1 **Supplementary tables:**

2

3 **Table S1: Sensitivity analyses using multiple imputation and inter- and extrapolation**

Main outcomes with imputation	Acetaminophen N=98	Fentanyl N=97	P-value
PRU at T2 (mean, SE)	126 (9.7)	152 (10.2)	0.07
PRU (mean, SE)			
T1	155 (8.4)	170 (7.7)	0.20
T3	61 (9.2)	79 (11.2)	0.20
T4	29 (4.6)	30 (4.7)	0.87
High platelet reactivity op T2 (%)	24 (24.5)	36 (36.9)	0.06
Ticagrelor concentration (mean, SE)			
T1	371 (50.8)	188 (31.7)	0.002
T2	509 (60.9)	273 (36.5)	0.001
T3	657 (50.7)	419 (32.3)	<0.001
T4	439 (26.4)	434 (36.6)	0.92
Ticagrelor active metabolite concentration (mean, SE)			
T1	44 (7.3)	21 (4.0)	0.01
T2	75 (9.8)	46.6 (7.4)	0.02
T3	144 (16.4)	86 (7.8)	0.001
T4	120 (7.4)	434 (36.6)	0.85
Ticagrelor concentration total (mean, SE)			
T1	414 (56.4)	209 (35.4)	0.002
T2	585 (69.0)	319 (43.1)	0.001
T3	801 (63.1)	504 (39.1)	<0.001
T4	558 (32.0)	556 (44.3)	0.96
Main outcome using inter- and extrapolation	**Acetaminophen N=98**	**Fentanyl N=97**	**P-value**

PRU at T2 (median, IQR)	115 [45-191]	171 [93-218]	0.01

1 IQR: interquartile range; PRU: platelet reactivity units; T1: before primary PCI; T2:

2 immediately after primary PCI; T3: 1-hour after primary PCI; T4: 6 hours after primary PCI

3

4

1 **Table S2: Post-hoc analysis of difference (delta) between PRU at T1 and T2, and T2 and**

2 **T3 and their ratios**

	Acetaminophen	Fentanyl	P-value
Delta PRU T1 and T2 (median, IQR)	-17 [-57 - 17]; n=84	-5.5 [-51 - 20] n=76	0.31
Delta PRU T2 and T3 (median, IQR)	-31 [-115 - -3]; n=72	-38 [-134 - -1]; n=68	0.87
Ratio PRU T1 and T2 (median, IQR)	0.83 [0.51-1.09]; n=84	0.96 [0.43-1.10]; n=76	0.81
Ratio PRU T2 and T3 (median, IQR)	0.48 [0.12-0.91]; n=72	0.61 [0.16-0.97]; n=68	0.80

3 PRU: platelet reactivity units; T1: before primary PCI; T2: immediately after primary PCI;

4 T3: 1-hour after primary PCI

5

6

1 **Table S3: Post-hoc analysis of PRU and ticagrelor concentration in patients without**

2 **vomiting**

No vomiting	Acetaminophen (N=95)	Fentanyl (N=83)	P-value
PRU T1 (median, IQR)	165 [94-222]	193 [134-223]	0.13
PRU T2 (median, IQR)	101 [36-206]	162 [49-218]	0.30
PRU T3 (median, IQR)	27 [4-82]	49 [7-131]	0.21
PRU T4 (median, IQR)	8 [3-29]	8 [4-39]	0.54
Ticagrelor concentration T1 (median, IQR)	157 [33-525]	69 [13-228]	0.02
Ticagrelor concentration T2 (median, IQR)	341 [99-805]	171 [37-380]	0.006
Ticagrelor concentration T3 (median, IQR)	505 [312-987]	400 [134-660]	0.004
Ticagrelor concentration T4 (median, IQR)	381 [225-580]	334 [222-580]	0.34
Ticagrelor metabolite concentration T1 (median, IQR)	11 [0-51]	11 [0-20]	0.06
Ticagrelor metabolite concentration T2 (median, IQR)	38 [5-105]	17 [3-59]	0.05
Ticagrelor metabolite concentration T3 (median, IQR)	117 [42-201]	83 [17-129]	0.007
Ticagrelor metabolite concentration T4 (median, IQR)	104 [79-157]	97 [53-159]	0.30

Ticagrelor concentration total T1 (median, IQR)	168 [35-589]	75 [13-255]	0.02
Ticagrelor concentration total T2 (median, IQR)	376 [109-933]	188 [39-438]	0.007
Ticagrelor concentration total T3 (median, IQR)	592 [370-1187]	490 [150-803]	0.005
Ticagrelor concentration total T4 (median, IQR)	517 [349-741]	452 [284-726]	0.25

1 PRU: platelet reactivity units; T1: before primary PCI; T2: immediately after primary PCI;

2 T3: 1-hour after primary PCI; T4: 6 hours after primary PCI

3
4
5

Table S4: Pain reduction stratified for TIMI 0 pre-PCI

		Acetaminophen	Fentanyl	P-value
TIMI 0 Pre-PCI	Pre-PCI	2 [1-3]	2 [1-4]	0.27
	Post-PCI	5 [4-7]	5 [4-7]	0.91
TIMI ≥ 1 Pre-PCI	Pre-PCI	3 [1-6]	2 [1-5]	0.71
	Post-PCI	5 [3-7]	5 [3-7]	0.65

PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction