Circulation

ORIGINAL RESEARCH ARTICLE

Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction

The ARIC Community Surveillance Study

Editorial, see p 1057

Sameer Arora, MD
George A. Stouffer, MD
Anna M. Kucharska-Newton, PhD
Arman Qamar, MD
Muthiah Vaduganathan, MD, MPH
Ambarish Pandey, MD, MSCS
Deborah Porterfield, MD, MPH
Ron Blankstein, MD
Wayne D. Rosamond, PhD
Deepak L. Bhatt, MD, MPH
Melissa C. Caughey, PhD

BACKGROUND: Sex differences are known to exist in the management of older patients presenting with acute myocardial infarction (AMI). Few studies have examined the incidence and risk factors of AMI among young patients, or whether clinical management differs by sex.

METHODS: The Atherosclerosis Risk in Communities (ARIC) Surveillance study conducts hospital surveillance of AMI in 4 US communities (MD, MN, MS, and NC). AMI was classified by physician review, using a validated algorithm. Medications and procedures were abstracted from the medical record. Our study population was limited to young patients aged 35 to 54 years.

RESULTS: From 1995 to 2014, 28 732 weighted hospitalizations for AMI were sampled among patients aged 35 to 74 years. Of these, 8737 (30%) were young. The annual incidence of AMI hospitalizations increased for young women but decreased for young men. The overall proportion of AMI admissions attributable to young patients steadily increased, from 27% in 1995 to 1999 to 32% in 2010 to 2014 (*P* for trend=0.002), with the largest increase observed in young women. History of hypertension (59% to 73%, *P* for trend<0.0001) and diabetes mellitus (25% to 35%, *P* for trend<0.0001) also increased among young AMI patients. Compared to young men, young women presenting with AMI were more often black and had a greater comorbidity burden. In adjusted analyses, young women had a lower probability of receiving lipid-lowering therapies (relative risk [RR]=0.87; 95% confidence interval [CI], 0.80–0.94), nonaspirin antiplatelets (RR=0.83; 95% CI, 0.75–0.91), beta blockers (RR=0.96; 95% CI, 0.91–0.99), coronary angiography (RR=0.93; 95% CI, 0.86–0.99) and coronary revascularization (RR = 0.79; 95% CI, 0.71–0.87). However, 1-year all-cause mortality was comparable for women versus men (HR=1.10; 95% CI, 0.83–1.45).

CONCLUSIONS: The proportion of AMI hospitalizations attributable to young patients increased from 1995 to 2014 and was especially pronounced among women. History of hypertension and diabetes among young patients admitted with AMI increased over time as well. Compared with young men, young women presenting with AMI had a lower likelihood of receiving guideline-based AMI therapies. A better understanding of factors underlying these changes is needed to improve care of young patients with AMI.

Key Words: acute myocardial infarction ■ epidemiology ■ sex differences

Sources of Funding, see page 1055

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In this community-based surveillance spanning 2 decades, the proportion of acute myocardial infarction hospitalizations attributable to young patients increased and was most pronounced among women.
- This trend parallels an increase in cardiovascular risk factors, including hypertension and diabetes mellitus, among young patients hospitalized with acute myocardial infarction.
- Relative to young men, young women had a higher comorbidity burden, and a lesser likelihood of undergoing an invasive strategy or being managed with guideline-based acute myocardial infarction medications.

What Are the Clinical Implications?

- An integrated, multifaceted approach is needed to promote effective primordial, primary, and secondary prevention strategies among at-risk women.
- Clinical trials designed specifically for women are required to understand further the distinct cardiovascular risk profile and to define treatment pathways in women.
- Expanding initiatives such as the American Heart Association Go Red for Women campaign to increase awareness about cardiovascular disease risk in women through media and other outlets should also be encouraged.

Although there has been a dramatic decrease in mortality from coronary artery disease over the past 4 decades in the United States, this favorable trend does not appear to extend to young adults, especially younger women.[1,2] Similarly, acute myocardial infarction (AMI) hospitalizations among young adults have not declined,[2] highlighting the need to investigate AMI in the young, a demographic group often overlooked in cardiovascular research. An increasing prevalence of obesity, cardiometabolic risk factors, and adverse health behaviors have been postulated to contribute to the observed plateau in life expectancy in the United States[3,4] and other countries.[5] Greater burden of cardiometabolic risk factors may also lead to earlier incidence of AMI at a younger age. Previous investigations from the Atherosclerosis Risk in Communities (ARIC) study have reported a decline in AMI incidence among adults aged 35-74 years from 1987 to 2008.[6] In the present investigation, we examine contemporary trends in the incidence of AMI admissions among young women and men (aged 35-54 years), who were sampled from 21 hospitals by the ARIC Surveillance study from 1995 to 2014. We also examine whether clinical management and mortality differ by sex in young patients with AMI. Although sex differences in AMI management have been well-described in older populations,[7,8] it is uncertain whether this trend extends to younger patients presenting with AMI.

METHODS

ARIC Study Community Surveillance

The ARIC study's data and materials are publicly available.[9] As previously described[6,10] the ARIC study has conducted community surveillance of hospitalizations for AMI in 4 geographically-defined regions of the United States (Forsyth County, North Carolina; Washington County, Maryland; Jackson, Mississippi; and 8 Northwest suburbs of Minneapolis, Minnesota). All surveillance protocols were approved by local Institutional Review Boards. Informed consent was not required, because data were anonymized by redacting personal identifiers. Community residents aged 35 to 74 years were considered eligible for surveillance in 1987 to 2004, with eligibility expanded to 35 to 84 years from 2005 to 2014. Hospitalizations were randomly sampled among strata based on race, sex, ARIC community, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge codes: 402, 410 to 414, 427, 428 and 518.4. The underlying population size of residents within the 4 ARIC Communities was interpolated and extrapolated from the US Census population estimates, as previously described.[6] For the purposes of this analysis, we considered patients aged 35 to 54 years to be "young", a cutpoint consistent with prior studies[2] and representative of the lower half of the original age distribution sampled in ARIC. Importantly, hospitalizations were not sampled within any particular strata of age, provided that cases were aged 35 to 74 in 1987 to 2004, and aged 35 to 84 in 2005 to 2014. Our analysis was limited to young patients (35–54 years old), with the proportion of AMI hospitalizations attributable to young patients estimated from the total sample of AMI patients aged 35 to 74 years. We excluded patients 75 to 85 years of age as this age group was only sampled between years 2005 to 2014.

