Sex, survival bias, and mortality following acute myocardial infarction

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Several though not all studies have found an up to 2-fold increase in 30-day mortality in women compared to men admitted to hospital for ST-elevation myocardial infarction (MI), even after adjustment for baseline variables. These data however do not take into account the pre-hospital period. Indeed, three large WHO MONICA reports that included out-of-hospital events found no significant gender difference in overall 28-day mortality from MI, with more men dying before reaching the hospital (presumably of ventricular tachyarrhythmias) and more women dying after hospital admission (presumably of heart failure). Women compared to men exhibit enhanced vagal activity, both under basal conditions and during angioplasty-induced coronary occlusion, and this may afford protection against malignant ventricular arrhythmias. Epidemiological data indicate that women dying of ischemic heart disease are less prone to sudden death than men. Taken together, the above findings suggest that, following acute MI, significant gender differences lie not so much in overall mortality, but in the timing and mechanisms of death.

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Several studies[1-5] have found a significant, up to 2-fold, increase in 30-day mortality from acute myocardial infarction (MI) in women compared to men. Women with ST-elevation MI are older, more often diabetic and hypertensive, and more susceptible to serious bleeds than men[1,6-10]. Yet, even after adjustment for these variables, female mortality has been reported to exceed that in men[1-5]. A paradox is therefore generated, with the lower female incidence of ischemic heart disease, compared to men, in apparent contrast with their higher mortality after MI. The above sex-based mortality difference, however, has not been confirmed in other similar studies[6-9,11]. More importantly, the data are drawn from trials and registers that included only cases reaching the hospital alive[1-5], and may differ substantially from data obtained in community-based populations comprising out-of-hospital events.

There are at least three analyses of 28-day mortality after acute MI applied to the general population that include the pre-hospital period. All come from the WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project. The first report, on 5106 New Zealand patients aged 25 to 64 years (27% women), found that women, despite a more unfavorable risk profile, had a lower mortality before hospital admission (adjusted odds ratio 0.72; 95% confidence interval 0.60-0.86), but no significant difference in total mortality at 28 days, compared to men[12]. A second study, on 79 669 cases from 29 other MONICA populations, also found a lower female mortality before hospitalization (64 vs 70% of all deaths), with a correspondingly increased in-hospital female mortality[2] (in the 40 to 49-year-old group, however, overall mortality was significantly *higher* for women than men, which might reflect delayed recognition and treatment of MI in younger female patients, more severe disease, or different pathophysiological mechanisms[2]). The third report, on 5542 cases from Scotland, found an age-adjusted 28-day mortality rate of 49.8% in men and 48.5% in women (p = NS); 74% of all male deaths occurred out of hospital, vs 68% in women (p = 0.0004), and a smaller proportion of men than women lived longer than 1 hour from the onset of MI (p < 0.0001)[13]. In a retrospective analysis of two large thrombolytic trials (GUSTO-I and INJECT), even in-hospital deaths occurred approximately 2 hours sooner in men than in women[5].

On the whole, these MONICA data show no significant gender difference in overall 28-day mortality following acute ST-elevation MI, with a higher proportion of men than women dying before hospital admission and a higher proportion of

women than men dying after admission to hospital. In turn, more women than men reaching the hospital develop cardiogenic shock, heart failure, cardiac rupture, stroke, and major bleeds[1,3,4,6,9,10,13]. Thus, the reported sex-based difference in total mortality from acute ST-elevation MI based on in-hospital data may be more elusive than real. On the other hand, important gender differences seem to exist in the timing and mechanisms of death following MI, men dying more of early arrhythmias and women more of delayed heart failure.

A known but rather neglected gender-difference concerns the autonomic nervous system and its response to myocardial ischemia, which may be critical for the early arrhythmic deaths related to acute MI. In healthy middle-aged subjects, analyses of heart rate variability and heart rate dynamics show enhanced vagal tone in women compared to men[14,15]. A decreased vagal withdrawal has been reported in women more than in men during conditions that stimulate the adrenergic autonomic system, including waking, upright posture and REM sleep[14-17]. In addition, women have been found to exhibit enhanced vagal activation during angioplasty-induced coronary occlusion[18], with a higher incidence of bradycardia, hypotension, or both, paralleled by increased heart rate variability[18]. Overall, these findings indicate a shift of cardiac autonomic balance towards enhanced vagal activity in women compared to men. This may provide women with some protection against malignant arrhythmias and sudden cardiac death[19,20].

Prospective studies in the general population[21] and in patients with stable angina[22] indicate that women do in fact exhibit a lower incidence of sudden death than men at any level of multivariate risk. The Framingham study, in subjects aged 30 to 62 years at entry, followed over 38 years, found that 16 vs 34% of all coronary deaths were sudden in 2873 women vs 2336 men ($p < 0.0004$)[21]. In the Swedish Angina Pectoris Aspirin Trial, among 2035 patients with stable angina (on average 67 years old; 48% women) followed for a median of 4 years, the combined incidence of MI and sudden death was also about one half in women compared to men (relative risk 0.44; 95% confidence interval 0.33-0.61)[22]. This sex-based difference in outcome among patients with chronic angina does not appear to be explained by differences in the severity of coronary atherosclerosis[23]. As in men, sudden cardiac death in women is usually a ventricular-arrhythmic death[24].

Thus, gender differences in the incidence of sudden death and in autonomic nervous activity (under basal conditions and in response to coronary occlusion or to adrenergic stimulation) suggest that women with acute MI may be less prone to early malignant arrhythmias compared to men. The available data suggest that enhancement of strategies for the early management and prevention of ventricular tachyarrhythmias in men and for the early detection and treatment of heart failure in women should prove useful to reduce the death toll from acute MI. The apparent paradox between a lower female incidence of ischemic heart disease and the higher female mortality after ST-elevation MI probably needs to be revised in light of the evidence of similar overall mortalities in men and women when out-of-hospital deaths are considered.

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