ORIGINAL RESEARCH

Acute Coronary Syndrome: The Risk to Young Women

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***Background*—**Although acute coronary syndrome (ACS) mainly occurs in patients >50 years, younger patients can be affected as well. We used an age cutoff of 45 years to investigate clinical characteristics and outcomes of "young" patients with ACS.

***Methods and Results*—**Between October 2010 and April 2016, 14 931 patients with ACS were enrolled in the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) registry. Of these patients, 1182 (8%) were aged ≤45 years (mean age, 40.3 years; 15.8% were women). The primary end point was 30-day all-cause mortality. Percentage diameter stenosis of ≤50% was defined as insignificant coronary disease. ST-segment–elevation myocardial infarction was the most common clinical manifestation of ACS in the young cases (68% versus 59.6%). Young patients had a higher incidence of insignificant coronary artery disease (11.4% versus 10.1%) and lesser extent of significant disease (single vessel, 62.7% versus 46.6%). The incidence of 30-day death was 1.3% versus 6.9% for the young and older patients, respectively. After correction for baseline and clinical differences, age ≤45 years was a predictor of survival in men (odds ratio, 0.24; 95% confidence interval, 0.10–0.58), but not in women (odds ratio, 1.35; 95% confidence interval, 0.50–3.62). This pattern of reversed risk among sexes held true after multivariable correction for in-hospital medications and reperfusion therapy. Moreover, younger women had worse outcomes than men of a similar age (odds ratio, 6.03; 95% confidence interval, 2.07–17.53).

***Conclusion*—**ACS at a young age is characterized by less severe coronary disease and high prevalence of ST-segment–elevation myocardial infarction. Women have higher mortality than men. Young age is an independent predictor of lower 30-day mortality in men, but not in women.

***Clinical Trial Registration*—**URL: http://clinicaltrials.gov/. Unique identifier: NCT01218776. **(*J Am Heart Assoc*. 2017;6: e007519. DOI: 10.1161/JAHA.117.007519.)**

Key Words: acute coronary syndrome • women • young

Although acute coronary syndrome (ACS) mainly occurs in individuals >50 years, younger adults can be affected as well. Forty-five years as the upper limit of defining young adults has been used in various studies and appears to be a reasonable boundary.[1–10] The same age definition has been, therefore, used in the current study on clinical characteristics and outcomes of ACS in young adults.

Young women with ACS comprise an especially interesting group, given the protective effect of estrogen; however, which clinical factors are predictive of ACS and related mortality in this uncommon cohort is still poorly understood. Indeed, there is a paucity of studies on ACS in the young adults defined as previously described,[1–10] and the records of these analyses are often dated. The most known of these studies is based on the Get With the Guidelines-Coronary Artery Disease registry data.[1] Approximately 10% of patients with ST-segment–elevation myocardial infarction (STEMI) were young patients, and 2% of these patients were women. Women were more likely to have lower quality of care and experienced less favorable short-term outcomes than men.

However, it is still unknown whether there is a sex-age interplay among the clinical presentation of coronary artery disease (CAD) (STEMI versus non–ST-segment–elevation ACS) and associated outcomes. Furthermore, almost entirely

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Clinical Perspective

What Is New?

- Young women with acute coronary syndrome have a higher 30-day mortality compared with young men, despite similar quality-of-care and in-hospital procedures. Young age is an independent predictor of lower 30-day mortality in men, but not in women. These findings suggest a sex-specific influence on acute coronary syndrome and provide a possible explanation for sex differences in outcomes.

What Are the Clinical Implications?

- The young women's risk paradox in patients with acute coronary syndrome cannot be explained by a lower quality of care, as assessed by prior work. Although our study cannot explore further causality, there are multiple potential factors that may contribute to high risk in younger women, including psychological and social stressors. Future investigations are warranted to explore potential mechanisms for acute coronary syndrome in young women.

unexplored is the role of the underlying coronary anatomical features. Women typically have less extensive CAD and, often, nonobstructive CAD.[11] The extent of significant CAD and prognosis may vary between populations of younger patients with different types of ACS.

The purpose of this study was to investigate the clinical presentation and outcome of patients aged ≤45 years hospitalized for ACS in a large international cohort. To analyze specific differences, findings of young patients were compared with those of the older population (aged >45 years). Furthermore, we assessed angiographic data to correlate sex differences in clinical presentation with the magnitude of vascular disease burden as a function of age.

Methods

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.[12]

Setting and Design

The ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) is a large observational and multinational registry.[12–16] Data were collected from 41 centers. Among these centers, there were 22 tertiary healthcare services providing advanced medical investigation and treatment, including percutaneous coronary intervention (PCI) and/or cardiac surgery, and 19 secondary healthcare services providing intensive care in critical coronary care units. The data coordinating center has been established at the University of Bologna (Bologna, Italy). The study was approved by the local research ethics committee from each hospital. Because patient information is collected anonymously, institutional review boards waive the need for individual informed consent.

Study Population

The study population consisted of 14 931 eligible patients with ACS enrolled between October 2010 and April 2016. Appropriateness of inclusion was adjudicated by a cardiology specialist, considering clinical history, physical examination findings, ECG, and cardiac biomarkers.[17] Patients included in the analysis were categorized into 2 groups: young patients, aged ≤45 years; and old patients, aged >45 years.

Angiographic Analysis

The angiographic substudy of ISACS-TC was performed in the 22 tertiary healthcare services providing PCI and/or cardiac surgery, and it included 7723 angiograms. All angiograms were reviewed for complete 3-vessel assessment of extent and burden of CAD. The presence of significant coronary disease was defined as a stenosis of at least 50% in a major epicardial vessel. Coronary thrombus was defined as an intraluminal filling defect or an area of contrast staining noted within the stenosis. Multivessel disease was defined as at least 2 main branches of the epicardial coronary artery with ≥50% stenotic lesions or ≥50% stenosis in the left main coronary artery.

End Points and Definitions

The primary end point was 30-day all-cause mortality. In-hospital within 24 hours medication and the use of PCI or fibrinolysis was noted. Baseline risk was estimated using the TIMI (Thrombolysis in Myocardial Infarction) Risk Index score, which was calculated for each patient using the following equation: [heart rate×(age/10)^2/systolic blood pressure].[18] Patients were grouped into 2 simplified risk categories: low risk (range, <12.5) and medium-high risk (range, ≥12.5).