Clinical Covariates and Demographic Data

Clinical and demographic data were collected from the hospital record by trained abstractors, using physician notes, laboratory reports, patient histories, and discharge summaries. Diabetes mellitus was defined by documented history of diabetes mellitus or glucose-lowering therapy use. Hypertension was defined by documented hypertension in the medical record.

Electrocardiography

The first, third, and the last 12-lead electrocardiograms (ECG) over the course of hospitalization were obtained from the medical record and coded electronically at the Minneapolis ECG Reading Center.[11]

Chest Pain

Presence of chest pain was abstracted from the medical record, with origin determined by review of physician notes. Any mention of substernal pressure, tightness, or pain

precipitated by exertion or excitement was considered evidence of chest pain of cardiac origin. Chest pain specified in the physician notes as "unknown origin" or "undiagnosed" was considered "unknown."

AMI Classification

As previously described,[10,11] events were classified by the ARIC study as definite, probable, suspected, or no MI, based on ECG evidence (evolving diagnostic, diagnostic, evolving ST-segment/T-wave changes, equivocal, or absent/uncodable), presence of chest pain, and cardiac biomarkers (which were considered "abnormal" if ≥2x the upper limit of normal (ULN), and "equivocal" if exceeding the ULN but <2x the ULN).[6] Classification criteria remained constant over the study period and are detailed in the ARIC Study surveillance manual.[12] Classification of an event as definite or probable AMI required the presence of at least 1 of the following: (1) evolving diagnostic ECG pattern; (2) diagnostic ECG pattern and abnormal biomarkers; (3) cardiac pain and abnormal biomarkers; (4) cardiac pain and equivocal biomarkers with evolving ST-segment/T-wave pattern or diagnostic ECG pattern; or (5) abnormal biomarkers with evolving ST-segment/T-wave pattern.

Biomarkers

Laboratory values for biomarkers of cardiac injury were recorded for the first 4 days of hospitalization. The laboratory-specified ULN was recorded, and biomarker values were abstracted chronologically, recording up to 3 measurements per day.

Medical Therapies

Medications were recorded if administered during hospitalization or prescribed at hospital discharge. Aspirin required routine rather than *pro re nata* administration for abstraction. Nonaspirin antiplatelet therapy was recorded as a single category and included $P2Y_{12}$ inhibitors (cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine), glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), phosphodiesterase 3 inhibitors (cilostazol), phosphodiesterase 5 inhibitors (dipyridamole), and protease-activated receptor-1 antagonists (vorapaxar). Beta blockers included β_1 adrenergic antagonists. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ACEi/ARB) were recorded as a single category. Lipid-lowering agents included statins, niacin, and fibrates.

Procedures

Echocardiography, stress testing, angiography and revascularization procedures were abstracted from the medical record. Echocardiography included transthoracic and transesophageal echocardiograms. Stress testing included exercise testing (treadmill or bicycle ergometer), stress echocardiography, cardiac stress MRI, and nuclear stress tests. Revascularization included percutaneous coronary intervention or coronary artery bypass graft surgery.

Mortality Outcomes

In-hospital, 28-day, and 1-year mortality were ascertained by the ARIC Study, which linked hospitalizations with the National Death Index. Cardiovascular death was defined by death due to "diseases of the circulatory system" (ICD-9 codes 390–459 and ICD-10 codes I00-I99).

Statistical Analysis

All statistical analyses were carried out using SAS 9.4 (SAS Institute; Cary, NC). Statistical tests and models accounted for the stratified sampling design and were weighted by the inverse of the sampling probability.[13] Continuous variables were assessed for normality and compared using the difference in least square means from weighted linear regression. Categorical variables were compared using Rao-Scott χ^2 tests. The annual incidence of AMI hospitalizations among young patients was calculated by dividing the weighted number of sampled AMI hospitalizations by the total number of ARIC residents aged 35 to 54 years. Although the ARIC study expanded the sampling to include patients aged 75 to 84 from 2005 to 2014, we analyzed the percentage of young community residents relative to the total population of 35- to 74-year-old residents of the ARIC communities. Similarly, the proportion of AMI hospitalizations attributable to young patients was examined among 35- to 74-year-old patients admitted with AMI across all years of observation. Trends over time were visually plotted and analyzed across 5-year intervals (1995–1999, 2000–2004, 2005–2009, 2010–2014) using logistic regression, with year categories regressed as an ordinal variable. Trends in the prevalence of cardiovascular risk factors were limited to comorbidities routinely abstracted across all study periods.

Among young patients, the relative probabilities of women versus men receiving guideline-directed AMI medications (aspirin, other antiplatelets, beta blockers, and lipid-lowering medications) or undergoing invasive procedures (angiography and revascularization) were compared in 5-year intervals and in the aggregate. Associations were derived from multivariable logistic regression, with odds ratios converted into relative risks (RR) and 95% confidence intervals (CI).[14] Models were adjusted for race, geographic region, and year of admission. As sensitivity analyses, we also stratified the models by race, limited the population to patients with first-occurring AMI, and additionally adjusted for comorbidities and complications (diabetes mellitus, acute heart failure/pulmonary edema, ventricular fibrillation, cardiac arrest, and cardiogenic shock). One-year all-cause mortality was compared between young women and men using multivariable Cox regression, adjusted for race, geographic location, and year of admission.

