Angiotensin converting enzyme insertion or deletion polymorphism and coronary restenosis: meta-analysis of 16 studies

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Abstract

Objective To assess the association between genotype at the insertion or deletion polymorphism of the angiotensin converting enzyme gene and risk of coronary restenosis after percutaneous coronary intervention.

Design Meta-analysis of studies before July 2001 that reported on these genotypes and risk of coronary restenosis after a percutaneous coronary intervention, with or without coronary stenting.

Results 16 studies, involving 4631 patients undergoing a percutaneous coronary intervention, yielded 1683 patients with restenosis after a mean weighted follow up of 5.5 months. The combined odds ratio for restenosis in people with the DD genotype was 1.23 (99% confidence interval 1.03 to 1.46). When studies were grouped by size, however, the combined odds ratios for restenosis in people with the DD genotype were 1.94 (1.39 to 2.71) for studies with less than 100 cases, 1.33 (0.92 to 1.93) for studies with 100-200 cases, and 0.92 (0.72 to 1.18) for studies with more than 200 cases (trend P=0.02). Similarly, when studies were grouped by genotyping procedures, significantly larger odds ratios were found in the studies that did not conceal disease status from laboratory staff and in the studies that did not use a second polymerase chain reaction amplification to reduce genetic mistyping.

Conclusion Compared with other studies, larger and more rigorous studies show a weaker association between the angiotensin converting enzyme gene DD genotype and restenosis. Publication bias or detection biases can produce artefactual associations at least as large as those that might be expected for common polymorphisms in complex diseases, suggesting the need for larger and more rigorous genetic epidemiological investigations than are now customary.

Introduction

Restenosis after a percutaneous coronary intervention is one of the principal limitations of this technique, occurring in up to 50% of patients undergoing the procedure without stenting and in about 20% of patients receiving stents. Despite a lack of good evidence that susceptibility to restenosis is genetically determined, several studies have investigated polymorphisms that might be associated with restenosis. As the angiotensin converting enzyme insertion or deletion (I/D) polymorphism is strongly associated with plasma and cellular angiotensin converting enzyme concentrations, it has been considered a strong candidate. It has been suggested that the incidence of coronary restenosis after a percutaneous coronary intervention is much higher in patients with the angiotensin converting enzyme DD genotype (which is associated with particularly high plasma angiotensin converting enzyme levels) than in others, but published
observational studies are conflicting.\textsuperscript{3–18} To help clarify the evidence we considered all available relevant studies in a meta-analysis.

Methods

We sought studies published before July 2001 of the angiotensin converting enzyme insertion or deletion polymorphism and coronary restenosis after a percutaneous coronary intervention, with or without coronary stenting, by computer based searches (Medline, Embase, PubMed, Web of Science), reviews of reference lists, hand searching relevant journals, and correspondence with authors. For the electronic searches we used combinations of key words relating to the angiotensin converting enzyme gene (for example, angiotensin converting enzyme, ACE, polymorphism, insertion/deletion, I/D, D/I) and to restenosis (for example, coronary, restenosis, percutaneous, angioplasty, PTCA, stent, stenting). We included all identified studies. Articles in languages other than English were translated.

From each study we abstracted (supplemented by correspondence with investigators) geographical location, race of participants, numbers of cases and controls, the coronary intervention procedure, definition of restenosis, frequency of insertion or deletion genotypes, genotyping methods and laboratory procedures, mean age, and duration of follow up.

We estimated odds ratios by comparing cases who developed coronary restenosis after a percutaneous coronary intervention with controls who did not within the same study. We did this under the prior hypothesis that individuals who were homozygous for the angiotensin converting enzyme D allele were predisposed to restenosis compared with those with the ID or II genotypes.\textsuperscript{3–10}