Statistical Analysis

We compared the baseline characteristics, management, angiographic findings, and clinical outcomes between young patients (aged ≤45 years) and old patients (aged >45 years). Baseline characteristics were reported as numbers and percentages for categorical variables and as mean±SD or median and interquartile percentile range for continuous variables. Comparisons between groups were

Table 1. Baseline Characteristics of the Study Population

Variables	Young Patients (≤45 y)				Old Patients (>45 y)				
	Overall (N=1182)	Men (n=995)	Women (n=187)	*P* Value†	Overall (N=13 749)	Men (n=9219)	Women (n=4530)	*P* Value‡	*P* Value*
Age, y	40.3±4.5	40.2±4.6	40.7±3.7	0.21	64.6±10.3	63.4±9.9	67.7±10.4	<0.001	<0.001
Cardiovascular risk factors									
Hypercholesterolemia, n/total (%)	409/1060 (38.6)	346/886 (39.0)	63/174 (36.2)	0.48	5008/11 839 (42.3)	3302/7960 (41.5)	1706/3879 (43.9)	0.01	0.019
Diabetes mellitus	117 (9.9)	95 (9.5)	22 (11.8)	0.48	3624 (26.4)	2189 (23.7)	1435 (31.7)	<0.001	<0.001
Hypertension	523 (44.2)	433 (43.5)	90 (48.1)	0.43	9616 (69.9)	6130 (66.5)	3486 (76.9)	<0.001	<0.001
Current smoker	723 (61.2)	630 (63.3)	93 (49.7)	0.002	4636 (33.7)	3568 (38.7)	1068 (23.6)	<0.001	<0.001
Body mass index, kg/m^2	27.4±4.5	27.2±2.8	26.8±3.4	0.03	27.1±2.9	27.2±2.8	26.9±3.2	0.0009	0.0004
Family history of CAD	469 (39.7)	394 (39.6)	75 (40.1)	0.57	4096 (29.8)	2662 (28.9)	1434 (31.7)	<0.001	<0.001
Clinical history of ischemic heart disease									
Prior angina pectoris	122 (10.3)	97 (9.7)	25 (13.4)	0.13	3118 (22.7)	1988 (21.6)	1130 (24.9)	<0.001	<0.001
Prior myocardial infarction	126 (10.7)	109 (10.9)	17 (9.1)	0.44	2440 (17.7)	1719 (18.6)	721 (15.9)	<0.001	<0.001
Prior PCI	129 (10.9)	111 (11.2)	18 (9.6)	0.54	1702 (12.4)	1216 (13.2)	486 (10.7)	<0.001	0.14
Prior CABG	9 (0.8)	9 (0.9)	…	0.19	373 (2.7)	289 (3.1)	84 (1.8)	<0.001	<0.001
Comorbidities									
Prior heart failure	26 (2.2)	21 (2.1)	5 (2.7)	0.63	817 (5.9)	522 (5.7)	295 (6.5)	0.048	<0.001
Prior stroke	7 (0.6)	4 (0.4)	3 (1.6)	0.049	635 (4.6)	385 (4.2)	250 (5.5)	<0.001	<0.001
Prior peripheral artery disease	12 (1.0)	9 (0.9)	3 (1.6)	0.38	339 (2.5)	243 (2.6)	96 (2.1)	0.066	0.002
Chronic kidney disease	20 (1.7)	15 (1.5)	5 (2.7)	0.33	921 (6.7)	592 (6.4)	329 (7.3)	0.012	<0.001
Clinical presentation									
STEMI	804 (68.0)	682 (68.5)	122 (65.2)	0.37	8193 (59.6)	5603 (60.8)	2590 (57.2)	<0.001	<0.001
NSTEMI	305 (25.8)	257 (25.8)	48 (25.7)	0.96	4167 (30.3)	2696 (29.2)	1471 (32.5)	<0.001	<0.001
Unstable angina	73 (6.2)	56 (5.6)	17 (9.1)	0.07	1389 (10.1)	920 (9.9)	469 (10.3)	0.49	<0.001
SBP at baseline, mm Hg	139.6±22.1	139.5±21.1	140.7±26.9	0.49	140.9±24.1	140.8±23.6	141.0±24.9	0.55	0.09
HR at baseline, beats/min	81.0±23.1	81.2±24.3	80.1±15.0	0.55	81.3±21.6	80.9±20.7	82.2±23.3	0.0007	0.65
TIMI Risk Index	9.8±5.1	9.8±5.5	9.8±2.3	0.87	25.6±13.5	24.2±12.5	28.4±14.9	<0.001	<0.001
Medium-high TIMI Risk Index	143 (12.1)	118 (11.9)	25 (13.4)	0.56	12 896 (93.9)	8572 (93.1)	4324 (95.7)	<0.001	<0.001
Time from symptom onset to hospital admission ≤12 h	769 (65.1)	661 (66.4)	108 (57.7)	0.07	8326 (60.6)	5681 (61.6)	2645 (58.4)	<0.001	0.001
In-hospital within 24 h medications									
Aspirin	1157 (98.4)	977 (98.6)	180 (97.3)	0.20	13 199 (96.8)	8900 (97.3)	4299 (95.8)	<0.001	0.003
Clopidogrel	1092 (92.9)	919 (92.8)	173 (93.1)	0.92	12 071 (88.9)	8190 (89.9)	3881 (86.9)	<0.001	<0.001