RESULTS

The annual incidence of AMI hospitalizations decreased from 1995 to 2014 among male ARIC community residents aged 35 to 54. In contrast, a declining incidence of AMI hospitalizations was not observed for women aged 35 to 54 (Figure 1A). Evidence of population aging was noted for both sexes, with the percentage of ARIC community residents aged 35 to 54 declining over time relative to the entire population of 35 to 74-year-old residents (Figure 1B). However, the annual proportion of AMI admissions attributable to young patients steadily

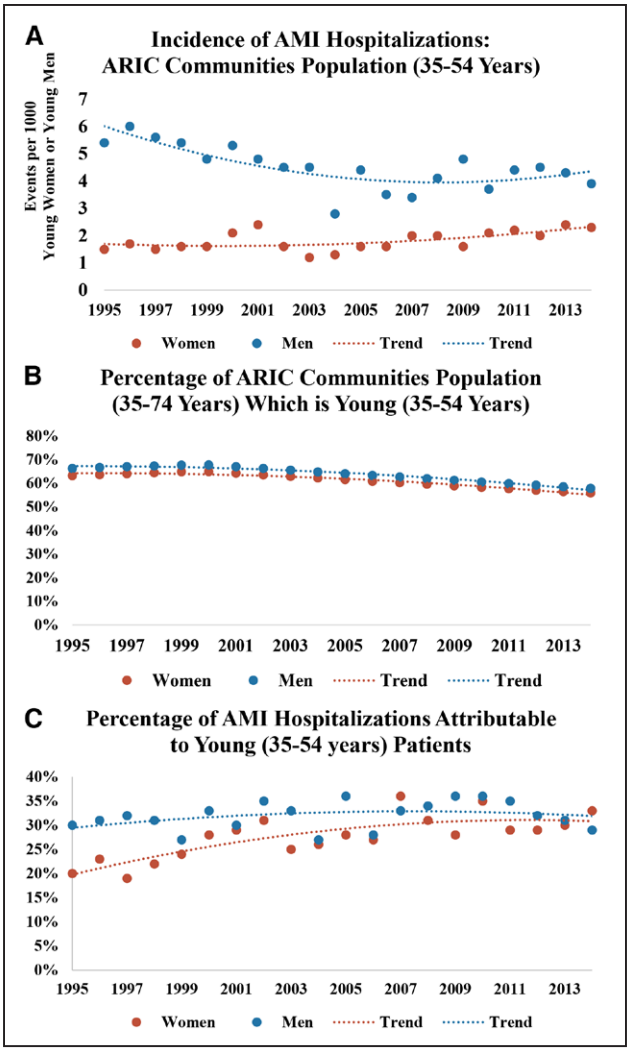

Figure 1. Population and hospitalization trends.
Temporal trends in the incidence of acute myocardial infarction among residents of the ARIC communities who are young (35–54 years), (**A**); the percentage of total ARIC communities' residents (35–74 years) who are young (35–54 years), (**B**); and the percentage of 35-74-year-old patients admitted with acute myocardial infarction who are young (35–54 years), (**C**). The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.

increased over time, with the largest increase observed in women (Figure 1C). When analyzed across 5-year intervals (1995–1999, 2000–2004, 2005–2009, and 2010–2014), the proportion of AMI admissions attributable to young patients significantly increased, from 27% to 32%; *P* for trend<0.0001 (21% to 31% among women [*P* for trend <0.0001] and 30% to 33% among men [*P* for trend = 0.1]. Stratified trends among black women, white women, black men, and white men are shown in Table 1.

From 1995 to 2014, medical records from 28 732 weighted AMI hospitalizations (15 081 unweighted) were abstracted from sampled patients aged 35 to 74. Of these, 8737 (30%) were young, constituting our study population (Table 2). Compared with young men, young women were more often black (52% versus 41%), and more likely to have medical insurance (85% versus 78%), history of hypertension (71% versus 64%), diabetes mellitus (39% versus 26%), chronic kidney disease (24% versus 19%), and prior stroke (10% versus 6%), when aggregated across 1995 to 2014. However, young women were less likely to be smokers (48% versus 57%). During the hospital visit, acute pulmonary edema/heart failure was more frequent among women (28% versus 22%). On the other hand, young women were less likely to have ST-segment elevation myocardial infarction (STEMI) compared with their male counterparts (16% versus 26%).

Among young women and men admitted with AMI, the annual prevalence of smoking steadily decreased, while the prevalence of hypertension and diabetes increased (Figure 2). History of previous AMI remained stable over time. When examined across 5-year intervals, the overall prevalence of hypertension significantly increased (59% to 73%, *P* for trend<0.0001) as did prevalence of diabetes mellitus (25% to 35%, *P* for trend<0.0001). On the other hand, prevalence of smoking significantly decreased (60% to 52%, *P* for trend=0.0002) and history of prior AMI remained comparable (32% to 27%, *P* for trend=0.1), Table 3.

Compared with young men, at the time of hospitalization, young women were less likely to be administered lipid-lowering medications (63% versus 72%; *P*<0.0001), nonaspirin antiplatelet therapy (51% versus 62%; *P*<0.0001), beta blockers (81% versus 84%; *P*=0.04), or ACEi/ARBs (59% versus 64%; *P*=0.02); and less often underwent invasive coronary angiography (59% versus 66%; *P*=0.0009) or revascularization (38% versus 50%; *P*<0.0001). However, women were more likely to be imaged by echocardiography (58% versus 53%; *P*=0.008). Aspirin administration (86% versus 89%; *P*=0.09); and noninvasive stress testing (7% versus 8%; *P*=0.6) did not differ by sex. Annual trends in the administration of therapies for young women and men presenting with AMI are shown in Figure 3.

When aggregated across 1995 to 2014 and adjusted for race, ARIC center, and year of admission, women had a 13% lower probability of receiving lipid-lowering agents (RR=0.87; 95% CI, 0.80–0.94), 17% lower probability of receiving nonaspirin antiplatelets (RR=0.83; 95% CI, 0.75–0.91), 7% lower probability of receiving angiography (RR=0.93; 95% CI, 0.86–0.99), and 21% lower probability of receiving revascularization (RR=0.79; 95% CI, 0.71–0.87). The adjusted probabilities of aspirin administration (RR=0.98; 95% CI, 0.94–1.01) and receipt of beta blockers (RR=0.96; 95% CI, 0.91–0.99) were comparable. As shown in Figure 4, lower utilization of nonaspirin antiplatelets and lipid-lowering agents persisted for women relative to men, irrespective of non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction classification. However, the overall sample of patients classified with ST-segment elevation myocardial infarction was small (n=1788). Adjusted probabili-

Table 1. Proportion of Patients Admitted With Acute Myocardial Infarction Who are Young (35–54 Years), Relative to the Entire Demographic Subgroup Sample of 35-74-Year-Old Patients Presenting With Acute Myocardial Infarction

	1995–1999		2000–2004		2005–2009		2010–2014		20-Year
	Total	Proportion	Total	Proportion	Total	Proportion	Total	Proportion	Trend
AMI	Sampled	Young	Sampled	Young	Sampled	Young	Sampled	Young	*P* Value
All	7605	2073 (27%)	6398	1941 (30%)	6563	2118 (32%)	8166	2605 (32%)	0.002
Women	2548	546 (21%)	2219	622 (28%)	2398	722 (30%)	3209	993 (31%)	<0.0001
Men	5056	1527 (30%)	4179	1319 (32%)	4166	1396 (34%)	4956	1612 (33%)	0.1
Black women	769	248 (32%)	776	292 (38%)	935	368 (39%)	1582	605 (38%)	0.2
White women	1779	298 (17%)	1443	330 (23%)	1462	355 (24%)	1627	388 (24%)	0.003
Black men	1024	454 (44%)	1072	478 (45%)	1273	615 (48%)	2114	825 (39%)	0.1
White men	4033	1072 (27%)	3107	841 (27%)	2893	781 (27%)	2842	787 (28%)	0.6

The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.

ties of guideline-directed AMI therapies were consistently lower for young women compared to young men when stratified by race, when limiting the population to patients with first-time AMI, or with additional adjustment for clinical course and comorbidities (Tables I-III in the online-only Data Supplement).

Table 2. Demographics and Clinical Characteristics of Young Patients (35–54 Years) Admitted With Acute Myocardial Infarction

	Women	Men	
Characteristic	N=2884	N=5853	*P* Value
Demographics			
Age (mean±SE)	48±0.2	48±0.1	0.2
Black	1513 (52%)	2372 (41%)	<0.0001
Heath insurance*	1449 (85%)	2342 (78%)	0.003
Medical history			
Smoking	1348 (48%)	3276 (57%)	<0.0001
Hypertension	2023 (71%)	3715 (64%)	0.0005
Diabetes mellitus	1110 (39%)	1534 (26%)	<0.0001
Chronic kidney disease†	433 (24%)	612 (19%)	0.07
Prior revascularization	642 (22%)	1418 (24%)	0.3
Prior myocardial infarction	750 (26%)	1588 (28%)	0.5
Stroke	280 (10%)	338 (6%)	0.0003
Hospital visit			
ST-segment elevation‡	420 (16%)	1368 (26%)	<0.0001
Acute heart failure/ pulmonary edema	797 (28%)	1289 (22%)	0.004
Cardiogenic shock	82 (3%)	120 (2%)	0.2
Ventricular fibrillation/ cardiac arrest	203 (7%)	316 (5%)	0.09

SE indicates standard error. The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.

*Health insurance status not routinely abstracted prior to 2005, and available for 4699 patients

†Serum creatinine not routinely abstracted prior to 2005, and available for 3719 patients. Chronic kidney disease defined by estimated glomerular filtration rate <45 mL/min/1.73 m^2 using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, or receipt of hemodialysis.

‡Classifications of ST-segment elevated myocardial infarction vs. non-ST-segment elevation myocardial infarction available in a subset of patients (n=7844) with sufficient electrocardiographic data.

When grouped into 5-year intervals, emerging sex differences were observed for receipt of lipid-lowering agents and coronary revascularization (Table 4); probabilities of receiving other guideline-directed therapies changed little over time between the 2 sexes.

Among these young AMI patients, the overall all-cause mortality was modest and similar between women and men (1% versus 2% for in-hospital, 4% each for 28-day, and 9% versus 7% for 1-year). Annual trends in all-cause mortality are shown in Figure I in the online-only Data Supplement. Cardiovascular mortality was also similar between women and men (1% each for in-hospital, 2% each for 28-day), but marginally higher for women by 1 year of follow up (5% versus 3%; *P*=0.08). After adjustment for race, hospital geographic location, and year of admission, the hazard of 1-year all-cause mortality was comparable for women versus men (HR=1.10; 95% CI, 0.83–1.45).

DISCUSSION

In this community-based surveillance of patients hospitalized with AMI, we observed a significant increase in patients presenting with AMI who were <55 years of age from 1995 to 2014. This trend parallels an increase in cardiovascular risk factors, including hypertension and diabetes mellitus, in this population. However, the increasing proportion of AMI attributable to young patients was most pronounced among women. Relative to young men, young women had a higher comorbidity burden, and a lesser likelihood of undergoing an invasive strategy or being managed with guideline-based AMI medications.

Previous studies in the US have investigated hospitalizations among young patients using administrative claims records.[2] In contrast, the ARIC Surveillance study classifies AMI by standardized physician review of the medical record, providing a more comprehensive event classification and allowing an analysis of trends spanning several decades. The increase in AMI hospitaliza-

