Correspondence

Gender and outcome from acute myocardial infarction and secondary stroke

Dear Sirs,

Research on sex difference in mortality after myocardial infarction (MI)since the 1990s has been debated and increased. Several observational studies have shown that younger women, in particular, seemed to have higher mortality rates than men of similar age during the two-year or longer follow-up, although these studies were mainly from the USA.[1-3] Recent American studies have also found that, even after full adjustment for potential risk factors, excess risk for in-hospital mortality for women was still noted, particularly among those <50 years old with acute ST-segment elevation MI, leading to 98% (odds ratio [OR] 1.98, 95% confidence interval [CI] 1.26 to 3.12) greater odds of death than men.[4] What was additionally observed was that, in general, female patients tended to have significantly higher comorbidity scores, and were less likely to undergo revascularisation (percutaneous coronary intervention or coronary artery bypass grafting surgery) than their counterparts during hospitalisation. Moreover, during hospitalisation women were found to be less likely to have ventricular tachycardia and ventricular fibrillation, but more likely to have atrial tachycardia and atrial fibrillation, than men.

Fatal and non-fatal stroke events higher in women post-MI

In Sweden, a recent study has reported that mortality after acute MI complicated by ischaemic stroke has decreased for both men and women between 1998 and 2008,[5] and the authors concluded that evidence-based therapies seemed to explain the reduction of mortality post-MI. However, the proportions in females have actually increased over the last decade, from 38.2% to 42.1% in non-fatal stroke events and from 46.4% to 50.1% in all stroke events, including both fatal and non-fatal. Were those therapies better for men only? On the other hand, some concerns on the adherence to evidence-based pharmacotherapy and long-term mortality after acute MI could be of interest.

In Canada,[6] among statin users, compared with their high-adherence counterparts, the risk of mortality was greatest for low adherers (deaths in 261/1071 [24%] *vs.* 2310/14,345 [16%]; adjusted hazard ratio 1.25; 95% CI 1.09–1.42; p=0.001) and was intermediary for intermediate adherers (deaths in 472/2407 [20%]; adjusted hazard ratio 1.12; 95% CI 1.01–1.25; p=0.03). A similar but less pronounced dose-response-type adherence-mortality association was also observed for beta blockers, although mortality was not associated with adherence to calcium channel blockers.

The possibility of low-adherence to pharmacotherapy among Swedish women is, however, unclear. Another Canadian study has revealed that psychosocial factors such as post-MI depression can be a predictor of one-year cardiac mortality and the risk effect could be minimised with the advancement of social support.[7] In other words, by providing more social support, depression symptoms can be lessened leading to an improved prognosis for MI and a better survival, together with increasing higher adherence of pharmacotherapy. The disparity in the survival post-MI between male and female patients is continuing to widen, and we need to close the gap in survival rates among patients to prevent further unnecessary deaths in a timely manner.

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Conflict of interest

None declared.

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A response from Professor Jagdish Sharma

Dr Shiue and colleagues have highlighted two aspects of acute myocardial infarction (AMI) in relation to mortality with reference to gender differences. The first is of higher mortality in women after AMI and secondly a higher mortality in patients developing stroke following AMI.

There has been great interest in gender differences in AMI-related mortality over the last 30 years or so. There has been a steady decline in AMI and the related mortality in both men and women during this period, probably due to effective preventive measures of the risk factors and the management of AMI in acute phase with well-researched interventions of thrombolysis and percutaneous coronary intervention (PCI).

The authors refer to two studies, one by Zhang et al.[4] describing higher AMI mortality in young women with ST-elevation myocardial infarction (STEMI) and the other by Brammås et al.[5] who describe a falling trend of myocardial mortality in Sweden over the 10-year period from 1998, but, more significantly, a higher mortality in patients developing stroke after AMI. Women have, however, also benefitted from the reducing rates of AMI during the study period, albeit to a slightly lesser extent. It is, however, not possible to draw any conclusions on the basis of these two studies.

Women admitted with AMI have a higher burden of risk factors, tend to be older and have pre-morbid disability. In addition, they have a spectrum of risk factors unique to female gender, which may not only predispose them to more severe AMI, but may also lead to an

attenuated response to interventions. In the study by Zhang et al.,[4] women had a lower level of acute intervention and this may be an explanation of their higher mortality, in addition to any gender-related hormonal factors. Less intervention in females has been shown to be associated with poor outcome,[8] but not if they receive equal interventions, which is associated with adjusted mortality similar to men.[9] Thus, women have an equal response to intervention and the higher mortality in the Zhang et al. study may simply be explained by fewer interventions being offered to women. A German study has revealed higher mortality in younger women as compared with men following AMI, possibly due to their higher prevalence of diabetes and cardiac failure and less inpatient intervention.[10]

