Reviewer’s report

Title: ACE gene insertion/deletion polymorphism has a moderate influence on the acute development of left ventricular dysfunction in patients with ST elevation myocardial infarction treated with primary PCI

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Reviewer: Philip Binkley

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In this manuscript, the investigators describe the relation between the presence of the Deletion polymorphism (D) of the ACE gene to a variety of measures in patients who have undergone PCI for acute coronary artery syndromes. They find in particular, after adjustment for other covariates, a relation between presence of the D polymorphism and increased end-systolic volume normalized for body surface area and ejection fraction with higher volumes and lower ejection fractions in those with the D polymorphism. In addition, those with the D polymorphism had a higher level of ACE activity. The tacit implication is that owing to the relation between ventricular volumes and ejection fraction and long term outcome following myocardial infarction, the presence of the D polymorphism may predict outcome in patients undergoing PCI for acute coronary events.

A major flaw of this investigation is the assumption that the Insertion/Deletion (I/D) genotypes of the ACE gene constitute the functional polymorphisms governing ACE activity and outcomes. More recent data published in 2009 by Johnson and colleagues in Clinical Pharmacology and Therapeutics describe two promoter polymorphisms that appear to be the true functional gene variants demonstrated by allelic expression imbalance studies. A multitude of previous studies examining I/D genotypes have had such variable results in associating cardiovascular outcomes that there has emerged genuine doubt regarding the functional significance of the I/D polymorphism. The identification of promoter polymorphisms that are associated with genuine expression imbalances and have been shown to have impact on outcomes in hypertensive populations strongly suggests that these gene variants are truly functional and therefore most likely associated with outcomes. Therefore, the reliance of this study on the D/I genotypes which have become suspect in terms of functional significance greatly weakens the findings of this paper.

Although the authors find statistically significant differences in genotypic groups, these differences are small and it is difficult to believe they are clinically relevant. The differences in end-systolic volume and ejection fractions are of marginal clinical significance, even if statistically significant. Similarly, it Table 2, many of the associations are weak although there is a statistically significant linear relationship. For example, although there is a significant relationship between the
EDV normalized for body surface area and ACE activity, only 9% of the variation of ACE activity is explained by the EDV.

The authors state that the genotypic groups remain independent predictors even when adjusting for other variables. However, this is not the same as testing for confounding. Two variables may remain as independent predictors in a statistical model, yet one may still confound the other. This is usually reflected in large changes in the coefficients of one of the variables when the confounding variable is added. To this point, a larger proportion of patients having the D polymorphism were diabetic. It is of course known that diabetic patients have worse outcomes and therefore, without more information regarding the modeling process, the claim that the genotypes independently predict outcomes is difficult to support. To this point, better descriptions of the modeling process, what variables were tested as covariates, and the results of different models would strengthen the manuscript. It is stated that logistic regression modeling was used in some cases. Yet it is unclear as to what was the outcome variable.

There are other methodological concerns. The authors note that Teicholz method of ejection fraction determination was used in some subjects. This is a much less reliable measure and appears to have been mixed with two dimensional estimates of ejection fraction. If one group had a greater proportion of ejection fractions determined by the Teicholz methods, a difference in ejection fractions could have resulted on this basis alone. The authors also report determining ventricular dP/dT based on measures from a fluid filled catheter system. Unless such a system is appropriately damped for such readings, the measures are unreliable.

It is unclear why the proportion of male participants is so great in both genotypic groups. Women are afflicted by coronary artery events to the same, or in some groups, greater extent as men. The great majority of men enrolled in the study may reflect a study bias that can alter findings.

The discussion is entirely too long. Much of the discussion reviews past literature rather than describing how the authors feel their findings add to this literature or explain gaps in the understanding the impact of genetic variations on disease outcomes.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have no declarations.