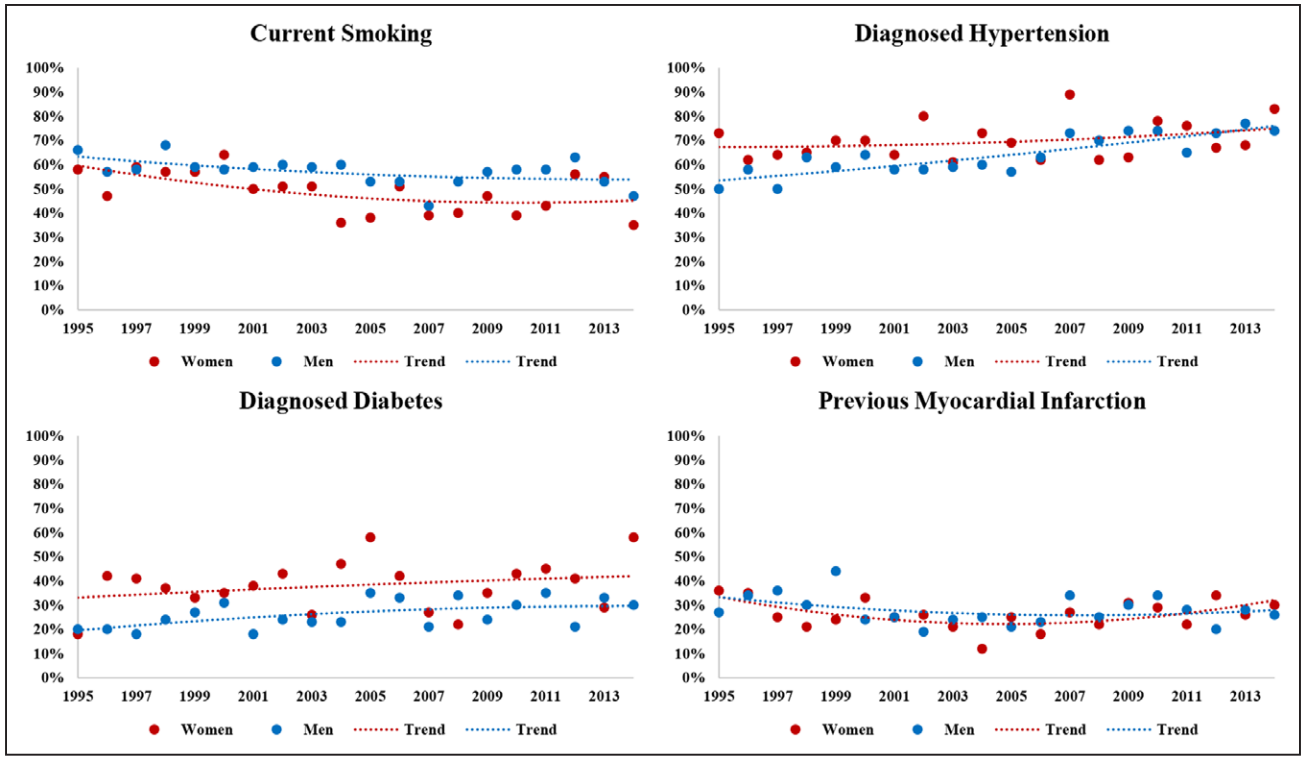

Figure 2. Prevalence and temporal trends in cardiovascular risk factors among young (35–54 years) women and men presenting with acute myocardial infarction.
The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.

tions attributable to young patients is staggering in the background of the aging general US population.[15] Ideally, prevention of atherosclerotic cardiovascular disease should begin early in adolescence and young adulthood; however, few tools exist to assess the risk of coronary disease in these age groups.[16] This likely results in decreased recognition of risk factors in young adults and suboptimal utilization of preventive strategies. An analysis from the Partners YOUNG-MI registry reported a low proportion (12.5%) of young adult patients on statins at the time of AMI; the authors advocate for improved risk assessment tools in this age group.[17] Sim-

Table 3. Prevalence and Temporal Trends in Cardiovascular Risk Factors Among Young (35-54-Year-Old) Patients Presenting With Acute Myocardial Infarction

	1995–1999	2000–2004	2005–2009	2010–2014	Trend
Entire sample	**N=2073**	**N=1941**	**N=2118**	**N=2605**	***P* Value**
Smoking	1188 (60%)	1085 (57%)	1023 (49%)	1329 (52%)	0.0002
Hypertension	1178 (59%)	1221 (63%)	1432 (68%)	1906 (73%)	<0.0001
Diabetes mellitus	516 (25%)	552 (28%)	666 (31%)	910 (35%)	<0.0001
Prior MI	641 (32%)	457 (24%)	537 (26%)	703 (27%)	0.1
Women	N=546	N=622	N=722	N=993	
Smoking	282 (56%)	310 (51%)	306 (43%)	449 (46%)	0.01
Hypertension	352 (66%)	432 (70%)	500 (70%)	740 (75%)	0.05
Diabetes mellitus	186 (34%)	237 (38%)	257 (36%)	429 (36%)	0.07
Prior MI	149 (28%)	151 (24%)	174 (25%)	276 (28%)	0.8
Men	N=1527	N=1319	N=1396	N=1612	
Smoking	906 (62%)	774 (59%)	716 (52%)	880 (56%)	0.02
Hypertension	827 (56%)	789 (60%)	932 (68%)	932 (68%)	<0.0001
Diabetes mellitus	330 (22%)	315 (24%)	409 (29%)	481 (30%)	0.001
Prior MI	492 (34%)	306 (23%)	363 (27%)	427 (27%)	0.06

MI indicates myocardial infarction. The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.