Patients developing acute stroke (AS) after AMI have a higher mortality, 36.5% versus 18.3% in the Brammås study. A number of non-neurological variables predict stroke mortality. Cardiovascular factors of atrial fibrillation, but more significantly, the presence of cardiac failure is highly predictive of mortality following AS.[11] Interestingly, the patients dying after AMI, with or without AS, in the Brammås study had a much higher prevalence of congestive cardiac failure (CCF) and were, thus, on diuretics. In this study, there was a falling trend of mortality from 1998 in AS following AMI in the whole cohort. This is mirrored by a falling prevalence of CCF during the study period from 25.8% in 1998 to 22.1% in 2008, despite a rise in atrial fibrillation (AF). Gender-related trends in mortality are not fully described in the paper by Brammås, but it is possible that women had a higher trend to mortality secondary to a higher frequency of CCF, since they have a higher frequency of AF. The explanation might be a more severe AMI in women leading to cardiac dysfunction as a cause of stroke and subsequent mortality. Female stroke patients have a higher level of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) (unpublished data). Interestingly, in the Brammås study, the patients who developed AS and mortality had less acute intervention for AMI. There is evidence that the patients developing CCF after AMI continue to have poor survival,[12] and the prevalence of CCF after AMI may be rising.[13]

The relative trend in falling mortality after AMI was less pronounced in women. There is, thus, a concern that women may not be doing well after any vasculo-occlusive events, be it an acute myocardial infarct or acute stroke, and may not respond equally well to interventions. Some of this might be secondary to hitherto unrecognised genetic and genomic differences in men and women. The fact that women have some unique gender- and hormonal-related risk factors for poor outcome after AMI and AS is further signified by the American Heart Association and American Stroke Association developing specific guidelines for stroke prevention in women.[14] More research is required to unravel gender-related differences with a reference to unique risk factors in women for mortality and longer-term outcome following acute MI and stroke. In the current practice, preventive measures should be appropriately and judiciously applied equally to prevent vasculo-occlusive disease in men and women.

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References

1. Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? *Circulation* 1995;**91**:1861–71. http://dx.doi.org/10.1161/01.CIR.91.6.1861

2. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM; for the National Registry of Myocardial Infarction 2 Participants. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med* 1999;**341**:217–25. http://dx.doi.org/10.1056/NEJM199907223410401

3. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173–81. http://dx.doi.org/10.7326/0003-4819-134-3-200102060-00007

4. Zhang Z, Fang J, Gillespie C, Wang G, Hong Y, Yoon PW. Age-specific gender differences in in-hospital mortality by type of acute myocardial infarction. *Am J Cardiol* 2012;**109**:1097–103. http://dx.doi.org/10.1016/j.amjcard.2011.12.001

5. Brammås A, Jakobsson S, Ulvenstam A, Mooe T. Mortality after ischemic stroke in patients with acute myocardial infarction: predictors and trends over time in Sweden. *Stroke* 2013;**44**:3050–5. http://dx.doi.org/10.1161/STROKEAHA.113.001434

6. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;**297**:177–86. http://dx.doi.org/10.1001/jama.297.2.177

7. Frasure-Smith N, Lespérance F, Gravel G *et al*. Social support, depression, and mortality during the first year after myocardial infarction. *Circulation* 2000;**101**:1919–24. http://dx.doi.org/10.1161/01.CIR.101.16.1919

8. Jneid H, Fonarow GC, Cannon CP *et al*. Sex differences in medical care and early death after acute myocardial infarction. *Stroke* 2008;**118**:2803–10. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.789800

9. Nauta ST, Jaap WD, van Domburg RT, Akkerhuis KM. Sex related trends in mortality in hospitalised men and women after myocardial infarction between 1985 and 2008. Equal benefit for women and men. *Circulation* 2012;**126**:2184–9. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.113811

10. Heller G, Babitsch B, Gunser C, Mockel M. Mortality following myocardial infarction in women and men. *Dtsch Arztebl Int* 2008;**105**:279–85. http://dx.doi.org/10.3238/arztebl.2008.0279

11. Sharma JC, Fletcher S, Vassallo M, Ross I. Cardiovascular disease and outcome of acute stroke influence of pre-existing cardiac failure. *Eur J Heart Failure* 2000;**2**:145–50. http://dx.doi.org/10.1016/S1388-9842(00)00067-2

12. Chen J, Hsieh AF, Dharmarajan K, Masoudi FA, Krumholz HM. National trends in heart failure hospitalisation after acute myocardial infarction for medicare beneficiaries. *Circulation* 2013;**128**:2577–84. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003668

13. Velagalleti RS, Pencina MJ, Murabito JM *et al*. Long term trends in incidence of heart failure after myocardial infarction. *Circulation* 2008;**118**:2057–62. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.784215

14. Bushnell C, McCullough LD, Awad IA *et al*. Guidelines for prevention of stroke in women. A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;published online 6 February 2014. http://dx.doi.org/10.1161/01.str.0000442009.06663.48