Young Women With Acute Myocardial Infarction and the Post-Hospital Syndrome

Running title: Gabizon et al.; Young Women with Acute Myocardial Infarction

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Our awareness and understanding of ischemic heart disease (IHD) in women has evolved substantially over the past two to three decades. The myth that heart attacks are “male diseases” was clearly dispelled and we know now that cardiovascular diseases (CVD), including heart disease and stroke, are common and represent the number one killer of women in the United States and worldwide. In the Framingham Heart Study it was estimated that among women free of CVD at 50 years of age lifetime risk for developing CVD was 39.2%. We have learned that clinically manifest IHD usually develops a decade later in women than in men, although younger women are surely not immune from heart disease and more than 30,000 women younger than 55 years of age are hospitalized with acute myocardial infarction (AMI) every year in the United States. Women with heart disease have been shown to have a higher burden of cardiovascular (CV) risk factors and of other comorbidities. While the classical CV risk factors are similar in women and men, their relative contribution to CV risk differs by gender and women with CVD have often a clustering of risk factors such as diabetes, hypertension, obesity, physical inactivity and dyslipidemia. Additionally, women may be affected by gender specific risk factors, such as preeclampsia or eclampsia, polycystic ovary syndrome and use of hormone replacement therapy after menopause, or inflammatory autoimmune disorders, such as lupus or rheumatoid arthritis not restricted to, but more common in women. Psychosocial risk factors are also more common in women and impact adversely not only on the risk for IHD, but also on outcomes after an acute ischemic event. We have also learned that there are substantial differences between women and men with IHD in chest pain perception and reporting and women frequently present with subtle or “atypical” symptoms, leading to frequent delays in diagnosis and treatment. There are also gender differences in the pathophysiology of IHD with less extensive obstructive epicardial coronary artery lesions and more abnormalities in coronary
vasomotion and in microvascular reactivity, coronary artery dissection, and stress induced cardiomyopathy masquerading as acute myocardial infarction in women.\textsuperscript{5-7} Women with acute coronary syndromes (ACS) have worse outcomes, including higher mortality, attributable in part, but not fully, to older age, comorbidities and treatment differences. Finally, gender bias with less consistent use of proven evidence-based therapies in women is well documented, although recent studies suggest that this bias is diminishing.\textsuperscript{5-7}

The study by Dryer et al. in the current issue of \textit{Circulation} focuses on younger women (aged less than 65 years) with AMI.\textsuperscript{8} As emphasized by the study investigators, younger women with IHD are a distinct high-risk phenotype. A prior recent analysis of a national US database conducted in part by the same group of investigators reported important sex differences among younger patients with AMIs.\textsuperscript{9} The study analyzed 230,684 hospitalizations for AMI in 30-to-50 year-old patients. Younger women with AMIs had a higher prevalence of CV risk factors and other illnesses, higher in-hospital mortality and longer length of stay (LOS) compared with men of similar age. Mortality was about 30\% higher in women and was noted in all age subgroups, although from 2001 to 2010 the in-hospital mortality decreased significantly in women, exceeding the decrease in mortality observed in men in this time period. African American women were identified as a particularly high-risk population in this analysis with high prevalence of CV risk factors and worse in-hospital outcomes. Similar findings of higher mortality rates in younger women with AMI compared to younger men were shown in several, but not all, other studies from the US, Europe and China and were attributed to a heavier risk factor burden, more comorbidities, less frequent presentation with typical chest pain resulting in delays in diagnosis in treatment and to lower application of effective evidence-based interventions.\textsuperscript{6} However, in most studies adjusting for these differences could not fully explain
the observed mortality differences, suggesting that additional differences in pathophysiology and possibly other factors may contribute to gender differences in prognosis.

The current publication focuses on early readmissions after hospitalizations for AMI. The study is based on the analysis of a large inpatient administrative database from California, from 2007 to 2009. Among 42,518 patients with AMI aged 18-to-64 years, 4,775 (11.2%) had at least one early hospital readmission, within 30 days of discharge. The main findings of this study can be summarized as follows: first, the all-cause 30-day hospital readmission rate was almost twice as high in women as in men (15.5% vs. 9.7%, P<0.0001); second, for both sexes, readmission risk was highest on days 2-4 after discharge and declined thereafter and third, over 40% of readmissions were for non-cardiac reasons for both women and men. These are novel and important observations. Early readmission after hospital discharge is a very relevant outcome, as it is associated with substantial morbidity and disruption of usual lifestyle routines and carries major implications with regards to health care utilization and costs.

