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Female sex as a biological variable: A review on younger patients with acute coronary syndrome☆,☆☆

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ABSTRACT

Although acute coronary syndrome (ACS) mainly occurs in individuals >60 years, younger adults can be affected as well. Women continue to be at higher risk of 30-day mortality after ST-segment elevation myocardial infarction (STEMI) even in the current era of percutaneous coronary intervention (PCI). Importantly, the excess mortality among women is only significant at younger ages. Previous work has suggested that the reason for the differences in outcome is likely multifactorial and may partially be explained by some of the following factors: atypical presentation, delayed presentation, under-recognition of STEMI at initial medical contact, and underuse of medications because of concern regarding increased risk of bleeding. While these hypotheses may be true in some occasions, recent studies pointed out that the proportion of women presenting within 2 h after symptom onset was greater in the younger than in older cohorts. In addition, sex differences in administration of adjunctive medical therapies were greater in the older than in the younger cohort. Thus, there is not any one of the abovementioned factors able to explain the increase in mortality in the young women. Disparities alone could not account for the gap in mortality across sexes. Unless the effects of sex are studied, we will continue to have gaps in the knowledge of potential different mechanisms leading young women and men to die after ACS, which may result in missed opportunities for implementing a better health in our community. Randomizing or balancing the sexes as well as powering studies to detect sex differences is warranted in future research.

Introduction

Although acute coronary syndrome (ACS) mainly occurs in individuals >60 years, younger adults can be affected as well. A recent study [1] has shown that women continue to be at higher risk of 30-day mortality after ST-segment elevation myocardial infarction (STEMI) even in the current era of percutaneous coronary intervention (PCI). Data on 8,834 patients with STEMI in 41 hospitals in Europe were obtained from the International Survey of Acute Coronary Syndromes (ISACS-TC) registry between 2010 and 2016. Participants consisted of 2,657 women (mean age, 66.1 years) and 6,177 men (mean age, 59.9 years). The analysis indicated that women had a significantly higher 30-day mortality risk than men (11.6% versus 6%). After limiting the evaluation to participants undergoing primary PCI, the disparity in sex-specific mortality shrunk to 7.1% for women and 3.3% for men. Early mortality risk was higher among women younger than 60 years than among men in the same age cohort when adjusting for medications and other comorbidities (OR 1.88, 95% CI 1.04–3.26). Sex differences in 30-day mortality risk were not significant among participants aged 60 to 70 years (OR 1.28, 95% CI 0.88–1.88) and those older than 75 years (OR 1.17, 95% CI 0.8–1.73). The extent to which mortality rate differences between young men and women are related to disparities in treatment or dissimilarities in pathophysiology remains a matter of debate. Nevertheless, this study is the first investigation that demonstrates that differences between younger men and younger women in STEMI mortality rates are unrelated even to disparities in treatment. Sex-related pathophysiological differences may contribute to the higher mortality in younger women compared with men of the same age category. This review article strongly supports the view that female sex is a biological variable and contributes to implement the Sex and Gender Equity in Research (SAGER) guidelines that were developed to assist researchers in reporting sex and gender information in publications [2]

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Sex matters

"If the present arrangements of society will not admit of woman's free development, then society must be remodeled, and adapted to the great wants of humanity" **(*Elizabeth Blackwell*)**

