

SUPPLEMENTAL MATERIAL

Sex differences in investigations and outcomes among patients with type 2 myocardial infarction

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Running title: Kimenai et al.; Men and women with type 2 MI

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Supplemental Table 1. Number (%) of missing values of clinical characteristics

Variable	Overall (n = 63,749)	Women (n = 23,120)	Men (n = 40,629)	Type 1 MI (n = 57,264)	Type 2 MI (n = 6485)
Demographics					
Age	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body mass index	3813 (6.0%)	1748 (7.6%)	2065 (5.1%)	3128 (5.4%)	685 (10.6%)
Risk factors					
Current smoking	4451 (7.0%)	2048 (8.9%)	2403 (5.9%)	3567 (6.2%)	884 (13.6%)
Hypertension	356 (0.6%)	111 (0.5%)	245 (0.6%)	310 (0.5%)	46 (0.7%)
Diabetes	99 (0.2%)	39 (0.2%)	60 (0.1%)	92 (0.2%)	7 (0.1%)
Hyperlipidemia	264 (0.4%)	93 (0.4%)	171 (0.4%)	236 (0.4%)	28 (0.4%)
eGFR	1855 (2.9%)	733 (3.2%)	1122 (2.8%)	1525 (2.7%)	330 (5.1%)
Medical history					
Previous myocardial infarction	342 (0.5%)	118 (0.5%)	224 (0.6%)	293 (0.5%)	49 (0.8%)
Previous CABG	170 (0.3%)	71 (0.3%)	99 (0.2%)	152 (0.3%)	18 (0.3%)
Previous PCI	537 (0.8%)	205 (0.9%)	332 (0.8%)	460 (0.8%)	77 (1.2%)
Heart failure	2087 (3.3%)	793 (3.4%)	1294 (3.2%)	1861 (3.2%)	226 (3.5%)
Previous stroke	206 (0.3%)	85 (0.4%)	121 (0.3%)	177 (0.3%)	29 (0.4%)

COPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dementia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous or present cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECG findings					
Heart Rhythm	433 (0.7%)	136 (0.6%)	297 (0.7%)	380 (0.7%)	53 (0.8%)
Ischemic findings	807 (1.3%)	300 (1.3%)	507 (1.2%)	663 (1.2%)	144 (2.2%)
In-hospital examination and intervention					
Echocardiography	58 (0.1%)	22 (0.1%)	36 (0.1%)	52 (0.1%)	6 (0.1%)
Coronary angiography	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PCI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CABG	311 (0.5%)	121 (0.5%)	190 (0.5%)	257 (0.4%)	54 (0.8%)
Angiographic findings*	17930 (28.2%)	8323 (36.0%)	9607 (23.6%)	13741 (24.0%)	4189 (64.6%)
Left ventricular ejection fraction*	15114 (23.8%)	6311 (27.3%)	8803 (21.7%)	12807 (22.4%)	2307 (35.6%)
Medication at discharge					
Aspirin	917 (1.4%)	374 (1.6%)	543 (1.3%)	789 (1.4%)	128 (2.0%)
P2Y12 inhibitors	914 (1.4%)	372 (1.6%)	542 (1.3%)	787 (1.4%)	127 (2.0%)
Anticoagulants	926 (1.5%)	373 (1.6%)	553 (1.4%)	798 (1.4%)	128 (2.0%)
B-blockers	916 (1.4%)	372 (1.6%)	544 (1.3%)	789 (1.4%)	127 (2.0%)

ACEI	933 (1.5%)	372 (1.6%)	561 (1.4%)	804 (1.4%)	129 (2.0%)
ARB	919 (1.4%)	373 (1.6%)	546 (1.3%)	793 (1.4%)	126 (1.9%)
Statins	915 (1.4%)	371 (1.6%)	544 (1.3%)	788 (1.4%)	127 (2.0%)
Cardiac troponin T	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration of hospital stays (days)	15 (0.0%)	1 (0.0%)	14 (0.0%)	14 (0.0%)	1(0.0%)

*Number (%) of which no coronary angiogram or echocardiogram is performed.

Supplemental Table 2. Associations of clinical characteristics with major cardiovascular adverse events in type 2 myocardial infarction, stratified by sex

	Total	Men	Women	
Clinical characteristics	HR (95% CI)	HR (95% CI)	HR (95% CI)	<i>P</i> _{interaction} with sex
Sex (men, ref category)	0.94 (0.86-1.02)	-	-	-
Age (per 10 years)	1.57 (1.49-1.65)*	1.57 (1.46-1.68)	1.58 (1.47-1.70)	0.829
Current smoking	1.24 (1.09-1.41)*	1.17 (0.98-1.40)	1.32 (1.10-1.60)	0.302
Hypertension	0.95 (0.87-1.04)	0.94 (0.83-1.07)	0.95 (0.83-1.09)	0.833
Diabetes	1.34 (1.21-1.48)*	1.35 (1.18-1.55)	1.40 (1.21-1.62)	0.246
Hyperlipidemia	0.97 (0.88-1.07)	0.93 (0.81-1.06)	1.04 (0.91-1.20)	0.008 [†]
Coronary artery disease	1.22 (1.10-1.35)*	1.04 (0.91-1.20)	1.43 (1.24-1.65)	<0.001 [†]
Congestive heart failure	1.57 (1.40-1.76)*	1.67 (1.44-1.95)	1.50 (1.26-1.78)	0.553
Ischemic stroke	1.37 (1.22-1.54)*	1.29 (1.10-1.51)	1.45 (1.22-1.73)	0.178
ST-segment depression	1.34 (1.20-1.51)*	1.28 (1.09-1.51)	1.37 (1.16-1.61)	0.353
Ln eGFR	0.66 (0.60-0.72)*	0.67 (0.60-0.75)	0.66 (0.58-0.76)	0.609
COPD	1.52 (1.36-1.69)*	1.46 (1.25-1.70)	1.58 (1.35-1.85)	0.460
Dementia	1.23 (0.80-1.87)	1.14 (0.61-2.13)	1.24 (0.69-2.20)	0.974
Previous cancer	1.28 (1.09-1.49)*	1.27 (1.05-1.54)	1.31 (1.00-1.71)	0.729
Ln hs-cTnT	1.13 (1.09-1.17)*	1.12 (1.06-1.17)	1.16 (1.10-1.22)	0.311

*Analyses are adjusted for all assessed variables including hospital and admission year. $P_{interaction}$ refers to the interaction of sex with the multivariable-adjusted association of each respective covariate with clinical outcome. * $P < 0.05$. † $P < 0.1$.*

Supplemental Table 3. Risk of all-cause death and major adverse events for patients with type 2 myocardial infarction compared to type 1 myocardial infarction stratified by sex (STEMI patients included)

	Total		Men		Women	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause death*						
(Type 1 MI ref category)						
Model 1 (crude)	2.42 (2.31-2.54)	<0.001	3.32 (3.11-3.55)	<0.001	1.80 (1.68-1.94)	<0.001
Model 2 (model 1 + adjusted for comorbidities)	1.40 (1.33-1.47)	<0.001	1.49 (1.39-1.59)	<0.001	1.30 (1.21-1.40)	<0.001
MACE[†]						
(Type 1 MI ref category)						
Model 1 (crude)	2.07 (1.98-2.17)	<0.001	2.65 (2.49-2.82)	<0.001	1.65 (1.54-1.76)	<0.001
Model 2 (model 1 + adjusted for comorbidities)	1.28 (1.22-1.34)	<0.001	1.32 (1.24-1.41)	<0.001	1.22 (1.14-1.31)	<0.001

*Total, n=73,100 (STEMI, n=25,430, NSTEMI, n=47,760); women, n=24,213 (STEMI, n=7,549, NSTEMI, n=16,664); men, n=48,887 (STEMI, n=17,791, NSTEMI, n=31,096). $P_{interaction} MI\ status * sex = 0.005$ †Total, n= 70,118 (STEMI, n=24,255, NSTEMI, n=45,863); women, n=23,282 (STEMI, n=7,244, NSTEMI, n=16,038); men, n=46,836 (STEMI, n=17,011, NSTEMI, n=29,825). $P_{interaction} MI\ status * sex = 0.124$. Model 1: MI type, sex, hospital site, year; model 2: model 1 + age, current smoking, hypertension, diabetes, hyperlipidemia, previous myocardial infarction, congestive heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, COPD, dementia, previous or present cancer. In sex-stratified analysis, sex is not included in the models.

Supplemental Table 4. Risk of all-cause death and major adverse cardiovascular events for men and women with type 2 myocardial infarction (STEMI patients included)

	HR (95% CI)	P-value
All-cause death* (men, reference category)		
Model 1 (crude)	0.83 (0.76-0.91)	<0.001
Model 2 (model 1 + adjusted for comorbidities)	0.83 (0.75-0.91)	<0.001
Major adverse cardiovascular events† (men, reference category)		
Model 1 (crude)	0.88 (0.81-0.96)	0.003
Model 2 (model 1 + adjusted for comorbidities)	0.92 (0.84-1.01)	0.067

*Type 2 MI patients, n=4,390 (STEMI, n=271, NSTEMI, n=4,119). †Type 2 MI patients, n=4,242 (STEMI, n=263, NSTEMI, n=3,979). Model 1: sex, hospital site, year; model 2: model 1 + age, current smoking, hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, COPD, dementia, previous or present cancer.

Supplemental Table 5. Risk of all-cause death and major adverse events for patients with type 2 myocardial infarction compared to type 1 myocardial infarction stratified by sex (adjusted for coronary status)

	Total		Men		Women	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause death*						
(Type 1 MI, ref category)						
Model 1 (adjusted for coronary status)	1.59 (1.43-1.77)	<0.001	2.13 (1.85-2.45)	<0.001	1.15 (0.97-1.36)	0.111
Model 2 (model 1 + adjusted for comorbidities)	1.29 (1.15-1.45)	<0.001	1.31 (1.13-1.52)	<0.001	1.28 (1.07-1.53)	0.007
Model 3 (model 2 + adjusted for hs-cTnT concentrations)	1.29 (1.15-1.44)	<0.001	1.31 (1.14-1.52)	<0.001	1.26 (1.06-1.51)	0.011
MACE†						
(Type 1 MI, ref category)						
Model 1 (adjusted for coronary status)	1.43 (1.31-1.57)	<0.001	1.76 (1.56-1.98)	<0.001	1.15 (1.01-1.32)	0.040
Model 2 (model 1 + adjusted for comorbidities)	1.15 (1.05-1.27)	0.003	1.09 (0.96-1.23)	0.192	1.26 (1.10-1.46)	0.001
Model 3 (model 2 + adjusted for hs-cTnT concentrations)	1.15 (1.05-1.26)	0.004	1.09 (0.96-1.23)	0.187	1.25 (1.08-1.44)	0.002

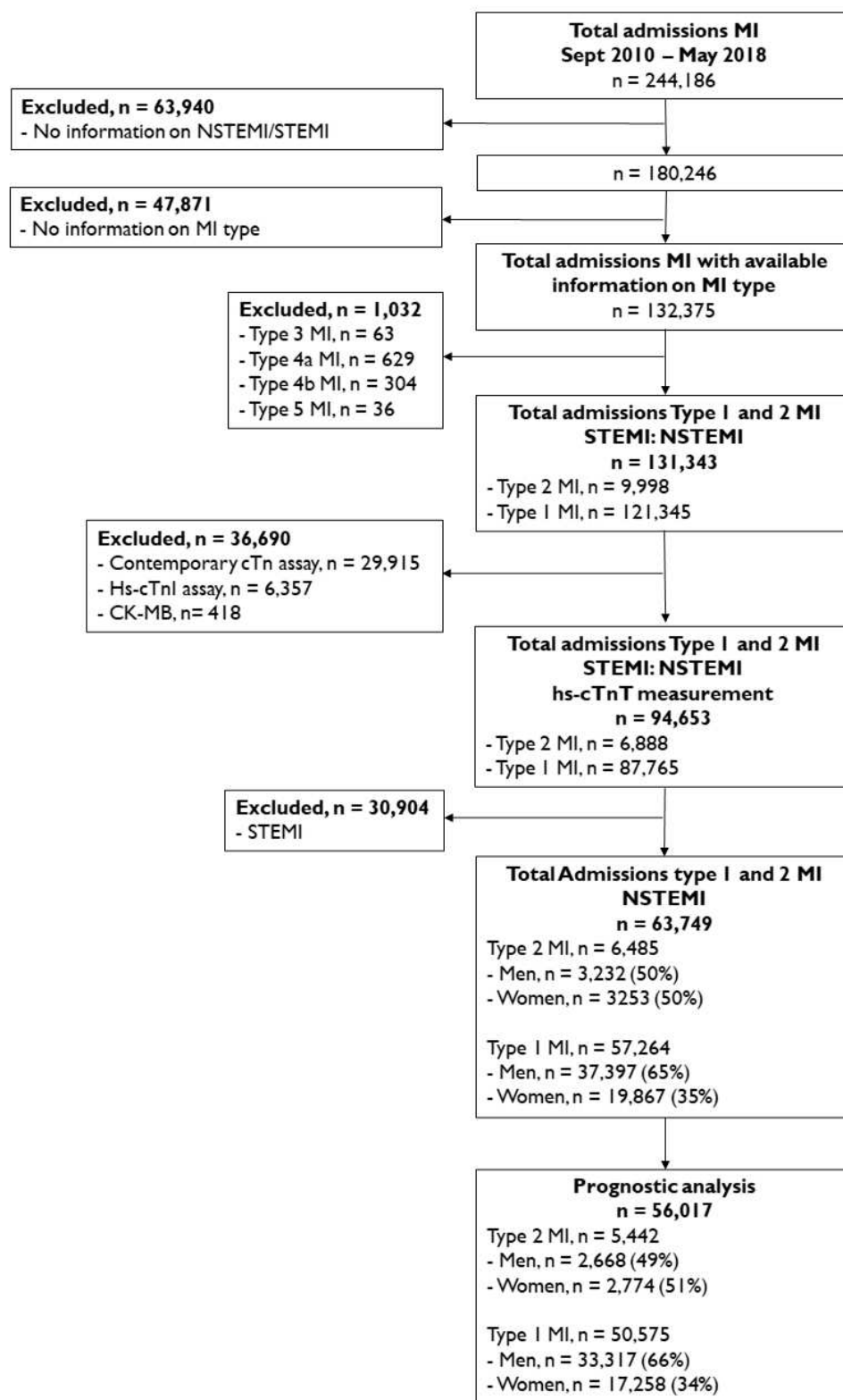
*Total, n=32,743; women, n=11,874; men, n=25,369. $P_{interaction} MI\ status*sex = 0.312$. †Total, n=35,649; women, n=11,368; men, n=24,281. $P_{interaction} MI\ status*sex = 0.497$.

Model 1: MI type, sex, hospital site, year, coronary status; model 2: model 1 + age, current smoking, hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, COPD, dementia, previous or present cancer, coronary artery status; model 3: model 2 + hs-cTnT. In sex-stratified analysis, sex is not included in the models.

Supplemental Table 6. Risk of all-cause death and major adverse cardiovascular events for men and women with type 2 myocardial infarction (adjusted for coronary status)

	HR (95% CI)	P-value
All-cause death* (men, reference category)		
Model 1 (adjusted for coronary status)	0.65 (0.53-0.80)	<0.001
Model 2 (model 1 + adjusted for comorbidities)	0.80 (0.63-1.01)	0.059
Model 3 (model 2 + adjusted for hs-cTnT concentrations)	0.80 (0.63-1.01)	0.060
Major adverse cardiovascular events† (men, reference category)		
Model 1 (adjusted for coronary status)	0.77 (0.65-0.92)	0.004
Model 2 (model 1 + adjusted for comorbidities)	1.03 (0.85-1.26)	0.740
Model 3 (model 2 + adjusted for hs-cTnT concentrations)	1.03 (0.85-1.26)	0.739

* type 2 MI, NSTEMI patients, n=1,761. † type 2 MI, NSTEMI patients, n=1,673. Model 1: sex, hospital site, year, coronary status; model 2: model 1 + age, current smoking, hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, previous stroke, ST-segment depression, estimated glomerular filtration rate, COPD, dementia, previous or present cancer, coronary artery status; model 3: model 2 + hs-cTnT. Coronary status is based on coronary angiography findings.



Supplemental Figure 1. Study flow diagram.