Continued

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Table 1. Continued

Variables	Young Patients (≤45 y)				Old Patients (>45 y)				
	Overall (N=1182)	Men (n=995)	Women (n=187)	*P* Value†	Overall (N=13 749)	Men (n=9219)	Women (n=4530)	*P* Value‡	*P* Value*
Heparins	840 (83.7)	704 (83.7)	136 (83.9)	0.93	9112 (81.6)	6208 (81.5)	2904 (81.6)	0.92	0.087
β Blockers	321 (27.4)	278 (28.1)	43 (23.5)	0.19	4075 (30.0)	2764 (30.4)	1311 (29.3)	0.21	0.06
ACE inhibitors	301 (25.6)	263 (26.5)	38 (20.5)	0.08	4294 (31.6)	2928 (32.1)	1366 (30.5)	0.059	<0.001
Revascularization therapy									
Patients with STEMI (n=8997)									
PCI	575 (71.5)	495 (72.6)	80 (65.6)	0.11	4890 (59.7)	3450 (61.6)	1440 (55.6)	<0.001	<0.001
Door-to-balloon time, median (IQR), min	50 (25–94)	50 (25–100)	37.5 (23–58.5)	0.07	45 (27–80)	45 (30–80)	45 (25–80)	0.24	0.72
Fibrinolysis	119 (14.8)	104 (15.2)	15 (12.3)	0.39	948 (11.6)	679 (12.1)	269 (10.4)	0.02	0.0075
Door-to-needle time, median (IQR), min	30 (15–51)	25 (15–45)	40 (30–65)	0.07	25 (15–41)	28 (15–40)	27.5 (15–45)	0.52	0.63
CABG	2 (0.2)	2 (0.3)	…	0.55	67 (0.8)	48 (0.9)	19 (0.7)	0.56	0.08
Patients with NSTE-ACS (n=5934)									
PCI	233 (61.6)	198 (63.2)	35 (53.8)	0.11	2411 (43.4)	1718 (47.5)	693 (35.7)	<0.001	<0.001
CABG	12 (3.2)	11 (3.5)	1 (1.5)	0.40	292 (5.3)	193 (5.3)	99 (5.1)	0.70	0.07
Outcomes									
30-d All-cause mortality	16 (1.3)	7 (0.7)	9 (4.8)	<0.001	950 (6.9)	540 (5.9)	410 (9.0)	<0.001	<0.001

Data are given as number (percentage) or mean±SD, unless stated otherwise. ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; HR, heart rate; IQR, interquartile range; NSTE, non–ST-segment–elevation; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

**P* value derived from comparison between overall young patients and overall old patients.

†*P* value derived from comparison between women and men in the young population.

‡*P* value derived from comparison between women and men in the old population.

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Table 2. Angiographic Characteristics of the Study Population

Angiographic Findings	Young Patients (≤45 y)				Old Patients (>45 y)				
	Overall (N=691)	Men (n=578)	Women (n=113)	*P* Value†	Overall (N=7032)	Men (n=4937)	Women (n=2095)	*P* Value‡	*P* Value*
No. of lesions	1 (1–2)	1 (1–2)	1 (1–2)	0.56	2 (1–3)	2 (1–3)	2 (1–3)	<0.001	<0.001
Calcific lesion	4 (0.6)	3 (0.5)	1 (0.9)	0.45	164 (2.3)	124 (2.5)	40 (1.9)	0.30	<0.001
Bifurcation lesion	42 (6.1)	33 (5.7)	9 (7.9)	0.57	366 (5.2)	254 (5.1)	112 (5.3)	0.62	0.16
Ostial lesion	2 (0.30)	1 (0.2)	1 (0.9)	0.21	104 (1.5)	76 (1.5)	28 (1.3)	0.79	<0.001
Eccentric lesion	2 (0.3)	1 (0.2)	1 (0.9)	0.21	42 (0.6)	38 (0.8)	4 (0.2)	0.016	0.002
Thrombus	138 (19.9)	122 (21.1)	16 (14.2)	0.18	1273 (18.1)	925 (18.7)	348 (16.6)	0.06	0.18
Non obstructive	79 (11.4)	62 (10.7)	17 (15.0)	0.18	709 (10.1)	431 (8.7)	278 (13.3)	<0.001	0.26
1-Vessel disease	433 (62.7)	369 (63.8)	64 (56.4)	0.15	3279 (46.6)	2306 (46.7)	973 (46.4)	0.83	<0.001
LAD stenosis	232 (33.6)	196 (33.9)	36 (31.8)	0.66	1569 (22.3)	1110 (22.5)	459 (21.9)	0.58	<0.001
Circumflex artery stenosis	44 (6.4)	37 (6.4)	7 (6.0)	0.87	460 (6.5)	320 (6.5)	140 (6.7)	0.76	0.93
RCA stenosis	157 (22.7)	136 (23.5)	21 (18.6)	0.25	1250 (17.8)	876 (17.7)	374 (17.8)	0.92	0.0007
2-Vessel disease	129 (18.7)	109 (18.9)	20 (17.7)	0.77	1925 (27.4)	1388 (28.1)	537 (25.6)	0.033	<0.001
LAD and circumflex artery stenosis	35 (5.1)	27 (4.7)	8 (7.1)	0.28	416 (5.9)	292 (5.9)	124 (5.9)	NaN	0.39
LAD and RCA stenosis	58 (8.4)	52 (8.9)	6 (5.3)	0.20	887 (12.6)	651 (13.2)	236 (11.3)	0.03	0.002
Circumflex artery and RCA stenosis	36 (5.2)	30 (5.2)	6 (5.3)	0.96	622 (8.8)	445 (9.0)	177 (8.4)	0.78	0.01
3-Vessel disease§	50 (7.2)	38 (6.6)	12 (10.6)	0.13	1119 (15.9)	812 (16.4)	307 (14.6)	0.06	<0.001

Data are presented as number (percentage) or median (interquartile range). LAD indicates left anterior descending artery; NaN, not a number; and RCA, right coronary artery.
**P* value derived from comparison between overall young patients and overall old patients.
†*P* value derived from comparison between women and men in the young population.
‡*P* value derived from comparison between women and men in the old population.
§Three-vessel disease: ≥50% stenoses in 3 major epicardial vessels or ≥50% stenoses in the left main coronary artery.

made by either χ^2 test for baseline categorical variables and a 2-sample *t* test or Kruskal-Wallis rank-sum test for continuous variables. Multivariable logistic-regression analyses were performed to evaluate the relations between baseline characteristics and the occurrence of death at 30 days and clinical presentation of ACS at a young age. Fixed covariates included in the analyses were as follows: sex; cardiovascular risk factors (history of hypercholesterolemia, hypertension, and diabetes mellitus, smoking status, family history of CAD, and body mass index [BMI]); clinical history of ischemic heart disease (prior angina pectoris, prior myocardial infarction, prior PCI, and prior coronary artery bypass graft surgery); clinical history of cardiovascular disorders (prior peripheral artery disease, prior heart failure, and prior stroke); severity of clinical presentation (STEMI at index event, systolic blood pressure and heart rate at hospital admission, TIMI Risk Index, and chronic kidney disease); and time from symptom onset to hospital admission of ≤12 hours. Covariates introduced in the secondary analyses, as categorical variables, were as follows: in-hospital within 24 hours medication (specifically aspirin, clopidogrel, heparins, β blockers, and angiotensin-converting enzyme inhibitors) and reperfusion therapy, which included PCI and fibrinolysis. Further analyses were performed to evaluate sex differences in the severity of CAD (significant versus nonobstructive) and the extent of the disease (number of diseased vessels with significant stenosis).

