

Supplemental Material

Data S1.

ISACS-TC sites:

Bosnia and Herzegovina: Clinical Center of Banja Luka, Republika Srpska, Banja Luka; Clinical Center University of Sarajevo, Sarajevo; Opšta Bolnica:"Sveti Vracevi"; Opšta Bolnica, Gradiška; Klinički Centar, Kasindo; Dom Zdravlja "Dr Mladen Stojanović", Bačka Palanka; Opšta Bolnica "Sveti Apostol Luka", Doboj; Univesity Clinical Hospital Mostar. **Croatia:** University Hospital Centre of Zagreb, Zagreb; Clinical Hospital Merkur, Zagreb; Clinical Hospital Dubrava, Zagreb. **Italy:** Sapienza-Cuore Grossi Vasi, Rome. **Kosovo:** Clinical Center of Kosovo, Prishtina. **Lithuania:** Hospital of Lithuanian University of Health Sciences, Kaunas. **Macedonia:** University Clinic of Cardiology, Skopje. **Hungary:** University of Pecs, Medical School, 1st Department of Medicine, Division of Cardiology. **Moldova:** Hospital Center of Cardiology; Institute of Cardiology, Chişinău. **Montenegro:** Clinical Center of Montenegro, Podgorica; General Hospital Kotor; Opšta Bolnica Meljine, Herceg Novi; JZU Dom Zdravlja Plav - Interno Odjeljenje; General Hospital Pljevlja; Opšta Bolnica Berane; Opšta Bolnica Bijelo Polje; Opšta Bolnica Danilo I, Cetinje; PZU OB.MELJINE. **Romania:** Spitalul Clinic de Urgenta, Bucuresti; Spitalul Judetean, Baia Mare. **Russian Federation:** Institute of Therapy and Preventive Medicine in Novosibirsk, Russian Academy of Medical Sciences in Novosibirsk. **Serbia:** University of Belgrade, Clinical Center of Serbia, Belgrade; Clinical Hospital Center, Zemun; Zvezdara University Hospital Center; University Hospital Medical Center Bezanijska Kosa; Hospital of Valjevo; City Hospital, Mitrovica; Clinical Center Kragujevac; General Hospital Cuprija; General Hospital Dr. Djordje Joanovic; Cardiology Clinic, Institute for Treatment and Rehabilitation; General Hospital Jagodina; KBC Kosovska Mitrovica.

Table S1. Baseline characteristics of patients with contraindications to reperfusion therapy

Characteristics	Overall population N=953	Men (N=590)	Women (N=363)	P- value†
Age (years), mean±SD	65.8 ± 13.2	62.8 ± 13.4	70.6 ± 11.3	<0.001
Cardiovascular risk factors				
Hypercholesterolemia, <i>n</i> / <i>total</i> (%)	261/763 (34.2)	159/475 (33.5)	102/288 (35.4)	0.58
Diabetes, <i>n</i> (%)	261 (27.4)	147 (24.9)	114 (31.4)	0.09
Hypertension, <i>n</i> (%)	612 (64.2)	349 (59.1)	263 (72.4)	<0.001
Current smoker, <i>n</i> (%)	252 (26.4)	190 (32.2)	62 (17.1)	<0.001
Family history of CAD, <i>n</i> (%)	235 (24.7)	141 (23.9)	94 (25.9)	0.51
Clinical history of ischemic heart disease				
Prior angina pectoris, <i>n</i> (%)	144 (15.1)	87 (14.7)	57 (15.7)	0.69
Prior myocardial infarction, <i>n</i> (%)	172 (18.0)	119 (20.2)	53 (14.6)	0.03
Prior PCI, <i>n</i> (%)	96 (10.1)	65 (11.0)	31 (8.50)	0.21
Prior CABG, <i>n</i> (%)	30 (3.1)	23 (3.9)	7 (1.9)	0.09
Clinical history of cardiovascular disorders				
Prior heart failure, <i>n</i> (%)	56 (5.9)	33 (5.6)	23 (6.3)	0.63
Prior stroke, <i>n</i> (%)	77 (8.1)	45 (7.6)	32 (8.8)	0.51