The idea that there are sex-based differences in early mortality after myocardial infarction is not new. One study investigated mortality trend sex differences from 1994 to 1998. Data were collected from the National Registry of Myocardial Infarction (NRMI) on 691,995 patients [3]. The overall mortality rate during hospitalization was 16.7% among the women and 11.5% among the men. After adjustment for many clinical variables, women still had a higher risk of death compared with men. In patients who were less than 50 years of age, the mortality rate during hospitalization was more than twice as high among women. The difference in the rates decreased with increasing age and was no longer significant after the age of 74 years. This study also found that about one third of the sex-based differences in mortality was explained by risk factors, comorbidity and clinical characteristics on admission leaving fairly unexplained the higher risk of death of young women relative to men. Later, another study [4] examined the relationship between lack of chest pain and higher mortality observed in younger women with myocardial infarction still using the NRMI to analyze data from 1,143,513 patients (42% women). Separate models were made for each age-stratum, and results showed that the absence of chest pain was more common in younger women aged 55 years or less and that younger women presenting without chest pain had greater in-hospital mortality rates than men. On this background it seems odd to suggest that sex differences in outcomes after myocardial infarction in younger women constitute a 'hot topic' given that the first major report of this finding dates back over 15 years. Why is such interest still persisting? A huge storm of technological advances in precision medicine and drug development, changes in policy at major institutions, exaggeration by the media and some pushback by excellent scientists have generated a turbulence of dissenting voices. So, sex-based differences in early mortality after myocardial infarction is still a topic worthy of attention.

Contradiction in the literature

"Truth comes out of error more readily than out of confusion" **(*Francis Bacon*)**

Some scientists argued that the major flaw encountered in the above-mentioned research studies was the failure to calculate outcomes with separate analyses for patients with and without STEMI. Further, some of the early studies on sex difference in outcome predate the era of routine invasive approach and other current standard-of-care medications. One study found a sex-ACS subtype interaction in a large sample of participants in clinical trials, whereby women with STEMI fared worse, and women with non-STEMI (NSTEMI) fared better than men with similar clinical presentation [5]. Yet, no significant interaction was detected between sex and age in such investigation. A further study [6] investigated the NRMI registry and found that adjusted sex-related differences in mortality were age-dependent in STEMI but not NSTEMI cases. However, excess risk among STEMI women was found in the age groups below age 70. How young are "people below age 70″? Clearly, there is a huge discrepancy between definition of age categories in this study and that of prior work. A more recent report using population-level data [7] – investigated sex-based differences in the quality of care in the Minneapolis Heart Institute STEMI system registry including hospitals in Minnesota and Wisconsin for more than a decade (2003 to 2016) and found no sex differences in short or long-term age-adjusted mortality with the use of a standardized STEMI protocol designed to improve time to treatment and clinical outcomes. According to some observers, this finding suggests that sex may not matter for individual patients with STEMI. A new study by the Acute Coronary Syndrome Israeli Surveys (ACSIS) added to confusion over the role of sex and age in ACS [8]. In 3,949 young patients (<55 years) with ACS enrolled from 2000 through 2013, women had a higher in-hospital mortality rate than men (2.7% versus 1.0%), regardless of the ACS. subtype. Still, after adjusting for history of prior myocardial infarction, GRACE score >140, diabetes mellitus, hypertension, year of survey, PCI and low high-density lipoprotein, mortality stayed about 4-fold higher in women than in men. Of note, of the 3,949 patients that were studied in the Surveys, only 103 were with STEMI. We found the interpretation of all of these data very difficult to understand. As such, it remains unclear whether sex differences in mortality persist in young patients across the entire spectrum of ACS or just in STEMI, and which factors may contribute to this gap in mortality, if any.

Can we resolve the contradiction?