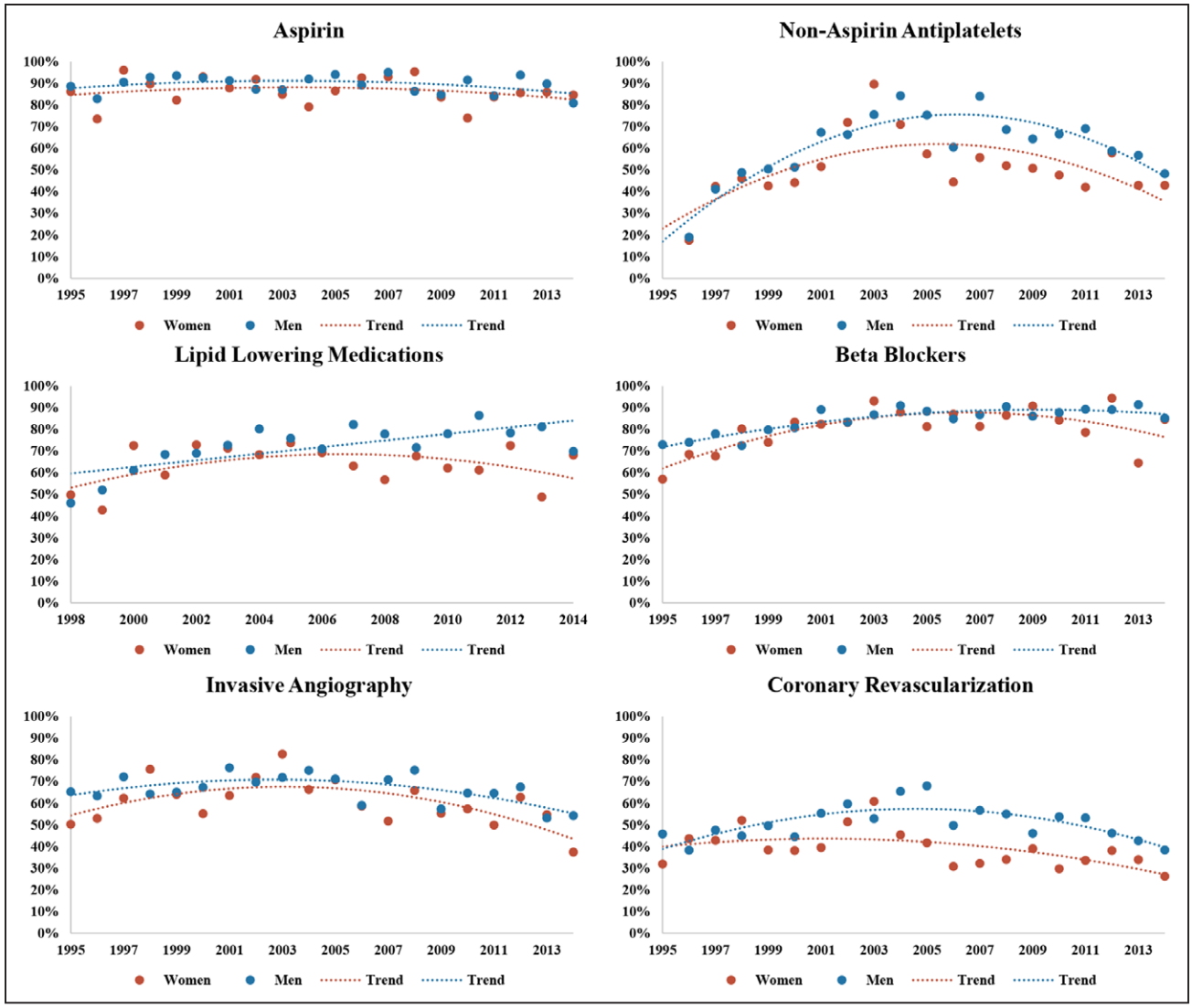

Figure 3. Annual trends in administration of guideline-directed therapies among young (35–54 years) women and men presenting with acute myocardial infarction.*

The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014. *Nonaspirin antiplatelets not routinely abstracted prior to 1996. Lipid lowering agents not routinely abstracted prior to 1998.

ilarly, in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, only half of young AMI patients believed they were at risk for heart disease prior their event, despite a high overall prevalence of cardiac risk factors.[18,19]

While the proportion of young AMI hospitalizations remained fairly stable across 1995 to 2014 among men, AMI hospitalizations attributable to young patients steadily increased among women, becoming comparable to that of young men in more recent years. Our observations complement Canadian registries reporting an increase in AMI hospitalizations among women.[20] The reasons for the rise in AMI hospitalizations among young women is likely multifactorial but may be related to modifiable risk factors. In the ARIC Community Surveillance study, young women presenting with AMI had more comorbidities and traditional risk factors than their male counterparts with AMI. This may be reflective of trends in the general nonhospitalized population. In an analysis from the National Health and Nutritional Examination Survey comparing 1988 to 1994 and 1999 to 2004, the mean Framingham coronary risk score improved for men while it worsened for women, narrowing the gap in cardiovascular risk between sexes.[21] We also noted that young women were more likely to be insured, which may have influenced care-seeking behavior and AMI hospitalizations.[22]

Clinical improvement in AMI management is an important priority for the Centers for Medicare and Medicaid Services Inpatient Quality Reporting program.[23] Quality improvement initiatives have led to better outcomes for patients with AMI, irrespective of sex.[23] In this analysis from the ARIC Community Surveillance, young women presenting with AMI had a higher co-

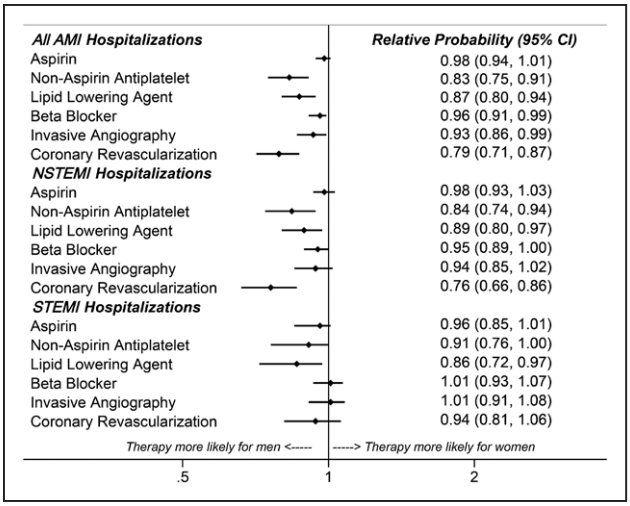

Figure 4. Relative probabilities of young women versus young men receiving guideline-directed therapies for acute myocardial infarction.* The Atherosclerosis Risk in Communities Surveillance study, 1995 to 2014.
*Models adjusted for race, geographic location (Forsyth County, NC; Jackson, MS; Minneapolis, MN; or Washington County, MD), and year of hospital admission.

morbidity burden and were less likely to undergo angiography or be managed by guideline-based AMI medications. These observations are consistent with the VIRGO study, which reported greater prevalence of diabetes mellitus, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and morbid obesity among women compared with men.[18,19] An association between higher comorbidity burden and lower likelihood of angiography or evidence-based care has been reported in older patients presenting with AMI.[24,25] Whether these associations extend to young adults with a lower likelihood of frailty is uncertain. It is possible that a greater proportion of women presented with type 2 myocardial infarction, given their greater comorbidity burden and decreased rates of revascularization. Although sex differences in management of AMI based are well known in older adults,[7,8] few studies to date have demonstrated sex-specific differences in management of AMI among young patients.[26,27]

Although the Centers for Medicare and Medicaid Services Inpatient Quality Improvement Program has focused on improving management and outcomes of patients with AMI, few initiatives have focused on improving cardiometabolic risk profiles, particularly for women.[1] Traditionally misconceived as a "man's disease", recognition of cardiovascular risk in female patients is lower than for male patients with similar risk profiles.[28] However, atherosclerotic cardiovascular disease is the leading cause of death in women.[1] Moreover, there are several nontraditional cardiac risk factors unique to women, such as gestational diabetes mellitus, preeclampsia, eclampsia, and early menopause or menarche.[29,30] Social determinants of health such as psychosocial stressors and poverty, both with higher prevalence in women, are also associated with increased cardiovascular risk.[28,31]

We believe an integrated, multifaceted approach is needed to promote effective primordial, primary, and secondary prevention strategies among at-risk women. To understand further the distinct cardiovascular risk profile and to define treatment pathways in women, clinical trials could be designed specifically for women. Guidelines focused on preventing cardiovascular diseases in women should continue to be updated and implemented in practice, to assist clinicians in clinical decision-making.[32] Expanding initiatives such as the American Heart Association Go Red for Women campaign to increase awareness about cardiovascular disease risk in women through media and other outlets should also be encouraged.