Clinical presentation

Atypical chest pain, <i>n/total</i> (%)	106/865 (12.2)	54/536 (10.1)	52/329 (15.8)	0.013
Systolic BP at baseline (mmHg), mean±SD	136.3 ±29.4	135.8 ± 29.7	136.9 ± 28.8	0.55
Heart rate at baseline (b.p.m.), mean±SD	83.3 ± 22.9	83.2 ± 23.4	83.5 ± 22.2	0.83
Chronic kidney disease, <i>n (%)</i>	103 (10.8)	60 (10.2)	463 (0.8)	0.59

In-hospital acute medications

Aspirin, <i>n (%)</i>	849 (89.1)	535 (90.7)	314 (86.5)	0.11
Clopidogrel, <i>n (%)</i>	652 (68.4)	415 (70.3)	237 (65.3)	0.11
Unfractionated heparin, <i>n (%)</i>	381 (39.4)	241 (40.8)	140 (38.6)	0.37
LMWH, <i>n (%)</i>	405 (42.5)	252 (42.7)	153 (42.1)	0.33
Fondaparinux, <i>n (%)</i>	29 (3.1)	19 (3.2)	10 (2.7)	0.36
B-blockers, <i>n (%)</i>	171 (17.9)	108 (18.3)	63 (17.4)	0.51
ACE-inhibitors, <i>n (%)</i>	168 (17.6)	111 (18.8)	57 (15.7)	0.33

Outcomes

30-day all-cause mortality, <i>n</i> (%)	162 (17.0)	88 (14.9)	74 (20.4)	0.03
---	------------	-----------	-----------	------

†*P*-value derived from comparison between men and women. BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S2. Baseline characteristics of patients with unknown time of symptom onset

Characteristics	Overall population N=1801	Men (N=1231)	Women (N=570)	P- value†
Age (years), mean±SD	62.5 ± 12.2	60.3 ± 11.5	67.4 ± 12.2	<0.001
Cardiovascular risk factors				
Hypercholesterolemia, <i>n/total</i> (%)	642/1431 (44.9)	429/972 (44.1)	213 /459 (46.4)	0.42
Diabetes, <i>n (%)</i>	457 (25.4)	290 (23.6)	167 (29.3)	0.02
Hypertension, <i>n (%)</i>	1177 (65.3)	753 (61.2)	424 (74.4)	<0.001
Current smoker, <i>n (%)</i>	728 (40.4)	563 (45.7)	165 (29.9)	<0.001
Family history of CAD, <i>n (%)</i>	576 (31.9)	397 (32.2)	179 (31.4)	0.89
Clinical history of ischemic heart disease				
Prior angina pectoris, <i>n (%)</i>	417 (23.1)	261 (21.2)	156 (27.4)	0.004
Prior myocardial infarction, <i>n</i> (%)	186 (10.33)	131 (10.6)	550 (9.6)	0.52
Prior PCI, <i>n (%)</i>	101 (5.6)	74 (6.0)	27 (4.7)	0.27
Prior CABG, <i>n (%)</i>	28 (1.55)	23 (1.9)	5 (0.9)	0.11
Clinical history of cardiovascular disorders				
Prior heart failure, <i>n (%)</i>	111 (6.2)	71 (5.8)	40 (7.0)	0.30
Prior stroke, <i>n (%)</i>	50 (2.8)	31 (2.5)	19 (3.3)	0.32

Clinical presentation

Atypical chest pain, <i>n/total</i> (%)	93/1691 (5.5)	62 (5.4)	31 (5.7)	0.75
Systolic BP at baseline (mmHg), mean±SD	136.6 ± 22.0	137.2 ± 20.3	135.5 ± 25.3	0.12
Heart rate at baseline (b.p.m.), mean±SD	80.5 ± 19.2	80.5 ± 20.0	80.4 ± 17.4	0.87
Chronic kidney disease, <i>n (%)</i>	98 (5.44)	54 (4.4)	44 (7.7)	0.003