Results

We identified 16 relevant studies concerning a percutaneous coronary intervention, 11 without stenting (2535 patients) and five with stenting (2096 patients), yielding 4631 patients (94% white) undergoing such interventions.\textsuperscript{5–7} All the studies used quantitative computer assisted methods to define restenosis as a narrowing of the coronary diameter by 50% or more at follow up compared with the minimal luminal diameter immediately after intervention. Overall, 1683 of these patients (mean age 60 years) developed coronary restenosis after a mean weighted follow up of 5.5 months. The studies were conducted in Australia, Chile, France, Germany, Italy, Japan, Spain, Turkey, the United Kingdom, and the United States.\textsuperscript{8–19} Following correspondence with the authors, it was confirmed that genotyping had been performed by staff unaware of the disease status of the patients in four of the five studies with more than 100 cases,\textsuperscript{12–15} compared with only two of the 11 studies with less than 100 cases.\textsuperscript{8–9}

Overall, the combined odds ratio for restenosis in people with the DD genotype was 1.23 (99% confidence interval 1.03 to 1.46; test for heterogeneity \(\chi^2=24.1, \text{df}=15, P=0.06\); fig 1). We found no significant heterogeneity between studies of percutaneous coronary intervention with stenting and those without stenting (combined odds ratios for the DD genotype of 1.17 \(v\) 1.27 respectively; \(\chi^2=0.23, \text{df}=1, P=0.6\)). When studies were grouped by size, however, the combined odds ratios for restenosis were 1.94 (1.39 to 2.71) for the 11 studies with less than 100 cases,\textsuperscript{3,5,7,9,11–15} 1.33 (0.92 to 1.95) for the three studies with 100-200 cases,\textsuperscript{8,10,16} and 0.92 (0.72 to 1.18) for the two studies with more than 200 cases (fig 2).\textsuperscript{17,18} A test for trend across these three groups of studies was significant (\(\chi^2=5.6, \text{df}=1, P=0.02\)). Similar results were observed when odds ratios for restenosis were calculated per D allele in these three groups (1.74 \(v\) 1.00; \(P=0.98\), respectively). When studies were grouped by genotyping procedures, significantly larger odds ratios were observed in the studies that did not conceal disease status from laboratory staff (combined odds ratios for the DD genotype of 1.87 \(v\) 1.92 respectively; \(\chi^2=9.7, \text{df}=1, P=0.002\)) and in the studies that did not use a second polymerase chain reaction amplification to reduce mistyping of angiotensin converting enzyme ID heterozygotes as DD (1.55 \(v\) 1.13, respectively; \(\chi^2=4.05, \text{df}=1, P=0.04\)).

Discussion

Weaker associations between the angiotensin converting enzyme DD genotype and restenosis were found in larger and more rigorous studies than in other studies. We had observed a similar trend in published studies of...
Restenosis after a percutaneous coronary intervention is one of the principal limitations of the technique. Genotype at the angiotensin converting enzyme insertion/deletion polymorphism is proposed to be important in restenosis.

What this study adds

Weaker associations between the angiotensin converting enzyme DD genotype and restenosis were found in larger and more rigorous studies than in other studies.

Publication bias or detection biases, or both, can produce artefactual associations at least as large as those that might be expected for common polymorphisms in complex diseases.

Science commentary: Coronary angioplasty and stenting

Two main interventions are available for opening up blocked coronary arteries: balloon angioplasty and open heart surgery. In percutaneous coronary angioplasty a wide lumen catheter is fed from the groin up to the aortic root and into the coronary arteries. A guide wire is passed through the catheter and across the stenosis in the coronary artery. The wire is used to guide a balloon (with a stent mounted on it if necessary) into the diseased section of the artery. The balloon is inflated, pushing the atheroma outwards and enlarging the lumen of the artery. A stent can be expanded to fill the artery. Once the stent is in place (confirmed by angiography), the wires and the catheter are removed.

Arterial restenosis remains a serious problem after percutaneous coronary angioplasty. It tends to occur within three months of the procedure and is due to proliferation of smooth muscle as a reaction to vessel injury. Restenosis used to occur in over 30% of patients after percutaneous coronary angioplasty, but with the use of stents and advances in stent design and improved techniques for implanting them the rates now lie between 10% and 20%. This is comparable to the 10% of vein grafts that are lost in the year after bypass grafting. The main risk factors for restenosis after percutaneous coronary angioplasty are diabetes, thrombus formation or inflammation in the coronary tree, and small vessel size.

Two recent trials found no difference between percutaneous coronary angioplasty plus stenting and bypass surgery for death or myocardial infarct in