Among younger patients with AMI, women were more likely to have a history of previous ACS, congestive heart failure, diabetes and stroke. Additionally younger women were also more likely to have other non-cardiac comorbidities such as chronic obstructive pulmonary disease, renal failure, cancer, major psychiatric disorders and a history of infection. Importantly, there were major sex differences in racial distribution, with a substantially higher proportion of younger women with AMI being African American. Insurance status also differed with more women on Medicare or Medicaid, while more men had private insurance. During the index AMI, men were more likely to have percutaneous coronary revascularization although rates of bypass graft surgery were similar and hospital LOS was higher in women. These gender differences at the time of presentation and during the index hospitalization explained about two thirds of the
association of female sex and early readmission. However, even after careful statistical adjustment for CV risk factors, comorbidities, racial differences, LOS, social and demographic factors, female sex emerged as a significant risk factor for early hospital readmission. Absolute rates of readmission both for cardiac and non-cardiac reasons were higher in women as compared to men. Importantly over two fifth of readmissions in both genders were for non-cardiac reasons. Risk of readmission was greatest between days 2 and 4 peaking at day 2 and this pattern did not vary by sex. This finding is very relevant and identifies a particularly vulnerable period early post-discharge. A similar pattern was observed for hospitalizations for other acute medical conditions and the term “post-hospital syndrome” was coined by Dr. Krumholz to describe this important observation. As highlighted by Dr. Krumholz, analyses of Medicare data show that overall nearly one fifth of patients discharged from hospital after an acute illness had a recurrent, often apparently unrelated, medical problem within the subsequent 30 days necessitating hospital readmission. While in such Medicare data elderly patients constitute a large proportion of the population analyzed, the current study identifies that the post-hospital syndrome is not restricted to the elderly and represents an important hazard also in younger patients with recent AMI. The explanations for this relatively newly described syndrome are multifaceted and relate both to physiological stress exacerbating underlying medical conditions, psychological stress associated with an acute illness, polypharmacy, lack of proper discharge planning and support in some cases, deconditioning associated with hospital stay and a general disruption of health homeostasis associated with hospital admissions.

The current study identifies younger women with AMI as a population at particularly high risk for the post-hospital syndrome. Although the study cannot explore in detail causality, the authors hypothesize that there are multiple factors contributing to the post-hospital syndrome
in young survivors of AMI including physiological, psychological and social stressors, generated or exacerbated by the acute hospitalization. Women may be particularly vulnerable to the psychological consequences of hospital admissions for AMI and may have fewer social supports and coping mechanisms.\textsuperscript{11,12} Additionally, gender bias in the management of younger patients with AMI, which may apply both to their acute and ongoing cardiac care and to the treatment of other non-cardiac conditions, may play a role.

Overall there are limited data on the risk of early hospital readmission in younger survivors of AMI. An analysis from the Global Registry of Acute Coronary Events (GRACE) large multinational registry of acute coronary syndromes reported that in Australia and New Zealand female gender was an independent predictor of early re-hospitalization within 30 days after an ACS.\textsuperscript{13} A publication from the Alberta Provincial Project for Outcome Assessments in Coronary Heart disease (APPROACH) registry in Canada analyzed rates of early readmission after ACS discharge.\textsuperscript{14} In this analysis female sex did not emerge as an independent predictor for early readmission, although the analysis did not focus on younger patients with AMI. Similar to the findings of Dreyer et al., this study also reported that early readmissions post ACS are common and often non-cardiac in nature, seemingly unrelated to the index hospitalization.

The current study has certain limitations. It is limited to a specific geographic region and it is unclear if the results can be generalized to other parts of the United States or to other countries. Moreover, important data are missing in this administrative database, such as information on smoking history, details on the use of drug therapies during the index AMI, data on social supports, education level, level of income and other psychosocial factors. Further studies are required to assess patterns of early readmission after AMI in various geographic regions, including areas with different racial make-ups and health care delivery models. In spite
of these limitations, the study provides important new data related to patterns of early readmission after AMI in younger patients. It draws our attention to young women surviving an AMI as a high-risk population for early hospital readmission, particularly those with underlying comorbidities, African American women and those with federal insurance and to the importance of the post-hospital syndrome. Clinicians have intuitively recognized the major disruptive consequences of acute hospitalizations, but defining and understanding in depth the causes for the post-hospital syndrome are important next steps in developing effective preventive strategies. Therefore, more research is urgently needed in this field. From a practical perspective, in an era of “performance measures” and increasing pressure to decrease hospital LOS even for patients with first manifestations of major life-threatening and life-altering illnesses, cardiologists and cardiac teams are reminded that the care of patients with acute cardiac conditions needs to extend beyond the revolving doors of the coronary care unit and the catheterization laboratory. It entails many other aspects such as careful discharge planning, utilizing a holistic approach, which addresses the disease underlying the acute index hospitalization but also other comorbidities, social supports, access to prompt medical attention and education post-discharge and the psychological stress associated with hospitalizations for acute medical conditions.

**Conflict of Interest Disclosures:** None.

**References:**


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