*"Contradiction is the lever of transcendence" (**Simone Weil**)*

We did resolve the contradiction at least partially. A key to understanding is first the recognition that STEMI is a unique clinical entity with epidemiology, incidence, and outcomes distinct from that of NSTEMI. STEMI and NSTEMI differ considerably in the management options. Treatment of patients with NSTEMI is more complex and challenging than treatment of patients with STEMI. In STEMI time to reperfusion is a basic factor influencing mortality. In NSTEMI, the acuity level of the clinical presentation is the key factor influencing outcomes. Risk should be categorized at admission and may influence decision on management as well. In our current era of quality-improvement initiatives, researchers might consider several approaches including matching to identify sex difference in outcomes sorted by selected phenotypic characteristics (e.g. STEMI versus NSTEMI). Strong justification from preliminary data, or other relevant considerations, must be provided for proposing to study ACS as a single clinical entity. A further key to understanding it is the misleading notion that population-level or "aggregate" relationships may represent individual-level relationships. For example, the Minneapolis Heart Institute article [7] examined the median reperfusion time for all the patients who underwent primary PCI, regardless of their own reperfusion time. In such a model, the aggregated median reperfusion time variable represents many factors that were changing with years from 2003 to 2016. Much more importantly, the study did not use the reperfusion time in the statistical model. The model was adjusted only for age. Many other factors may influence STEMI outcome at individual-level relationships, and it is necessary to include these variables into the statistical model. What the ISACS-TC registry did was to tease out the individual-level relationship of reperfusion time within 2 h and mortality in either women or men [1]. The same reasoning was applied to medications given at admission and other factors influencing 30-day mortality. Finally, researchers and policymakers would want to introduce programs that would lead physicians to achieve some measurable benchmarks of age categories. Yet, after 15 years of research and discussion, there is still a significant amount of ambiguity on the definition and application of the definition of young people with myocardial infarction.

Proposed working definition of a younger person

*"The first part of life is childhood. The second is your child's childhood. And then the third, old age." (**Barbara Kingsolver**)*

The results of subgroup analyses by age can result in either consistent or insignificant findings depending on the definition of age used in the study [9]. No subgroup analysis will attain practical usefulness when undertaken without any explanatory background, no matter how significant the results may be [10]. Thus, when does younger age begin in research studies? Our concept of the stages of life is a relative one: the "age" of individuals within a given cohort depends on the size of the other cohorts. This is a statistical interpretation of the what is nicely characterized by Barbara Kingsolver in the quotation we reproduced above. For matter of simplicity, the ISACS-TC registry initially proposed 45 years as the upper limit of defining young adults with ACS [11], as the same age definition has been used in many prior studies [12–21]. Thereafter, the ISACS-TC registry proposed 60 years according to the World Health Organization (WHO) Minimum Data Set Project on Aging and Health [22] and the United Nations "Population Aging Report" (2009) [23]. Further, the ISACS-TC registry acknowledged the diversity of old age by distinguishing the young old (≥60–74 years) from the old patients aged 75 years or older [1]. The purpose of the ISACS-TC registry was, indeed, to analyze 3 subgroups of patients based on ages that were predefined on a rational indication. However, the age at which one becomes an older person is a notion that changes over time. Yet, it is evident that today's 60-year-olds are often very different from their parents at the same age and have absolutely nothing in common with their grandparents at the same age.

Cardiovascular disease in the young: a specific role for diabetes in women?

*"The important thing is to not stop questioning. Curiosity has its own reason for existing" (**Albert Einstein**)*

According to the United Nations "Population Aging Report" (2009), the proportion of the global population aged less than 60 years was 92% in 1950, 90% in 2000, and is expected to reach 89% in 2050. Patients less than 60 years old represented 43.1% of all patients who presented with STEMI to hospitals enrolled in the ISACS-TC registry over a 6-year period [1]. Thus, there is a substantial number of younger patients who develops ischemic heart disease in its most serious form. In agreement with previous work, the ISACS-TC registry showed that heavy cigarette smoking higher body mass index and positive first-degree family history were the most common risk factors in younger patients [11,24], whereas older patients had higher rates of diabetes, hypercholesterolemia and hypertension. Smokers who were less than 50 years have the worst discrepancy in risk of STEMI: 8 times more than that of former and never smokers [25]. Nevertheless, none of these factors predicted mortality rates in the ISACS-TC registry series [1]. Only diabetes mellitus was a relevant risk factor to predict death, and, of note, statistical significance was reached only in the younger patients (adjusted OR 2.04, 95% CI 1.18–3.54) where sex differences in mortality were largely apparent (reference male; OR 1.88, 95% CI 1.08–3.26). One can speculate that differences in relative risk by sex are greatly reduced, although not eliminated, by the presence of diabetes. In other terms, diabetes may greatly attenuate the usual protective effect afforded by female sex in younger age, thereby expanding the relative gap in cardiovascular risk between the sexes.