In-hospital acute medications

Aspirin, <i>n (%)</i>	1695 (94.1)	1164 (94.6)	531 (93.2)	0.42
Clopidogrel, <i>n (%)</i>	1610 (89.4)	1099 (89.3)	511 (89.6)	0.95
Unfractionated heparin, <i>n (%)</i>	658 (36.5)	442 (35.9)	216 (37.9)	0.70
LMWH, <i>n (%)</i>	1,037 (57.6)	710 (57.7)	327 (57.4)	0.95
Fondaparinux, <i>n (%)</i>	50 (2.8)	34 (2.8)	16 (2.8)	0.96
B-blockers, <i>n (%)</i>	968 (53.7)	681 (55.3)	287 (50.3)	0.14
ACE-inhibitors, <i>n (%)</i>	973 (54.0)	674 (54.7)	299 (52.5)	0.63

Reperfusion therapy

Primary PCI, <i>n (%)</i>	1243 (69.0)	878 (71.3)	365 (64.0)	0.001
Fibrinolysis, <i>n (%)</i>	207 (11.5)	143 (11.6)	64 (11.2)	0.79

Outcomes

30-day all-cause mortality, <i>n</i> (%)	97 (5.4)	47 (3.8)	50 (8.8)	<0.001
---	----------	----------	----------	--------

†*P*-value derived from comparison between men and women. BP, blood pressure; CAD,

coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery
bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S3. Baseline characteristics of patients presenting within and after 12 hours from symptom onset

Characteristics	Patients within	Patients after	P-value
	12 hours (N=4650)	12 hours (N=1372)	
Age (years), mean±SD	60.0 ± 11.4	63.9 ± 12.3	<0.001
Women	1260 (27.1)	460 (33.5)	<0.001
Cardiovascular risk factors			
Hypercholesterolemia, <i>n/total</i> (%)	1649/4110 (40.1)	392/1152 (34.0)	<0.001
Diabetes, <i>n (%)</i>	959 (20.6)	369 (26.9)	<0.001
Hypertension, <i>n (%)</i>	2879 (61.9)	859 (62.6)	0.42
Current smoker, <i>n (%)</i>	2118 (45.5)	412 (30.0)	<0.001
Family history of CAD, <i>n (%)</i>	1345 (28.9)	498 (36.6)	<0.001
Clinical history of ischemic heart disease			
Prior angina pectoris, <i>n (%)</i>	519 (11.1)	194 (14.1)	0.003
Prior myocardial infarction, <i>n</i> (%)	546 (11.7)	190 (13.8)	0.036
Prior PCI, <i>n (%)</i>	640 (13.8)	193 (14.1)	0.77
Prior CABG, <i>n (%)</i>	37 (0.8)	20 (1.5)	0.026
Clinical history of cardiovascular disorders			

Prior heart failure, <i>n</i> (%)	121 (2.6)	65 (4.7)	<0.001
Prior stroke, <i>n</i> (%)	172 (3.7)	82 (5.9)	<0.001
Clinical presentation			
Atypical chest pain, <i>n/total</i> (%)	90/3390 (2.6)	130/1233 (10.5)	<0.001
Systolic BP at baseline (mmHg), mean±SD	140.9 ± 24.6	136.5 ± 26.9	<0.001
Heart rate at baseline (b.p.m.), mean±SD	80.0 ± 19.4	81.8 ± 31.6	0.01
Chronic kidney disease, <i>n</i> (%)	145 (3.1)	121 (8.8)	<0.001
In-hospital acute medications			
Aspirin, <i>n</i> (%)	4598 (98.9)	1313 (95.7)	<0.001
Clopidogrel, <i>n</i> (%)	4417 (94.9)	1146 (83.5)	<0.001
Unfractionated heparin, <i>n</i> (%)	3149 (67.7)	617 (44.9)	<0.001
LMWH, <i>n</i> (%)	1235 (26.6)	452 (32.9)	<0.001
Fondaparinux, <i>n</i> (%)	120 (2.6)	50 (3.6)	0.08
B-blockers, <i>n</i> (%)	1100 (23.7)	217 (15.8)	<0.001
ACE-inhibitors, <i>n</i> (%)	1204 (25.9)	222 (16.2)	<0.001

BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S4. Multivariate analysis of factors associated with 30-day all-cause mortality in patients presenting to hospital within 48 hours

	OR	95%CI	P-value
Women	1.61	1.27-2.05	<0.001
Age	1.06	1.05-1.07	<0.001
Hypercholesterolemia	0.99	0.94-1.03	0.70
Diabetes	1.07	0.99-1.14	0.052
Hypertension	1.02	0.92-1.12	0.75
Current smoker	1.05	0.97-1.14	0.24
Family history of CAD	1.06	1.01-1.11	0.012
Atypical chest pain	1.03	0.99-1.06	0.13
Heart rate at admission (per 1-SD increment*)	1.38	1.21-1.57	<0.001
Systolic blood pressure at admission (per 1-SD increment*)	0.57	0.51-0.63	<0.001
Prior angina pectoris	0.85	0.59-1.23	0.39
Prior myocardial infarction	1.07	0.74-1.54	0.69
Prior PCI/CABG	1.51	1.08-2.13	0.016
Prior heart failure	1.20	0.71-2.02	0.48
Prior stroke	1.99	1.32-3.00	0.001

Chronic kidney disease	1.35	1.18-1.53	<0.001
Time to presentation, per 1-hours increased	1.02	1.01-1.03	0.001

*SDs for heart rate and systolic blood pressure are 23 b.p.m. and 25 mmHg.

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table S5. Comparison of pre-hospital delays in patients who required and did not require transfer to a PCI capable hospital

	Men	Women	P-value
Median delays in patients who required transfer from a PCI non capable to a PCI capable hospital			
Time from first medical contact to hospital presentation (min), median (IQR)	150 (105-285)	167.5 (110-232.5)	0.95
Time to presentation (min), median (IQR)	360 (180-1076)	400 (205-1025)	0.50
Median delays in patients transferred by EMS ambulance directly to a PCI capable hospital			
Time from first medical contact to hospital presentation (min), median (IQR)	45.5 (35-70)	70 (44-106.5)	0.001
Time to presentation (min), median (IQR)	180 (95-430)	210 (120-725)	0.028
EMS, emergency medical services; IQR, interquartile range; PCI, percutaneous coronary intervention			

Table S6. Categorical variables: impact of various medications on the odds of mortality for women.

	OR (95% CI)	P value
Model 1: Overall study population adjusted for demographic and clinical factors		
30-day all-cause mortality	1.58 (1.27-1.97)	<0.001
Model 2: Model 1 including aspirin		
30-day all-cause mortality	1.57 (1.26-1.96)	<0.001
Model 3: Model 1 including aspirin and/or clopidogrel		
30-day all-cause mortality	1.57 (1.26-1.96)	<0.001
Model 4: Model 1 including unfractionated heparin		
30-day all-cause mortality	1.58 (1.27-1.97)	<0.001
Model 5: Model 1 including β blockers		
30-day all-cause mortality	1.57 (1.26-1.95)	<0.001
Model 6: Model 1 including ACE inhibitors		
30-day all-cause mortality	1.57 (1.26-1.95)	<0.001
ACE, angiotensin-converting-enzyme.		