Our study has some limitations. The ARIC Community Surveillance Study is localized to 4 US communities and may not be generalizable to the entire nation. Clinical data were limited by availability in the medical record and abstraction priority. Temporal changes in diagnostic testing and documentation may have influenced trends in risk factors over time. We were un-

Table 4. Relative Probabilities of Guideline-Directed Therapies, Comparing Young (34-54-Year-Old) Women and Men Presenting With Acute Myocardial Infarction

	Women vs Men (Ref.): Relative Probabilities*				Trend‡
Therapy	1995–1999	2000–2004	2005–2009	2010–2014	*P* Value
Aspirin	0.96 (0.86 - 1.02)	0.98 (0.90 - 1.04)	1.02 (0.93 - 1.06)	0.96 (0.86 - 1.03)	0.8
Non-aspirin antiplatelet†	—	0.95 (0.83 - 1.06)	0.75 (0.61 - 0.89)	0.79 (0.65 - 0.94)	0.3
Lipid lowering agent†	—	1.01 (0.89 - 1.11)	0.86 (0.72 - 0.98)	0.80 (0.67 - 0.91)	0.005
Beta blocker	0.94 (0.83 - 1.04)	1.00 (0.92 - 1.06)	0.98 (0.89 - 1.04)	0.92 (0.81 - 0.99)	0.2
Invasive angiography	0.94 (0.82 - 1.06)	0.95 (0.84 - 1.06)	0.91 (0.76 - 1.05)	0.88 (0.73 - 1.03)	0.3
Revascularization	0.97 (0.81 - 1.14)	0.88 (0.74 - 1.02)	0.63 (0.49 - 0.79)	0.72 (0.56 - 0.88)	0.002

Ref. indicates reference. The Atherosclerosis Risk in Communities Surveillance Study, 1995 to 2014.
*Models adjusted for race (black or white), geographic location (Forsyth County, NC; Jackson, MS; Minneapolis, MN; or Washington County, MD), and year of hospital admission.
†Non-aspirin antiplatelets not routinely abstracted prior to 1996. Lipid lowering agents not routinely abstracted prior to 1998.
‡Management trends over time assessed by testing the multiplicative interaction between sex and time, adjusted for race, geographic location, and year of admission

able to evaluate trends in obesity, but the prevalence of diabetes mellitus significantly increased from 1995 to 2014; associations between diabetes mellitus and obesity are well-established.[33,34] Substance use, such as cocaine and marijuana, was not abstracted from the medical record but is a known risk factor that is prevalent among young patients presenting with AMI.[35] Mortality in this young population was modest, limiting the statistical power of comparisons between women and men. Other clinically-relevant endpoints, such as hospital readmissions or major adverse cardiovascular events, may prove to differ by sex for young patients with AMI; however, these outcomes were not available for analysis. Finally, specific troponin assays and their associated sensitivities varied across hospital systems and over time, potentially influencing trends in AMI detection. Our study also has several noteworthy strengths. The ARIC Study provides a large, multi-year surveillance of 4 diverse US communities, allowing an analysis of contemporary trends spanning several decades. Clinical and laboratory values were meticulously collected by certified abstractors following standardized protocols. AMI was classified and adjudicated by physician review of the medical records, and mortality outcomes verified by the National Death Index.

CONCLUSIONS

Young patients presenting with AMI are becoming increasingly common, have high prevalence of cardiometabolic comorbidities, and face 1-year mortality rates that approach 10%. Relative to young men, young women presenting with AMI have a higher comorbidity burden and a lower likelihood of undergoing an invasive strategy or receiving guideline-based AMI therapies. These observations from the ARIC Community Surveillance study have important health implications considering the increased disability-adjusted life years associated with AMI at a younger age. There is an enduring need for effective preventive strategies to reduce the burden of cardiovascular disease in the young population, especially among young women. Ongoing primordial, primary, and secondary prevention efforts are urgently needed to promote uniform and guideline-based care targeting AMI, associated cardiometabolic comorbidities, and adverse health behaviors in the young population.

ARTICLE INFORMATION

Received July 30, 2018; accepted October 19, 2018.

Guest Editor for this article was Judith H. Lichtman, PhD.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.037137.

Correspondence

Melissa Caughey, PhD, Division of Cardiology, University of North Carolina, Chapel Hill NC, 27599. Email caughey@med.unc.edu

Affiliations

Division of Cardiology, University of North Carolina School of Medicine, Chapel Hill (S.A., G.S., M.C.) Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill (S.A., A.KN, W.R.) Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA (A.Q., M.V, D.L.B.). Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (A.P.). Social and Health Organizational Research and Evaluation Program, RTI International, Research Triangle Park, NC(D.P.); Division of Family Medicine, University of North Carolina School of Medicine, Chapel Hill (S.A.). Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (R.B.).

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Sources of Funding

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, HHSN268201700005I).

Disclosures

Dr Arman Qamar is supported by the NHLBI postdoctoral training grant T32 HL007604 and the American Heart Association Strategically Focused Research Network in Vascular Disease under award numbers 18SFRN3390085 (BWH-DH SFRN Center) and 18SFRN33960262 (BWH-DH Clinical Project). Dr Muthiah Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 UL 1TR002541), and serves on advisory boards for AstraZeneca, Bayer AG, and Baxter Healthcare. Dr Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: Fractyl, FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. The other authors have no relevant conflicts of interest to disclose.