The interplay between diabetes and ischemic artery disease

*"The very process of living is a continual interplay between the individual and his environment, often taking the form of a struggle resulting in injury or disease" (**Rene Dubos**)*

The ISACS-TC registry showed that in younger people the presence of diabetes conferred a similar risk of death from any cause, as did a history of prior PCI [1]. The same was not true for women and men older than 60 years, in whom the risk of death was lower for people with diabetes than for those with a history of prior PCI. These observations lend support to the finding that diabetes is not a coronary equivalent in all circumstances. Its effect is modulated by sex and age. Other studies have suggested that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction [26]. Overall, these findings suggest inadequacy of screening and risk factor control efforts among young people. These data also provide a rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in those patients with prior myocardial infarction.

Angiographic CAD burden and mortality in the young

*"The tragedy associated with coronary atherosclerotic heart disease is that it kills or disables people during their prime of life." (**Paul Dudley White**)*

Atherosclerosis of the coronary arteries is known to have an impact on the development and severity of ACS [27]. Given that young patients with ACS presented an average of two decades earlier than old patients and with fewer risk factors, it is conceivable that researchers observed less multivessel disease, less calcification, and fewer ostial lesions in young people compared with old people [1,11]. There was a predilection for the presence of significant coronary artery disease (CAD) in the left anterior descending artery in the young group, as previously documented [28,29]. Interestingly, the proportion of nonobstructive CAD in the clinical setting of ACS was similar in the young women and men (15% versus 10%), but the mortality rate was higher in women [11]. The less extensive CAD observed in young patients might suggest that premature ischemic heart disease is associated with rapid disease progression rather than with a gradually evolving process [19]. CAD is believed to progress in a nonlinear fashion, due to multiple plaque ruptures and STEMI typically occurs in non- obstructive plaques. The cause of excess mortality in young women is not explained by differences in the severity of angiographically documented disease. There is much speculation about coronary spasm with subsequent thrombosis and rapid reperfusion in women, and especially in young women [30,31]. However, which factors are predictive of death in this distinctly unusual cohort still remain poorly understood.

Sex disparities in treatment

*"Whatever women do they must do twice as well as men to be thought half as good" (**Charlotte Whitton**)*

Prior studies have suggested that women with ACS are treated less aggressively than men. In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) initiative, women were less likely to receive heparin and antiplatelet agents and less likely to undergo revascularization than men [32]. In the Canadian Registry of ACS I and II, women were shown to be less likely to

receive early aspirin, beta-blockers, and timely reperfusion therapies than men [33]. Interestingly, underutilization of beta-blockers was more striking for the female population, as women more frequently developed heart failure [33]. More recently, the Get with the Guidelines-Coronary Artery Disease (GWTG-CAD) registry [12] focused on STEMI and showed that women were more likely to have lower quality of care and experienced less favorable short-term outcomes than men. Sex difference in short-term mortality was greater in the younger cohort. However, this study was unable to effectively control for concomitant use or underuse of medications in its statistical analyses. Most importantly variables related to time from symptom onset to hospital presentation require adjustment because they determine the myocardial response capacity of a patient with STEMI. Use of reperfusion therapies that are administered early in the acute phase of STEMI needs to be adjusted for since it dramatically modifies prognosis [34,35]. When rates of timely coronary revascularization and evidence-based medications differ between men and women, the value of sex as a prognostic factor may be underestimated or overestimated by analyses that include patients with such markedly differences in treatment. In one of the ISACS-TC registry most recent studies [35], the paper outlined the measurement issues. The study assessed whether the worse prognosis of women was related to delay to hospital presentation by adjusting for all clinical variables, procedures, and medications given at admission. The study included in the covariates Killip class 3 and 4. Since acute pulmonary edema or cardiogenic shock may be considered mechanisms of death, these variables may fail to meet the criteria for being considered confounding factors. Consequently, these models could be formally regarded as inappropriate, but they aid in understanding the mechanisms by which women may die of STEMI more frequently than men. The study, indeed, found that 30-day mortality was largely explained by more severe "delay to treatment" profiles in women, not by their history of cardiovascular risk factors, comorbidity, or even by thrombolytic or PCI treatment.