Missing Values

We had complete data on age, sex, and 30-day mortality. Some patients had missing data on other variables. We imputed the missing values of the clinical variables whose missing rate was <10% using STATA software. For the clinical features, whose missing rate was >10%, we performed a Pearson χ^2 statistical test for independence between those features and mortality. Only the variable "hypercholesterolemia" had missing rates of >10%, and it was statistically dependent on the end point of mortality. We, therefore, did not dismiss this variable from the predictive model of mortality, and we kept it as missing.[19]

For all analysis, statistical significance was defined as $P<0.05$, and STATA 11 (StataCorp, College Station, TX) was used.

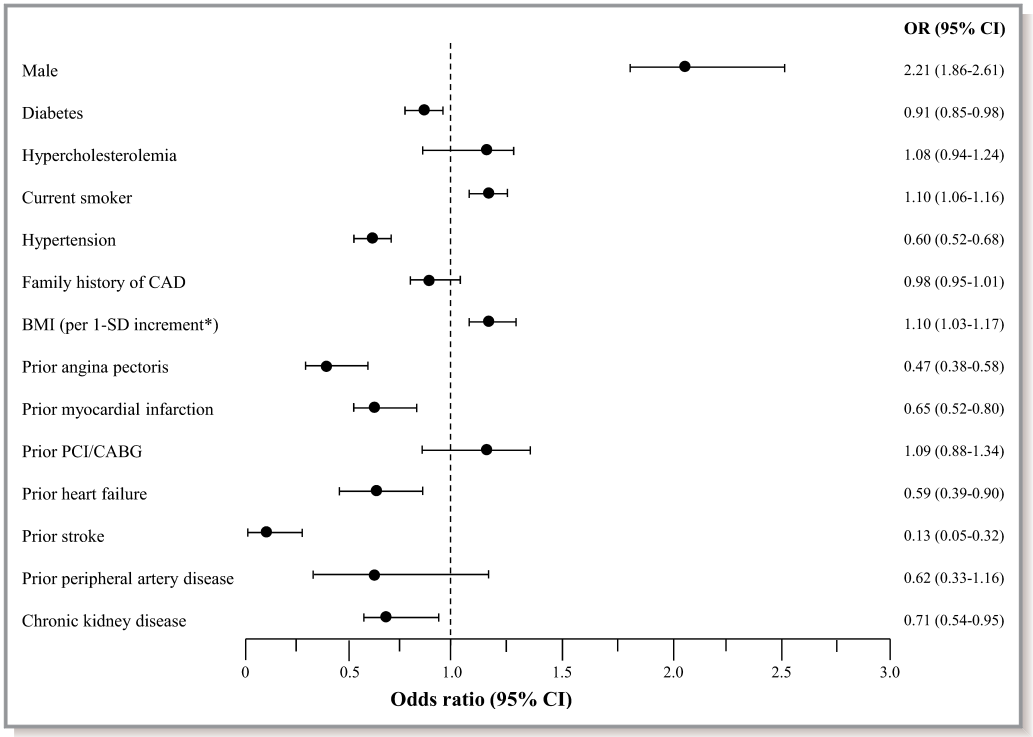

Figure 1. Independent predictors of acute coronary syndrome in the young population. BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; OR, odds ratio; and PCI, percutaneous coronary intervention. *SD for BMI was 3 kg/m^2.

Table 3. Multivariate Analysis of Factors Associated With 30-Day All-Cause Mortality in the Overall Population and According to Sex

	Overall Population (N=14 931)		Women (n=4717)		Men (n=10 214)	
Variables	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female sex	1.54 (1.32–1.80)	<0.001	…	…	…	…
Age ≤45 y	0.44 (0.23–0.82)	0.01	1.35 (0.50–3.62)	0.54	0.24 (0.10–0.58)	0.001
Diabetes mellitus	1.07 (1.01–1.13)	0.011	1.07 (0.98–1.17)	0.12	1.07 (1.004–1.14)	0.038
Hypercholesterolemia	0.43 (0.36–0.51)	<0.001	0.39 (0.30–0.52)	<0.001	0.45 (0.36–0.56)	<0.001
Current smoker	1.02 (0.96–1.07)	0.54	1.08 (1.003–1.15)	0.042	0.95 (0.87–1.04)	0.29
Hypertension	1.05 (0.97–1.14)	0.20	1.04 (0.91–1.18)	0.58	1.05 (0.94–1.17)	0.36
Family history of CAD	1.01 (0.98–1.04)	0.36	1.01 (0.96–1.05)	0.68	1.01 (0.97–1.06)	0.45
Body mass index (per 1-SD increment*)	0.86 (0.83–0.97)	0.008	0.92 (0.82–1.03)	0.18	0.87 (0.78–0.98)	0.021
Medium-high TIMI Risk Index	2.48 (1.42–4.32)	0.001	4.19 (1.45–12.10)	0.008	2.001 (1.05–3.82)	0.036
STEMI	1.45 (1.21–1.73)	<0.001	1.64 (1.24–2.16)	<0.001	1.35 (1.07–1.70)	0.010
SBP at baseline (per 1-SD increment*)	0.59 (0.55–0.65)	<0.001	0.59 (0.52–0.66)	<0.001	0.60 (0.54–0.66)	<0.001
HR at baseline (per 1-SD increment*)	1.25 (1.15–1.36)	<0.001	1.28 (1.12–1.45)	<0.001	1.22 (1.09–1.36)	<0.001
Time from symptom onset to hospital admission ≤12 h	0.95 (0.92–0.98)	0.002	0.95 (0.89–0.99)	0.038	0.95 (0.91–0.99)	0.031
Chronic kidney disease	1.32 (1.23–1.41)	<0.001	1.27 (1.14–1.42)	<0.001	1.35 (1.24–1.47)	<0.001
Clinical history of ischemic heart disease	1.16 (0.98–1.37)	0.075	1.01 (0.78–1.30)	0.93	1.26 (1.02–1.56)	0.033
Clinical history of cardiovascular disorders	2.11 (1.74–2.56)	<0.001	1.72 (1.25–2.36)	0.001	2.36 (1.84–3.03)	<0.001

CAD indicates coronary artery disease; CI, confidence interval; HR, heart rate; OR, odds ratio; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
*SDs for heart rate, systolic blood pressure, and body mass index are 22 beats/min, 24 mm Hg, and 3 kg/m^2, respectively.

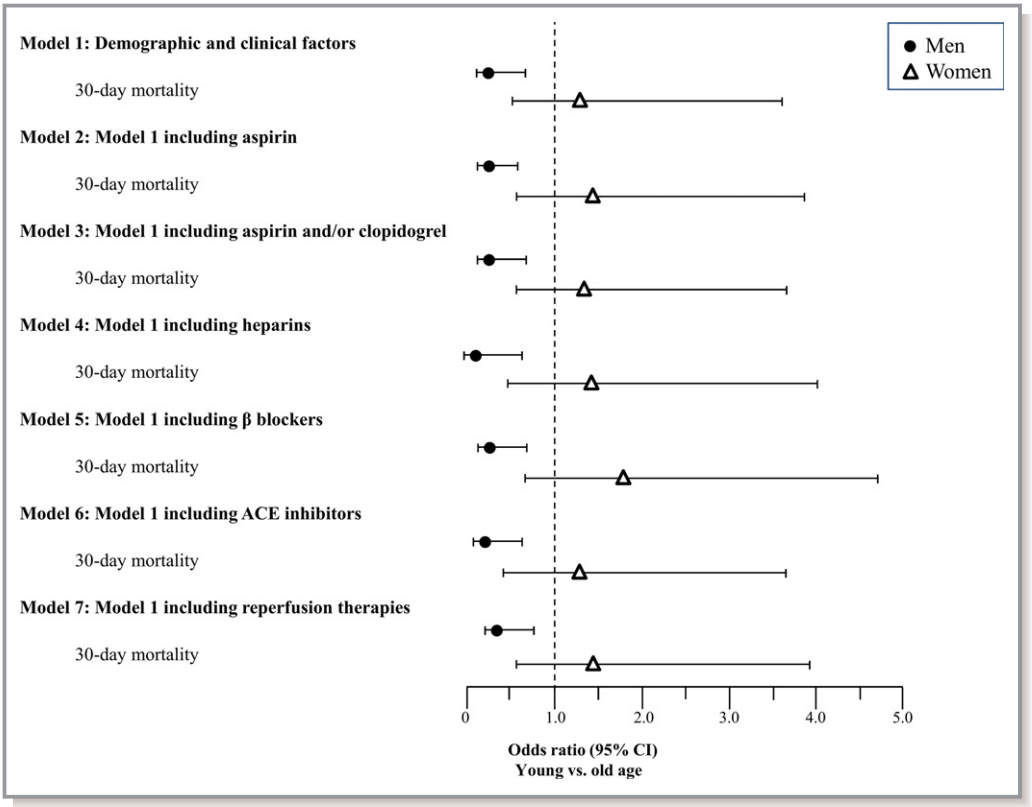

Figure 2. Impact of in-hospital medications and reperfusion therapy on the odds of mortality sorted by sex: young vs old age. Odds ratios and 95% confidence intervals (CIs) for 30-day mortality of young compared with old patients with acute coronary syndrome. ACE indicates angiotensin converting enzyme.

Results

There were 14 931 patients with a diagnosis of ACS enrolled in the ISACS-TC registry between October 2010 and April 2016. The mean age of our cohort was 62.6±11.9 years, and 4717 subjects (31.6%) were women. Of these patients, 1182 (7.9%) were aged ≤45 years. Of the 14 931 patients, 966 (6.5%) died at 30-day follow-up.

Patient Characteristics

Table 1 lists the characteristics of patients based on age. Young patients were more commonly men and more likely to be smokers compared with old patients. Young patients also had fewer comorbidities: they less commonly had diabetes mellitus, hypercholesterolemia, and hypertension. More young patients had a family history of CAD and had a higher BMI.

Angiographic Comparison

Baseline angiographic data in the young population ranged from 3-vessel disease in 7.2% to no significant stenoses in 11.4% of patients. Younger patients had a higher incidence of single-vessel disease (62.7% versus 46.6%). Conversely, 3-vessel disease was less common (7.2% versus 15.9%) in the young patients. Young patients had significantly less calcification. There was a predilection for the presence of significant CAD in the left anterior descending artery in the young group. There was a trend toward more nonobstructive disease in young women versus young men, although this did not reach statistical significance (15% versus 10.7%). The specific coronary arteries with disease are delineated for each population in Table 2.

Clinical Presentation and Management

The distribution of STEMI and non–ST-segment–elevation ACS was significantly different between young and old patients: STEMI was the most common clinical manifestation of ACS in the young cases (Table 1). Young patients were at lower risk, as assessed by the TIMI Risk Index. More young patients reached the hospital before 12 hours from symptom onset. Multivariate analysis showed 3 clinical variables that were identified as independent risk factors for the occurrence of ACS in the young population: male sex, smoking habit, and higher BMI (Figure 1).

Initial management of ACS in young patients differed slightly from the standard management in the old group. The

Table 4. Multivariate Analysis of Clinical Factors Associated With 30-Day All-Cause Mortality in the Young Population

Clinical Factors	OR	95% CI	*P* Value
Female sex	6.03	2.07–17.53	0.001
Diabetes mellitus	0.67	0.12–3.89	0.66
Hypercholesterolemia	1.94	0.63–5.97	0.24
Current smoker	0.97	0.52–1.80	0.92
Hypertension	0.80	0.27–2.32	0.68
Family history of CAD	1.01	0.78–1.31	0.92
Body mass index (per 1-SD increment*)	0.74	0.42–1.30	0.30
Medium-high TIMI Risk Index	1.66	0.30–9.21	0.55
STEMI	1.30	0.32–5.26	0.70
SBP at baseline (per 1-SD increment*)	0.89	0.49–1.60	0.71
HR at baseline (per 1-SD increment*)	0.91	0.38–2.14	0.82
Time from symptom onset ≤12 h	0.87	0.66–1.15	0.34
Chronic kidney disease	1	…	…
Clinical history of ischemic heart disease	0.74	0.18–3.02	0.68
Clinical history of cardiovascular disorders	1.38	0.15–12.28	0.79

CAD indicates coronary artery disease; CI, confidence interval; HR, heart rate; OR, odds ratio; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
*SDs for heart rate, systolic blood pressure, and body mass index are 22 beats/min, 24 mm Hg, and 3 kg/m^2, respectively.

rate of administration of aspirin and clopidogrel was higher in young patients. In contrast, young patients less frequently received angiotensin-converting enzyme inhibitors. More young patients received PCI, both for STEMI and non–ST-segment–elevation ACS (Table 1).

Clinical Factors Associated With 30-Day All-Cause Mortality

When all of the clinical baseline variables were assessed simultaneously in multivariable analysis (Table 3), there were 7 factors positively associated with 30-day all-cause mortality: female sex, history of diabetes mellitus, greater TIMI Risk Index, STEMI as the index event, chronic kidney disease, clinical presentation with a higher heart rate, and clinical history of cardiovascular disorders. Age of ≤45 years had a significant protective effect on mortality (odds ratio [OR], 0.44; 95% confidence interval, 0.23–0.82). Multiple regression analysis was then repeated separately for men and women (Table 3). Interestingly, young age remained a factor associated with survival in men (OR, 0.24; 95% confidence interval, 0.10–0.58), but not in women (OR, 1.35; 95% confidence interval, 0.50–3.62). The adjusted OR for mortality associated with younger age did not change when controlling for medications used at hospital admission and reperfusion therapy (Figure 2).

Mortality in the Young Population

Regression analysis in the young patients revealed that the only variable associated with 30-day mortality was female sex: younger women had worse outcomes than men of a similar age (OR, 6.03; 95% confidence interval, 2.07–17.53), even after adjusting for use of guideline-recommended medications and reperfusion therapy (Table 4 and Figure 3).

Discussion

In this study, we have shown, in a large contemporary cohort of young patients with ACS, that female sex is an independent predictor of 30-day mortality. Thirty-day mortality was 5 times higher in women than men. Although univariate analysis suggested a protective effect of young age (≤45 years), this mortality advantage of young patients did not withstand multivariate analysis accounting for differences in baseline characteristics and sex. Young age remained an independent predictor of lower 30-day mortality in men, but not in women. The young women cohort was treated as well as its male counterpart. They had equal use of evidence-based strategies, and a similar proportion of young women and young men experienced delays to hospital admission of >12 hours. Compared with older women, young women had a significantly lower TIMI Risk Index, but they underwent more PCI. Delays to hospital admission of >12 hours were more frequent with advanced age.[20] These findings, therefore, provide compelling evidence that the young women's paradox of higher short-term mortality compared with men among patients with ACS cannot be explained by a lower quality of care, as assessed by prior work.[1,21–25]

Demographic and Clinical Profiles of the Young Patients

The demographic and clinical profiles of the young patients enrolled in the ISACS-TC registry are comparable with those of young patients in other large studies of patients with ACS.[3,7,26] The present study showed that ≈8% of all patients hospitalized with ACS were aged ≤45 years. In the GRACE (Global Registry of Acute Coronary Events) study, the frequency of young patients with ACS was 6.3%[7]; in the Thai ACS Registry and the ACS Spain Registry, the proportion of young people with ACS was 5.8% and 7%, respectively.[3,26] The mean age of our young ACS cohort was 40.3±6 years, which is consistent with prior work.[1,3,7] Sex distribution also

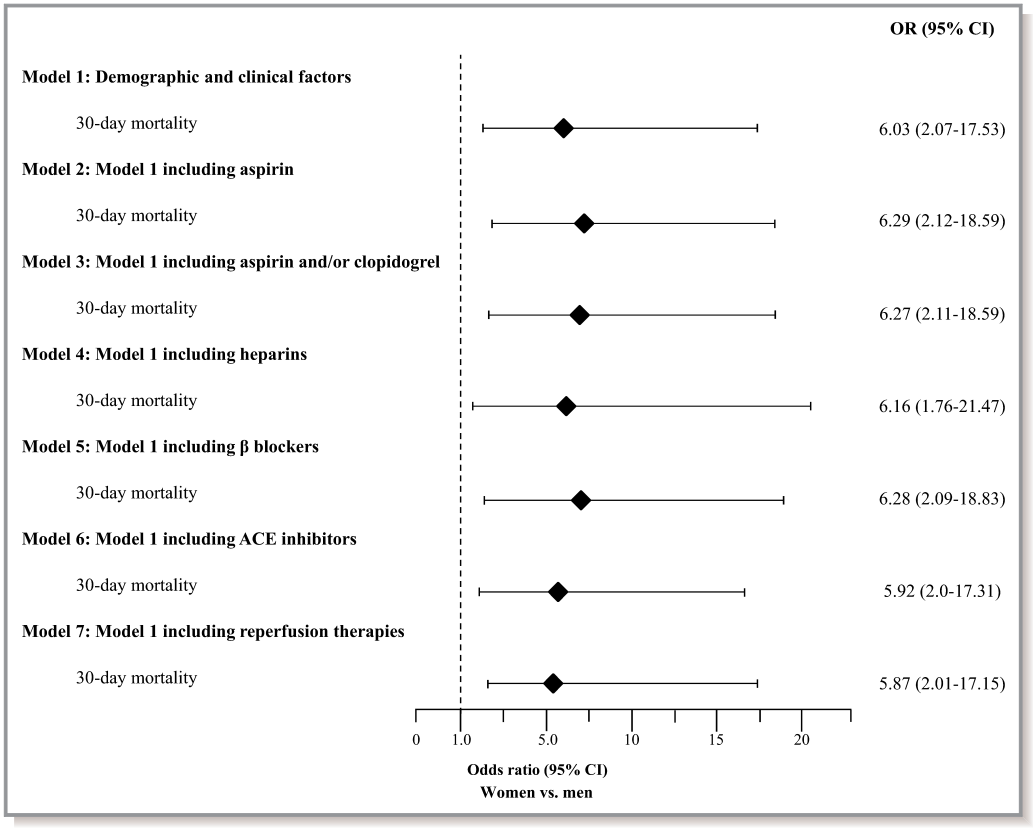

Figure 3. Young patients: impact of in-hospital medications and reperfusion therapy on the odds of mortality of women vs men. Odds ratios (ORs) and 95% confidence intervals (CIs) for 30-day mortality of young women vs young men with acute coronary syndrome. ACE indicates angiotensin converting enzyme.

followed a pattern already observed in previous studies, with a lower percentage of women in the young-age group.[1,3,7]

Risk Factor Profiles of the Young Patients

In the current study, smoking and a higher BMI were independent predictors of ACS in the young population. One potential explanation for these findings could be a lack of awareness and poorer control of risk factors among the young population. This is consistent with population-based estimates. The National Health and Nutrition Examination Survey reported that, although significant reductions were observed in the proportion of the US elderly population having traditional risk factors from 1999 to 2010, no significant declines were observed for women <60 years and men <40 years.[27] Our results are concordant with previous findings in which a high BMI was most predictive of death from cardiovascular disease among men and women in all age groups, but the relative increase in risk associated with a high BMI declined with increasing age.[28] Our data are also in keeping with recent data showing that smokers who were <50 years had the worst discrepancy in risk of STEMI: >8 times that of former and never smokers.[29] Overall, these findings suggest inadequacy of screening and risk factor control efforts among young people.

Thirty-Day Mortality

To our knowledge, we are the first to demonstrate that young age is independently predictive of lower 30-day mortality after multivariate analysis among men, but not women, with ACS. When multivariate regression was performed on outcomes from the Get With the Guidelines-Coronary Artery Disease registry, consistent with our data, the sex difference in short-term mortality was greater in the younger cohort than in the older cohort. However, differences across sexes (young versus old women or young versus old men) were not examined.[1] Differences between the results of that study and ours may be also attributable to inclusion of only patients with STEMI and lack of angiographic data on the severity and extent of CAD. Other studies have demonstrated that young age is associated with an increased relative risk of cardiovascular death[30,31] in women who present with acute myocardial infarction. However, these results are derived from long-term follow-up data rather than the early 30-day mortality that we present, and they are not specifically representative of the overall spectrum of patients with ACS. The definition of what constitutes a young patients often differs in such studies and may constitute a further barrier for comparison with our study.

Angiographic CAD Burden

Atherosclerosis of the coronary arteries is known to have an impact on the development and severity of ACS.[32] Given that young patients with ACS presented an average of 2 decades earlier than old patients and with fewer risk factors, it is conceivable that we observed less multivessel disease, less calcification, and fewer ostial lesions in young people compared with old people. There was a predilection for the presence of significant CAD in the left anterior descending artery in the young group, as previously documented.[33,34] An interesting observation is that the proportion of nonobstructive CAD was similar in the young women and men (15% versus 10%), but the mortality rate was higher in women. Thus, sex differences in 30-day mortality in young people are not explained by the difference in the severity of angiographically documented disease. Other aspects may account for the difference in outcomes between young women and men and may be related to vascular biological factors, such as lower coronary flow reserve, more vascular stiffness, and functional differences of smooth muscle cells in the vessel wall.[35,36] The issue of menopause is not thoroughly defined. The Framingham Heart Study reported a higher risk of cardiovascular disease in postmenopausal women that was even more pronounced in women aged 40 to 44 years,[37] whereas the Nurses' Health Study found no significant association with time since natural menopause.[38] Socioeconomic status and level of depression may also play an important role in ACS prognosis in women.[39,40]

Study Limitations

There are some limitations that must be noted. The current analysis is an observational study; therefore, we cannot excluded possible confounding variables that were not controlled. An ACS diagnosis in young patients could be problematic because myocarditis can mimic acute myocardial infarction. Thus, the prevalence of ACS at a young age might be influenced by an overdiagnosis or a misdiagnosis. We have no data about the use of substances in our patients, especially marijuana and sympathomimetic amines, which have been found to correlate with ACS at a younger age.[41] Furthermore, the lack of a universal definition of "young" patients made the comparison among the few studies performed on this issue hard.

Conclusions

We found that younger patients with ACS were more likely to be men. However, young women had a higher 30-day mortality compared with men, despite similar quality-of-care and in-hospital procedures. Young women also have similar times to hospital presentation and treatment after symptom onset compared with men. More important, young age was an independent predictor of lower 30-day mortality in men, but not in women, which suggests a sex-specific influence on ACS and provides a possible explanation for sex differences in outcomes. Future investigations should be performed to corroborate these findings and to explore potential mechanisms for ACS in women.

Disclosures

None.

References

1. Bangalore S, Fonarow GC, Peterson ED, Hellkamp AS, Hernandez AF, Laskey W, Peacock WF, Cannon CP, Schwamm LH, Bhatt DL; Get With the Guidelines Steering Committee and Investigators. Age and gender differences in quality of care and outcomes for patients with ST-segment elevation myocardial infarction. *Am J Med*. 2012;125:1000–1009.
2. Doughty M, Mehta R, Bruckman D, Das S, Karavite D, Tsai T, Eagle K. Acute myocardial infarction in the young: the University of Michigan experience. *Am Heart J*. 2002;143:56–62.
3. Morillas P, Bertomeu V, Pabón P, Ancillo P, Bermejo J, Fernández C, Arós F; PRIAMHO II Investigators. Characteristics and outcome of acute myocardial infarction in young patients: the PRIAMHO II study. *Cardiology*. 2007;107:217–225.
4. Hoit BD, Gilpin EA, Henning H, Maisel AA, Dittrich H, Carlisle J, Ross J Jr. Myocardial infarction in young patients: an analysis by age subsets. *Circulation*. 1986;74:712–721.
5. Chua SK, Hung HF, Shyu KG, Cheng JJ, Chiu CZ, Chang CM, Lin SC, Liou JY, Lo HM, Kuan P, Lee SH. Acute ST-elevation myocardial infarction in young patients: 15 years of experience in a single center. *Clin Cardiol*. 2010;33:140–148.
6. Garoufalis S, Kouvaras G, Vitsias G, Perdikouris K, Markatou P, Hatzisavas J, Kassinos N, Karidis K, Foussas S. Comparison of angiographic findings, risk factors, and long term follow-up between young and old patients with a history of myocardial infarction. *Int J Cardiol*. 1998;67:75–80.
7. Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP; GRACE Investigators. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2005;149:67–73.
8. Chen L, Chester M, Kaski JC. Clinical factors and angiographic features associated with premature coronary artery disease. *Chest*. 1995;108:364–369.
9. Pineda J, Marín F, Roldán V, Valencia J, Marco P, Sogorb F. Premature myocardial infarction: clinical profile and angiographic findings. *Int J Cardiol*. 2008;126:127–129.
10. Anderson RE, Pfeffer MA, Thune JJ, McMurray JJ, Califf RM, Velazquez E, White HD, Rouleau JL, Skali H, Maggioni A, Solomon SD. High-risk myocardial infarction in the young: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. *Am Heart J*. 2008;155:706–711.
11. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA*. 2005;293:477–484.
12. Bugiardini R, Badimon L; ISACS-TC Investigators and Coordinators. The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC): 2010–2015. *Int J Cardiol*. 2016;217(suppl):S1–S6.
13. Ricci B, Manfrini O, Cenko E, Vasiljevic Z, Dorobantu M, Kedev S, Davidovic G, Zdravkovic M, Gustiene O, Knežević B, Miličić D, Badimon L, Bugiardini R. Primary percutaneous coronary intervention in octogenarians. *Int J Cardiol*. 2016;222:1129–1135.
14. Manfrini O, Ricci B, Cenko E, Dorobantu M, Kalpak O, Kedev S, Kneževic B, Koller A, Milicic D, Vasiljevic Z, Badimon L, Bugiardini R; ISACS-TC Investigators. Association between comorbidities and absence of chest pain in acute coronary syndrome with in-hospital outcome. *Int J Cardiol*. 2016;217(suppl):S37–S43.
15. Bugiardini R, Cenko E, Ricci B, Vasiljevic Z, Dorobantu M, Kedev S, Vavlukis M, Kalpak O, Puddu PE, Gustiene O, Trninic D, Knežević B, Miličić D, Gale CP, Manfrini O, Koller A, Badimon L. Comparison of early versus delayed oral β