REFERENCES

1. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. *Circulation*. 2015;132:997–1002. doi: 10.1161/CIRCULATIONAHA.115.015293
2. Gupta A, Wang Y, Spertus JA, Geda M, Lorenze N, Nkonde-Price C, D'Onofrio G, Lichtman JH, Krumholz HM. Trends in acute myocardial in-

farction in young patients and differences by sex and race, 2001 to 2010. *J Am Coll Cardiol*. 2014;64:337–345. doi: 10.1016/j.jacc.2014.04.054
3. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352:1138–1145. doi: 10.1056/NEJMsr043743
4. Bilal U, Diez-Roux AV. Troubling trends in health disparities. *N Engl J Med*. 2018;378:1557–1558. doi: 10.1056/NEJMc1800328
5. Izadnegahdar M, Singer J, Lee MK, Gao M, Thompson CR, Kopec J, Humphries KH. Do younger women fare worse? Sex differences in acute myocardial infarction hospitalization and early mortality rates over ten years. *J Womens Health (Larchmt)*. 2014;23:10–17. doi: 10.1089/jwh.2013.4507
6. Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom AR. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. *Circulation*. 2012;125:1848–1857. doi: 10.1161/CIRCULATIONAHA.111.047480
7. Udell JA, Fonarow GC, Maddox TM, Cannon CP, Frank Peacock W, Laskey WK, Grau-Sepulveda MV, Smith EE, Hernandez AF, Peterson ED, Bhatt DL, Get With The Guidelines Steering Committee and Investigators. Sustained sex-based treatment differences in acute coronary syndrome care: Insights from the American Heart Association Get With The Guidelines Coronary Artery Disease Registry. *Clin Cardiol*. 2018;41:758–768. doi: 10.1002/clc.22938
8. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L; Get With the Guidelines Steering Committee and Investigators. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–2810. doi: 10.1161/CIRCULATIONAHA.108.789800
9. National Heart Lung and Blood Institute. https://biolincc.nhlbi.nih.gov/home/, accessed 10/7/18
10. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol*. 1996;49:223–233. doi: 0895435695000410
11. Myerson M, Coady S, Taylor H, Rosamond WD, Goff DC Jr; ARIC Investigators. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2009;119:503–514. doi: 10.1161/CIRCULATIONAHA.107.693879
12. Atherosclerosis Risk in Communities Study. https://www2.cscc.unc.edu/aric/sites/default/files/public/manuals/Updates%20Manual3_20151112.pdf. Accessed October 7, 2018.
13. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189. doi: 10.1136/bmj.i189
14. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280:1690–1691. doi: jsc80400
15. Ortman J, Velkoff V. *An aging nation: The older population in the United States. United States Census Bureau 2014*. https://www.census.gov/prod/2014pubs/p25-1140.pdf. Accessed October 7, 2018.
16. Gooding HC, Ning H, Gillman MW, Shay C, Allen N, Goff DC Jr, Lloyd-Jones D, Chiuve S. Application of a lifestyle-based tool to estimate premature cardiovascular disease events in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA Intern Med*. 2017;177:1354–1360. doi: 10.1001/jamainternmed.2017.2922
17. Singh A, Collins BL, Gupta A, Fatima A, Qamar A, Biery D, Baez J, Cawley M, Klein J, Hainer J, Plutzky J, Cannon CP, Nasir K, Di Carli MF, Bhatt DL, Blankstein R. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. *J Am Coll Cardiol*. 2018;71:292–302. doi: 10.1016/j.jacc.2017.11.007
18. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM, Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. *J Am Coll Cardiol*. 2015;66:1949–1957. doi: 10.1016/j.jacc.2015.08.859
19. Bucholz EM, Strait KM, Dreyer RP et al. Sex differences in young patients with acute myocardial infarction: a VIRGO study analysis. *Eur Heart J Acute Cardiovasc Care* 2017. doi: 10.1177/2048872616661847
20. Towfighi A, Markovic D, Ovbiagele B. National gender-specific trends in myocardial infarction hospitalization rates among patients aged 35 to 64 years. *Am J Cardiol*. 2011;108:1102–1107. doi: 10.1016/j.amjcard.2011.05.046
21. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. *Arch Intern Med*. 2009;169:1762–1766. doi: 10.1001/archinternmed.2009.318
22. Smolderen KG, Spertus JA, Nallamothu BK, Krumholz HM, Tang F, Ross JS, Ting HH, Alexander KP, Rathore SS, Chan PS. Health care insurance, financial concerns in accessing care, and delays to hospital presentation in acute myocardial infarction. *JAMA*. 2010;303:1392–1400. doi: 10.1001/jama.2010.409
23. Trivedi AN, Nsa W, Hausmann LR, Lee JS, Ma A, Bratzler DW, Mor MK, Baus K, Larbi F, Fine MJ. Quality and equity of care in U.S. hospitals. *N Engl J Med*. 2014;371:2298–2308. doi: 10.1056/NEJMsa1405003
24. Sonel AF, Good CB, Mulgund J, Roe MT, Gibler WB, Smith SC, Jr., Cohen MG, Pollack CV Jr, Ohman EM, Peterson ED; CRUSADE Investigators. Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). *Circulation*. 2005;111:1225–32. doi: 10.1161/01.CIR.0000157732.03358.64
25. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC Jr, Pollack CV Jr, Gibler WB, Ohman EM; CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA*. 2004;292:2096–104. doi: 10.1001/jama.292.17.2096
26. Deleted in proof.
27. 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. doi: 10.1016/j.amjmed.2011.11.016
28. Lee SK, Khambhati J, Varghese T, Stahl EP, Kumar S, Sandesara PB, Wenger NK, Sperling LS. Comprehensive primary prevention of cardiovascular disease in women. *Clin Cardiol*. 2017;40:832–838. doi: 10.1002/clc.22767
29. Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, Hu FB, Manson JE, Zhang C. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. *JAMA Intern Med*. 2017;177:1735–1742. doi: 10.1001/jamainternmed.2017.2790
30. Lubiszewska B, Kruk M, Broda G, Ksiezycka E, Piotrowski W, Kurjata P, Zielinski T, Ploski R. The impact of early menopause on risk of coronary artery disease (PREmature Coronary Artery Disease In Women–PRECADIW case-control study). *Eur J Prev Cardiol*. 2012;19:95–101. doi: 10.1177/1741826710394269
31. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9
32. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243–1262. doi: 10.1161/CIR.0b013e31820faaf8
33. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol*. 1997;146:214–222. doi: 10.1093/oxfordjournals.aje.a009256
34. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health*. 2000;54:596–602. doi: 10.1136/jech.54.8.596
35. DeFilippis EM, Singh A, Divakaran S, Gupta A, Collins BL, Biery D, Qamar A, Fatima A, Ramsis M, Pipilas D, Rajabi R, Eng M, Hainer J, Klein J, Januzzi JL, Nasir K, Di Carli MF, Bhatt DL, Blankstein R. Cocaine and marijuana use among young adults with myocardial infarction. *J Am Coll Cardiol*. 2018;71:2540–2551. doi: 10.1016/j.jacc.2018.02.047