Estimating sex differences in treatment effects using observational data

"If it were not for the great variability between individuals, medicine might as well be a science, not an art" ***(William Osler)***

Many studies have estimated an "average treatment effect" that implicitly assumes a similar treatment effect across sexes. In contrast, therapeutic strategies for ACS may have a different effect in women compared with men. A contemporary example of this is given by the glycoprotein IIb/IIIa inhibitors for which randomized clinical trials have demonstrated efficacy regardless of sex [36], and observational studies have shown differential effects across sexes. Low-risk profile women did not benefit from glycoprotein IIb/IIIa inhibitors, unlike men in the same risk category [37]. Understanding heterogeneity of treatment effect is, therefore, critical for decision making, and is relevant to most stakeholders. The implication is that the statistical models need to be reformulated to more accurately reflect the data. A key principle is that the observational studies should be designed and analyzed in the same manner as randomized controlled experiment. To do this, findings should be evaluated by testing for interaction; biases should be avoided by adhering to study design that reduces the potential for inclusion of immortal person-time and by evaluating balance on covariates within subgroups to assess the potential for confounding. The main advantage of matching or balancing is that it usually reduces statistical power to a lower extent than adjustments in the model. In one of the ISACS-TC registry articles on STEMI [1], the study created balanced baseline characteristics of women versus men using inverse probability of treatment weighting. Routine treatments such as antiplatelet drugs, heparin, and beta-blockers were similarly provided to a subsample of men and women. Time to hospital presentation was restricted to the guidelines recommended 120 min or less. Once this balance was achieved, outcome measurements were ascertained and compared between sexes. The estimated odds ratios for death of STEMI women versus men were: 1.56 (95% CI 1.05–2.32) for patients younger than 60 years, 1.49 (95% CI 1.15–1.92) for those aged 60 to 74 years, and 1.21 (95% CI 0.93–1.57) for those aged 75 years or older. In summary, the study created an analysis that resembles what would have occurred had the participants been randomly assigned. Younger women experienced more sex gap in mortality than the other age categories. The study failed to answer only one question: why?

Sex differences in pathophysiology

"Belief begins where science leaves off and ends where science begins." ***(Rudolf Ludwig Karl Virchow)***

There could be several reasons for why younger women are more likely to die than young men. Diabetes in women may have a more powerful role than in men [38]. One study found that diabetes was a factor associated with increased risk of 30-day all-cause mortality in the young, but not the old population, and was accompanied by a large sex gap in mortality [1]. Elevated triglycerides have been shown to be of greater risk to women than to men [39]. Autoimmune diseases may be implicated as well in sex differences in risk. In the Framingham Offspring Study, women with systemic lupus erythematous aged under 45 years were 50% more likely to have ACS than were women of the same age without autoimmune disease [40]. The socioeconomic status and level of depression may also play a significant role [41,42]. In a subgroup analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study, high objective hostility scores were associated with the presence of coronary artery calcification [43], and hostility predicted recurrent events among women [44]. Reports form the Women's Ischemia Syndrome Evaluation (WISE) study investigators have noted that the metabolic syndrome but not obesity (defined by body mass index) is associated with significant CAD [45], that apolipoprotein E polymorphism is an independent risk factor for the presence and severity of coronary atherosclerosis [46], and that serum amyloid A is independently associated with CAD measured by angiography in women [47]. 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, functional differences of smooth muscle cells in the vessel wall and concomitant small vessel disease or apical ballooning [30,48,49]. Younger women have less extensive CAD and, therefore, may have lesser myocardial ischemic preconditioning, resulting in a greater susceptibility to ischemia [50]. However, there are no sex-specific data available in our or other studies for supporting or refuting these hypotheses. Future investigations should be performed to explore potential mechanisms for excess mortality in young women.