blockers in acute coronary syndromes and effect on outcomes. *Am J Cardiol*. 2016;117:760–767.

16. Bugiardini R, Dorobantu M, Vasiljevic Z, Kedev S, Knežević B, Miličić D, Calmac L, Trninic D, Daullxhiu I, Cenko E, Ricci B, Puddu PE, Manfrini O, Koller A, Badimon L; ISACS-TC Investigators. Unfractionated heparin-clopidogrel combination in ST-elevation myocardial infarction not receiving reperfusion therapy. *Atherosclerosis*. 2015;241:151–156.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
18. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, de Lemos JA, McCabe CH, Braunwald E. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet*. 2001;358:1571–1575.
19. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health*. 2001;25:464–469.
20. Ting HH, Bradley EH, Wang Y, Lichtman JH, Nallamothu BK, Sullivan MD, Gersh BJ, Roger VL, Curtis JP, Krumholz HM. Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation myocardial infarction. *Arch Intern Med*. 2008;168:959–968.
21. Graham G. Acute coronary syndromes in women: recent treatment trends and outcomes. *Clin Med Insights Cardiol*. 2016;10:1–10.
22. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J*. 2011;161:91–97.
23. Radovanovic D, Nallamothu BK, Seifert B, Bertel O, Eberli F, Urban P, Pedrazzini G, Rickli H, Stauffer JC, Windecker S, Erne P; AMIS Plus Investigators. Temporal trends in treatment of ST-elevation myocardial infarction among men and women in Switzerland between 1997 and 2011. *Eur Heart J Acute Cardiovasc Care*. 2012;1:183–191.
24. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI—improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. *BMJ Open*. 2012;2:e000726.
25. Johnston N, Bornefalk-Hermansson A, Schenck-Gustafsson K, Held C, Goodman SG, Yan AT, Bierman AS. Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada? *Eur Heart J Acute Cardiovasc Care*. 2013;2:350–358.
26. Tungsubutra W, Tresukosol D, Buddhari W, Boonsom W, Sanguanwang S, Srichaiveth B; Thai ACS Registry. Acute coronary syndrome in young adults: the Thai ACS Registry. *J Med Assoc Thai*. 2007;90(suppl 1):81–90.
27. Fryar CD, Chen TC, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999–2010. *NCHS Data Brief*. 2012;103:1–8.
28. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341:1097–1105.
29. Lloyd A, Steele L, Fotheringham J, Iqbal J, Sultan A, Teare MD, Grech ED. Pronounced increase in risk of acute ST-segment elevation myocardial infarction in younger smokers. *Heart*. 2017;103:586–591.
30. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. *Arch Intern Med*. 2009;169:1767–1774.
31. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM; National Registry of Myocardial Infarction 2 Participants. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med*. 1999;341:217–225.
32. Roe MT, Halabi AR, Mehta RH, Chen AY, Newby LK, Harrington RA, Smith SC Jr, Ohman EM, Gibler WB, Peterson ED. Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction. *Am Heart J*. 2007;153:507–514.
33. Wolfe MW, Vacek JL. Myocardial infarction in the young: angiographic features and risk factor analysis of patients with myocardial infarction at or before the age of 35 years. *Chest*. 1988;94:926–930.
34. Davia JE, Hallal FJ, Cheitlin MD, Gregoratos G, McCarty R, Foote W. Coronary artery disease in young patients: arteriographic and clinical review of 40 cases aged 35 and under. *Am Heart J*. 1974;87:689–696.
35. Handberg E, Johnson BD, Arant CB, Wessel TR, Kerensky RA, von Mering G, Olson MB, Reis SE, Shaw L, Bairey Merz CN, Sharaf BL, Sopko G, Pepine CJ. Impaired coronary vascular reactivity and functional capacity in women: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE) Study. *J Am Coll Cardiol*. 2006;47:S44–S49.
36. Shaw LJ, Min JK, Budoff M, Gransar H, Rozanski A, Hayes SW, Friedman JD, Miranda R, Wong ND, Berman DS. Induced cardiovascular procedural costs and resource consumption patterns after coronary artery calcium screening: results from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study. *J Am Coll Cardiol*. 2009;54:1258–1267.
37. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease: the Framingham Study. *Ann Intern Med*. 1978;89:157–161.
38. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med*. 1987;316:1105–1110.
39. Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, Patel R, Eapen DJ, Neeland IJ, Pimple PM, Zafari AM, Quyyumi AA, Vaccarino V. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. *J Am Heart Assoc*. 2014;3:e000741. DOI: 10.1161/JAHA.113.000741.
40. Xu X, Bao H, Strait K, Spertus JA, Lichtman JH, D'Onofrio G, Spatz E, Bucholz EM, Geda M, Lorenze NP, Bueno H, Beltrame JF, Krumholz HM. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. *Circulation*. 2015;131:614–623.
41. Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. *Circulation*. 2001;103:502–506.