EDITORIAL

Outcome following percutaneous coronary intervention: not, so far, in our genes

B Keavney

The contribution of genes to outcome following percutaneous coronary intervention appears to be somewhat limited

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Certain well recognised clinical and angiographic factors predict a poor outcome following percutaneous coronary intervention (PCI). The majority of such poor outcomes, particularly after elective PCI, are caused by restenosis requiring re-intervention. Restenosis has been fitted, somewhat uncomfortably, into the standard multifactorial model of complex disease in which genetic susceptibility, combined with environmental exposure, determines disease risk. The basic tenet of this model is almost uniquely untestable for restenosis, since classical genetic epidemiologic studies of twins or extended families to establish the heritability of the phenotype are not practical. However, given the known importance of anatomical factors, procedural factors and diabetes in determining the risk of restenosis, any genetic effect seems *a priori* likely to be small. Possible genetic contributions to outcome after PCI can be relatively simply tested by comparing genotype frequencies at polymorphisms of candidate genes between cases—for example, of major adverse coronary events (MACE) after PCI—and suitably matched controls. A very large number of single nucleotide polymorphisms can now be easily typed by using the polymerase chain reaction (PCR) to amplify the genetic segment of interest, followed by a variety of techniques to identify the different alleles. As has been shown for a number of genetic polymorphisms hypothesised to contribute to the risk of coronary heart disease and other “complex” diseases, reliable results regarding the presence or absence of such small effects require individual studies or meta-analyses of thousands of cases.¹ A variety of polymorphisms have been typed in a large number of studies of patients undergoing PCI, most of which have involved less than 100 cases of restenosis or MACE.

In this issue, Hamon and colleagues report one of the larger investigations, including 1010 patients.² The long term occurrence of death, non-fatal myocardial infarction, unstable angina, and revascularisation was monitored to a median of two years following PCI. There were 361 events, of which 201 were revascularisations. (It is worth recalling that the power of such post-PCI studies comes, as for all prospective study designs, not from the total number of patients enrolled but the number of events occurring over the follow up period.) Hamon and colleagues typed the angio-

tensin I converting enzyme (ACE) insertion/deletion (I/D) polymorphism.² This polymorphism, which is strongly associated with plasma ACE concentrations, was originally found to be associated with myocardial infarction risk by Cambien and colleagues in 1992 in a study of 610 cases; larger scale investigations and meta-analysis of around 50 studies involving a total of over 10 000 cases subsequently failed to confirm the association.^{1,3} Given the central role of ACE in cardiovascular physiology, it is perhaps not surprising that the I/D polymorphism has been typed in case-control studies with many different end points, but for most of these, insufficient numbers of events have been studied for robust conclusions to be drawn. In general, the hypothesis tested has been that the DD genotype (which is associated with the highest plasma ACE concentrations) is associated with risk when compared with the ID and II genotypes. Hamon and colleagues found that recognised risk factors (age, diabetes, ejection fraction, and severity of coronary disease) predicted a poorer prognosis following PCI, but that there was no association between ACE genotype and outcome.²

ACE I/D POLYMORPHISM AND RESTENOSIS

These results add further weight to the view that the ACE I/D polymorphism is not significantly associated with restenosis or other adverse consequence after PCI. A recent meta-analysis of 16 studies including 1683 patients with restenosis among a total of 4631 participants showed an odds ratio for restenosis with the DD genotype of 1.23 (99% confidence interval (CI) 1.03 to 1.46), but also showed that, when studies were grouped by size, there was significant ($p = 0.02$) heterogeneity between estimates of the odds ratio with DD genotype in smaller and larger studies.⁴ Smaller studies tended to be more positive (combined odds ratio 1.94, 99% CI 1.39 to 2.71, for the 11 studies involving less than 100 cases of restenosis) than larger ones (combined odds ratio 0.92, 99% CI 0.72 to 1.18, for the two studies involving more than 200 cases of restenosis). A similar trend towards more extreme results in smaller genetic association studies had been observed in a meta-analysis of studies of myocardial infarction that had typed the ACE I/D

Correspondence to:
Dr Bernard Keavney,
Institute of Human
Genetics, Central Parkway,
Newcastle-upon-Tyne
NE1 3BZ, UK;
b.d.keavney@ncl.ac.uk

Abbreviations: ACE, angiotensin I converting enzyme; I/D, insertion/deletion; MACE, major adverse coronary events; PCI, percutaneous coronary intervention; PCR, polymerase chain reaction

polymorphism.¹ Thus, publication bias seems capable of producing artefactual associations at least as large as those that might be expected for genetic polymorphisms in complex diseases. It is to the credit of Hamon and colleagues that they draw attention to the critical importance of study size by contrasting their present negative results with those of a previous analysis showing positive findings in their first 368 patients.² The absence of an effect of genotype is entirely consistent with the results of randomised controlled trials of ACE inhibition after PCI, which have failed to show any significant effect on restenosis.⁵⁻⁶ It has been suggested that ACE genotype or ACE inhibition might be associated with restenosis only in patients receiving stents.⁷ However, randomised trial data are lacking, and meta-analysis of available genetic studies suggests no heterogeneity between patients treated with balloon angioplasty alone and with stenting with regard to the null effect of ACE genotype on restenosis.

OTHER POLYMORPHISMS

What of other polymorphisms that have been typed in patients undergoing PCI? The data are generally even weaker than for the ACE I/D polymorphism. A polymorphism of platelet glycoprotein IIIa known as Pl A1/A2 has been studied in some 4000 PCI patients (about 650 events) and was the subject of a recent meta-analysis.⁸ Glycoprotein IIIa is a key contributor to platelet function as it is a constituent of the platelet fibrinogen (glycoprotein IIb/IIIa) receptor. Genotype at the Pl A1/A2 polymorphism has been associated with aspects of platelet function. Platelets from A2 allele carriers have greater aggregation to adrenaline (epinephrine), and there are data to suggest they are less completely inhibited by abciximab.⁹ The polymorphism is thus a good candidate for early thrombotic complications after PCI, though the biological rationale for its hypothesised role in restenosis seems less clear. As the frequency of the A2 allele is only about 0.15, and A2A2 homozygotes therefore rare, most analyses have compared A2 allele carriers with non-carriers. Walter and colleagues found a fivefold increase in stent thrombosis in the first month in A2 allele carriers in just 11 cases and 307 controls⁹; although larger studies have not confirmed this, no study of one month events has, so far, enrolled greater than 100 cases.⁸⁻¹⁰⁻¹¹

With respect to restenosis, there is only one substantial study, that of Kastrati and colleagues involving 466 cases.¹² That study showed an odds ratio for restenosis in an analysis adjusted for a variety of patient and procedural variables of 1.35 (95% CI 1.07 to 1.70). Although a suggestive result, the width of the confidence interval illustrates the very substantial residual uncertainty, and a much larger number of patients would need to be studied to confirm or refute these preliminary findings. In view of the difficulty of establishing large single centre cohorts, how could this be done? One possibility is that entry to this field will be restricted to those

few investigators in possession of large cohorts originally derived from multicentre clinical trials. However, if the investigators who conducted the 16 studies of the ACE I/D polymorphism and restenosis published before July 2001 were to undertake a collaborative analysis of P1 A1/A2 genotype, the 1683 cases included in those studies would provide substantial power to resolve this issue. If genetic association studies in complex diseases are ever to escape from their image as unreliable science, a paradigm shift regarding collaborative analysis and publication of multiple datasets seems likely to be required. In the future, genetic factors influencing outcome may be identified by adequately powered studies. For the moment, however, PCR following PCI remains an uninformative investigation.

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