Trends in sex-related outcomes

"The problem seemed to me not that there are differences but rather how we value these differences" **(Sue Monk Kidd)**

Bhatt and colleagues examined Nationwide Inpatient Sample (NIS) data from 2004 to 2011 to assess temporal trends and sex differences in revascularization and in-hospital outcomes for younger patients with acute myocardial infarction [51]. The cohort consisted of 1,363,492 adults aged between 18 and 59 years. Of these, 632,930 patients (46.4%) had STEMI. Women were less

likely than men to present with STEMI (adjusted OR 0.74, 95% CI 0.73–0.75). The use of PCI for STEMI increased in both younger men (from 63.9% to 84.8%) and women (from 53.6% to 77.7%) between 2004 and 2011. Yet overall younger women with STEMI were less likely than men to receive reperfusion therapies. They also had higher rates of in-hospital mortality (adjusted OR 1.04, 95% CI 1.03–1.06). Most worrisomely, there was a temporal increase in risk-adjusted in-hospital mortality from 2004 to 2011 in both younger men and women with STEMI. The pattern of younger women being less likely than their male counterparts to receive revascularization follows that of the recent Variations in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study [34]. According to the authors, the reason for the disparity in outcome is likely multifactorial and may partially be explained by some of the following factors: atypical presentation, delayed presentation, under-recognition of STEMI at initial medical contact, and underuse of medications because of concern regarding increased risk of bleeding. While these hypotheses may be true in some occasions [8,35,52], it should be pointed out that administrative databases are unable to fully capture or differentiate patient-level variables that could be predictive of mortality. Indeed, one of the ISACS-TC registry study [1] found that the proportion of women presenting within 2 h after symptom onset was greater in the younger than in older cohorts. In addition, sex differences in administration of adjunctive medical therapies were greater in the older than in the younger cohort, which does not support the hypothesis that differences in early treatment may account for differences in risk of mortality. Thus, there is not any one of the abovementioned factors able to explain the increase in mortality in the young women, but a number of issues are not covered by the common clinical covariates, including those describing the pathophysiology of ischemic heart disease in women. In summary, sex disparities in treatment of STEMI and ACS still persist. These disparities alone could not account for the greater risk of mortality in young women compared with men.

What do you do next?

*"The laws of science do not distinguish between the past and the future." (**Stephen Hawking**)*

The United States (US) National Institutes of Health (NIH) now requires that scientists incorporate Sex as a Biological Variable (SABV) in its funded vertebrate animal research by considering whether the system under study operates differently in the two sexes through the comparison of males and females in at least some key experiments. The NIH's view pertains also to clinical trials and observational studies. A 2014 analysis of data released by the US Food and Drug Administration revealed important differences in the number and type of adverse events reported in women and men [53]. Both sexes play distinct roles in how health and disease processes differ across individuals, and consideration of these factors in research studies should inform the development and testing of preventive and therapeutic intervention. Sex biomedical research extends far beyond the territory of sex inequalities and disparities in heath. Unless the effects of sex are studied, we will continue to have gaps in the knowledge of potential different mechanisms leading young women and men to die after ACS, which may result in missed opportunities for implementing a better health in our community. To help researchers know what information is needed in publications, the SAGER guidelines [2] give some recommendations including: (1) Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected. (2) Where subjects can also be differentiated by gender, shaped by social and cultural circumstances, the research should be conducted similarly at this additional level of distinction (3) Authors should report how sex and gender were taken into account in the design of the study, whether they ensured adequate representation of males and females, and justify the reasons for any exclusion of males or females (4) Where appropriate, data should be routinely presented disaggregated by sex and gender. Sex- and gender-based analyses should be reported regardless of positive or negative outcome. In clinical trials, even data on withdrawals and dropouts should be reported disaggregated by sex.

Conclusions

*"We want to end gender inequality and to do that we need everyone to be involved" (**Emma Watson**)*

Consideration of sex may be critical to the interpretation, validation, and generalizability of research findings. Including sex/gender analysis in research could save more women from ischemic heart disease

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