

Coronary Heart Disease Risk Factors and Mortality

To the Editor: Dr Canto and colleagues¹ found that hospital mortality increased as the number of cardiovascular risk factors declined. This inverse relationship is perplexing and the potential explanations discussed by the authors appear not completely satisfactory.

The authors just considered the number of risk factors, whereas the severity of each factor was not evaluated. Blood pressure, plasma glucose, and lipids are continuous, not discrete, variables that exert a dose-dependent effect on cardiovascular risk.² It would be of interest to see the results of the analysis conducted considering these parameters, which also would help to clarify the still controversial association of the metabolic syndrome and mortality after myocardial infarction (MI).³

It also would be interesting to know if the inverse correlation is still present after correction for one of the most important predictors of mortality after acute coronary syndrome,⁴ the baseline infarct size.

Last, traditional cardiovascular risk factors do not fully explain the pathophysiological process of atherothrombosis in acute ischemic heart disease. Several studies have identified a series of emerging biomarkers reflecting thrombosis, inflammation, and oxidative stress.⁵ Do the authors have any data about this issue?

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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To the Editor: The study by Dr Canto and colleagues¹ provides an example of an epidemiological phenomenon that deserves wider recognition. Differential selection from an underlying population cohort into a study data set can reverse the direction of observed associations, making a deleterious factor appear protective. It is well-known that conditioning on a variable that is affected by both an exposure and outcome can produce a distortion

known as selection bias.² Admission into the analysis data set in this study was a function of both the exposure (number of cardiovascular risk factors) and the outcome (all-cause, in-hospital, or 30-day mortality) because deaths occurring before hospitalization and patients with existing cardiovascular disease diagnoses were excluded. Approximately 30% of MIs lead to death prior to hospitalization.³ In the study, 75% of those who were admitted to the hospital after their MI were excluded (1.62 million of 2.16 million; Figure 1 in the article).

The combined effect of these 2 selection mechanisms means that individuals with more cardiovascular risk factors were more likely to be excluded. If an increased number of risk factors accelerate mortality so that more events occur in the prehospital window rather than during hospitalization or 30-day follow-up, risk factors will appear to be protective.⁴ The study results are therefore understandable in terms of selection bias and require no elaborate speculation about pathophysiological processes¹ or "novel but as-yet uncharacterized and deadly CVD [cardiovascular disease] risk factors."⁵

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Table. Crude Hospital Mortality of Patients With Myocardial Infarction (MI) and Previous Cardiovascular Disease^a

	No. of Risk Factors at Presentation ^b					
	0	1	2	3	4	5
No. (%)						
MI (N = 630 210)	83 978 (13.3)	195 238 (31.0)	205 224 (32.6)	111 384 (17.7)	30 893 (4.9)	3493 (0.6)
Crude hospital mortality	15 790 (18.8)	30 825 (15.8)	25 894 (12.6)	10 336 (9.3)	2293 (7.4)	220 (6.3)

^aData are from the National Registry of Myocardial Infarction, 1994-2006. Excluded patients without prior cardiovascular disease, those who had been transferred, and those with missing data.

^bFive major risk factors: smoking, diabetes, dyslipidemia, hypertension, and family history of coronary heart disease.

4. Flanders WD, Klein M. Properties of 2 counterfactual effect definitions of a point exposure. *Epidemiology*. 2007;18(4):453-460.

5. Peterson ED, Gaziano JM. Cardiology in 2011—amazing opportunities, huge challenges. *JAMA*. 2011;306(19):2158-2159.

In Reply: Our study challenges conventional wisdom that patients with more coronary heart disease (CHD) risk factors have worse outcomes following their first MI. We found that patients with multiple CHD risk factors presented much earlier in life with MI and had lower hospital mortality than patients with fewer or no risk factors. We confirmed that the high prevalence of risk factor exposure in patients with MI was consistent with the prior literature.

Dr Santulli seeks additional information that may enhance our study, such as the influence of a dose-dependent effect of CHD risk factors, presence of the metabolic syndrome, other novel risk markers, and infarct size. Unfortunately, these factors were not available in the National Registry of Myocardial Infarction. Although baseline infarct size was not recorded, the finding of an inverse relationship between the number of CHD risk factors and mortality was consistently observed among patients with low-, intermediate-, and high-risk features using 2 well-validated measures of infarct severity (Killip classification and TIMI Risk Index).

Ms Banack and colleagues suggest that bias in the selection of our study cohort could have reversed the direction of observed associations, making a deleterious factor appear protective. An MI cohort with no previous cardiovascular disease represents a more uniform population to study given the differences in management and treatment after atherosclerosis is manifest. Excluding patients with previous cardiovascular disease simply presents findings generalizable only to patients without previous disease. When our analysis was rerun using only an MI cohort with previous cardiovascular disease (N=630 210), our results did not change appreciably (TABLE).

Banack et al also raise the possibility that patients with multiple CHD risk factors might have died disproportionately before hospitalization. This is merely speculative. No prior study has examined the relationship between the number of CHD risk factors and mortality among patients with suspected MI who died prior to hospital arrival, perhaps due to the challenges of confirming MI in the prehospital setting.

In the discussion of our findings, we devoted 4 paragraphs to methodological issues that may have limited generalizability and inferences of causality, including risk factor misclassification, bias with case ascertainment, residual confounding, healthy survivor bias, and index event bias.¹ Index event bias (also known as reverse epidemiology or collider stratification bias) may affect research that examines disease progression and severity when there are multiple risk factors for progression or for severity that are also risk factors for having the disease in the first place.¹ We also present biologically plausible alternative interpretations of our findings, including receipt of more aggressive treatments and follow-up care among patients with multiple CHD risk factors.

In summary, we report an unexpected and possibly controversial association that, like all observational findings, should be considered hypothesis-generating and further explored in terms of health care provided to patients who reach the hospital alive with first MI.

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Urinary Sodium Excretion and Cardiovascular Events

To the Editor: Dr O'Donnell and colleagues, in their study on urinary sodium excretion and risk of cardiovascular events,¹ reached the counterintuitive conclusion that sodium restriction increased the risk of cardiovascular events, which runs counter to the consistent evidence that, in individuals with hypertension, decreased sodium intake reduces blood pressure and improves the effectiveness of treatment with antihypertensive agents.²⁻⁴