=)		
%IPA using LTA with ADP 20 µmol/L												
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
>80% IPA with LTA with ADP 20 µmol/L												
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
>90% IPA with LTA with ADP 20 µmol/L												
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx ± xx	x.xx	x.xx

Data expressed as means %IPA±standard deviations and mean differences (95% confidence interval) with p-values from mixed models (for %IPA) or chisquare tests (for >80% and >90% IPA), interpretation of the p-values with Bonferroni correction. IPA: [%PA at baseline time 0 - %PA at time point t] / %PA at baseline time 0

*Primary endpoint, all other endpoints are secondary endpoints.

Data on other endpoints using alternative measurement techniques are provided in separate supplementary tables.

Table 6. Follow-ups

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-value	C vs cP p-value	T vs cP p-value	integer Prasugrel [iP] (N=)	iP vs cP p-values
At 48 hours								
Angina — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS I	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 2	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 3	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 4	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Systolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Diastolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Heart rate - beats/min (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
At 30 days								
Angina — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS I	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 2	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 3	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
CCS 4	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Systolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Diastolic arterial pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Heart rate - beats/min (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
Medications at 30 days								
Aspirin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
daily dose ≤100mg	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
daily dose 101-200mg	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
daily dose >200mg	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Prasugrel — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Clopidogrel — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Ticagrelor — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Oral anticoagulants — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Novel oral anticoagulants — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Statins — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Other lipid lowering drug — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ACE inhibitor — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
ATII antagonist — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Beta blocker — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Amiodarone — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Antiarrhythmic drug** — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Ca-antagonist — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Digoxin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Nitrates — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Diuretics — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Insulin — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Oral antidiabetic — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
NSAID — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
Antidepressant drug — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx
PPI — no. (%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x (xx%)	x.xx

Data expressed as n (%, p-values from Fisher's exact tests or chisquare tests) or means±standard deviations (p-values from t-tests).

Ticlopidin will be reported if still used.

NSAID: non-steriodal anti-inflammatory drugs; PPI: proton-pump inhibitor.

Supplemental Table 1. Platelet aggregation using alternative assessments

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-value	C vs cP p-value	T vs cP p-value	integer Prasugrel [iP] (N=)	iP vs cP p-values
%IPA using LTA with ADP 5 µmol/L								
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
>80% IPA with LTA with ADP 5 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
>90% IPA with LTA with ADP 5 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
%IPA using LTA with TRAP 5 µmol/L								
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
>80% IPA with LTA with TRAP 5 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
>90% IPA with LTA with TRAP 5 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
%IPA using LTA with TRAP 15 µmol/L								
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
>80% IPA with LTA with TRAP 15 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
>90% IPA with LTA with TRAP 15 µmol/L								
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	xx ± xx	x.xx
AUC using ADPtest								
at 0 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
AUC using TRAPtest								
at 0 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	xx ± xx	x.xx

Data expressed as LTA: means %IPA±standard deviations (p-values from ANOVAs); AUC means U units±standard deviations (p-values from ANOVAs); >80% and >90% IPA: counts (% of patients, p-values from Fisher's exact tests). P-values are interpreted using Bonferroni correction.

AUC: area under the curve

Supplemental Table 2. Platelet aggregation lumping the Prasugrel arms

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	chewed Prasugrel or integer Prasugrel (N=)	C vs T mean difference	C vs T p-value	C vs P mean difference	C vs P p-value	T vs P mean difference	T vs P p-value
%IPA using LTA with ADP 20 µmol/L									
at 15 minutes	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 30 minutes*	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 1 hour	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 2 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 3 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 4 to 6 hours	xx ± xx	xx ± xx	xx ± xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
>80% IPA with LTA with ADP 20 µmol/L									
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
>90% IPA with LTA with ADP 20 µmol/L									
at 15 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 30 minutes	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 1 hour	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 2 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 3 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
at 4 to 6 hours	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

Data expressed as means %IPA±standard deviations and mean differences (95% confidence interval) with p-values from mixed models (for %IPA) or chisquare tests (for >80% and >90% IPA), interpretation of the p-values with Bonferroni correction. IPA: [%PA at baseline time 0 - %PA at time point t] / %PA at baseline time 0

*Primary endpoint, all other endpoints are secondary endpoints.

Data on other endpoints using alternative measurement techniques are provided in separate supplementary tables.

Supplemental Table 3. Clinical outcomes at 30 days since PCI

	Cangrelor [C] (N=)	Tirofiban [T] (N=)	integer Prasugrel [iP] (N=)	chewed Prasugrel [cP] (N=)	C vs T p-values	C vs cP p-values	T vs cP p-values	iP vs cP p-values
NACE	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
All-cause Death	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Cardiac death	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Reinfarction (any)	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Definite or Probable Stent Thrombosis	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Definite Stent Thrombosis	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Probable Stent Thrombosis	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Repeat unplanned revascularisation (any)	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Urgent TVR	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Stroke	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
TIA	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Bleeding (any)	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Intracranial bleeding	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
Gastrointestinal bleeding	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
BARC bleeding events								
type 2, 3 or 5	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 1	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 2	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 3a	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 3b	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 3c	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 4	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 5a	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
type 5b	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
TIMI bleeding events								
major	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
minor	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
requiring medical attention	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
minimal	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
GUSTO bleeding events								
severe	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
moderate	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx
mild	x (xx%)	x (xx%)	x (xx%)	x (xx%)	x.xx	x.xx	x.xx	x.xx

Number of first events and raw percentages are reported (% of all randomized patients). Hazard ratios are estimated using the Cox regression method, except in the case of zero events when continuity corrected Risk Ratios. All p-values are from Fisher's exact test. All events were censored beyond 30 days, therefore possible stent thrombosis is not applicable.

TVR: target vessel revascularisation.

NACE: composite of death, non-fatal myocardial infarction, definite/probable stent thrombosis, non-fatal stroke and BARC 2, 3 or 5.

Endpoints reached at 48 hours since PCI will be reported in the text of the manuscript descriptively only.