Table S7. Interaction test between time to presentation of one hour or less (reference group) and delay of 12 hours or more

	OR	95%CI	P-value
Women	1.43	1.03-1.98	0.032
Delay of 12 hours or more	2.20	1.43-3.42	<0.001
Age	1.06	1.05-1.08	<0.001
Hypercholesterolemia	1.02	0.96-1.07	0.43
Diabetes	0.98	0.90-1.07	0.70
Hypertension	0.97	0.82-1.16	0.78
Current smoker	0.96	0.85-1.09	0.56
Family history of CAD	0.99	0.93-1.07	0.92
Atypical chest pain	1.02	0.96-1.08	0.45
Heart rate at admission (per 1-SD increment*)	1.37	1.14-1.65	0.001
Systolic blood pressure at admission (per 1-SD increment*)	0.59	0.51-0.68	<0.001
Prior angina pectoris	0.79	0.49-1.29	0.35
Prior myocardial infarction	1.03	0.64-1.66	0.89
Prior PCI/CABG	1.12	0.68-1.84	0.66
Prior heart failure	0.81	0.39-1.67	0.56
Prior stroke	1.76	1.02-3.04	0.043
Chronic kidney disease	1.54	1.22-1.93	<0.001

*SDs for heart rate and systolic blood pressure are 23 b.p.m. and 25 mmHg.

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

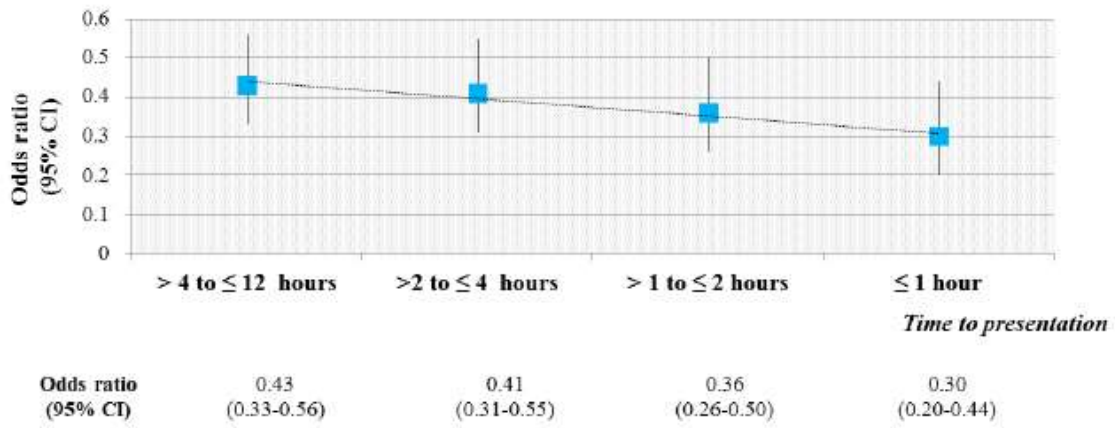
Table S8. Cardiogenic shock across the designated time delay cohorts. Rates are stratified by sex: women versus men.

	Cardiogenic shock rates, n (%)			Unadjusted		Adjusted*	
	Men (N=2820)	Women (N=1183)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Overall study population,	145(5.1)	102(8.6)	<0.001	1.74(1.33-2.26)	<0.001	1.56(1.18-2.05)	0.001
Time to presentation > 12 hours	46(6.2)	42(11.2)	0.004	1.89(1.22-2.93)	0.004	1.68(1.06-2.66)	0.026
Time to presentation > 4 to ≤ 12 hours	37(5.9)	27(10.3)	0.023	1.81(1.07-3.04)	0.025	1.80(1.04-3.14)	0.037
Time to presentation > 2 to ≤ 4 hours	26(4.2)	17(6.4)	0.16	1.55(0.82-2.91)	0.17	1.41(0.74-2.69)	0.30
Time to presentation > 1 to ≤ 2 hours	21(4.4)	10(6.2)	0.35	1.44(0.66-3.12)	0.35	1.22(0.55-2.73)	0.62
Time to presentation ≤ 1 hour	15(4.0)	6(5.0)	0.64	1.26(0.48-3.31)	0.64	1.21(0.45-3.28)	0.70

*Adjusted for demographic and clinical factors

Figure S1. Odds of 30-day mortality according to time to presentation in overall population (*panel a*) and in women (*panel b*); reference group: patients with time to presentation of more than 12 hours. CI: confidence intervals

a) Overall population



b) Women

