implications that under-use of health care options can have on the health of the population. Therefore, practice guidelines are necessary to influence decision making, but should not be used to enforce medical decisions. Sufficient flexibility and divergence from tailor-made diagnostic and therapeutic strategies should be allowed. Guidelines should be a reference standard against which individual decision making should be assessed, and if in the view of a responsible physician a particular strategy is justifiable, then it should be implemented. Hence the take home message is: coronary revascularization needs to be done when it needs to be done.

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Increased QT dispersion with the D-allele of the ACE polymorphism

See page 663 for the article to which this Editorial refers

Sudden cardiac death may account for up to half the mortality in patients with heart failure[1]. ACE inhibition reduces the risk of ventricular arrhythmia in heart failure, an effect paralleled by a reduction in sudden death of around 50% compared to vasodilator therapy[2]. The HOPE study[3] has extended our knowledge of the benefits of ACE inhibition in those at coronary risk but with normal left ventricular function, demonstrating reductions in death, myocardial infarction and cardiac arrest as well as heart failure. A recent meta-analysis has also confirmed that a substantial reduction in sudden cardiac death occurs in patients treated with an ACE inhibitor early after myocardial infarction[4]. Although ACE inhibitors are known to favourably influence the structural remodelling of the heart after myocardial infarction the mechanisms by which they improve survival are not well understood.

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Post myocardial infarction survival has improved with the advent of thrombolysis, early revascularization and the use of adjunctive therapies such as aspirin, beta-blockers, HMG-CoA reductase inhibitors, internal cardiac defibrillators and ACE inhibitors. However, sudden cardiac death due to arrhythmias remains a major cause of mortality among these patients. The relative risks/benefit ratio of pharmacotherapy in this setting and the increased mortality rate associated with some antiarrhythmic drugs has made the demonstration of a significant advantage over and above what has been achieved with established therapy difficult. The targeting of high risk patients from examination of their left ventricular function, heart rate variability, baroreflex sensitivity, late potentials and QT dispersion singly or in combination, post myocardial infarction, may offer ways of facilitating a demonstration of mortality rate benefit from these modalities.

Jeron et al.$^{[5]}$, in this issue, have examined QT dispersion values, as one such marker of high-risk groups, in relation to ACE I/D polymorphism in which the deletion (D) variant is associated with higher circulating and myocardial tissue ACE levels than the insertion (I) allele$^{[6]}$. The interlead variation in QT length on a standard ECG reflects regional repolarization differences in the heart and the dynamic changes in QT dispersion may reflect the underlying pattern of ventricular recovery and excitability which is most pronounced in the acute phase post myocardial infarction. It is a prolongation of this QT dispersion that the authors point out has been associated with ventricular arrhythmias post myocardial infarction and serves as an independent predictor of sudden cardiac death in this setting, as well as in a general population$^{[7]}$.

If higher ACE activity is indeed proarrhythmic, and the corroborating evidence regarding the antiarrhythmic activity of ACE inhibitors is mediated via reductions in ACE activity, we might expect the ACE DD genotype to be associated with prolonged QT dispersion post myocardial infarction. In their retrospective study of patients with a history of prior myocardial infarction from the population-based Augsburg MONICA registry, the authors demonstrate that this is indeed the case. Post myocardial infarction patients homozygous for the D allele had a significantly longer QT dispersion than those of the ID or II genotype. This was in contrast to the lack of an association in the control group of healthy siblings. Multivariate analysis indicates that the ACE polymorphism, left ventricular ejection fraction and left ventricular end diastolic diameter are strong independent predictors of QT dispersion in the myocardial infarction group. Evidently a degree of gene–environment interaction has taken place that is not dependent on a relation with left ventricular dysfunction but with other parameters contributing to, or resulting from, the infarction. The lack of association with left ventricular ejection fraction contrasts with previous findings of an increased ejection fraction in non-infarct patients and a decreased ejection fraction in post-infarct patients with the DD genotype, with evident interaction between the ACE polymorphism, infarction status and left ventricular ejection fraction$^{[8]}$.

**Why might the ACE I/D polymorphism have this effect?**

Not only is there evidence that reduction in ACE and antagonism of the renin-angiotensin system reduce QT dispersion as the authors highlight, but there is increasing evidence that these drugs reduce ventricular arrhythmias. There is extensive animal work demonstrating that ACE inhibitors reduce ventricular arrhythmias during coronary occlusion and protect against reperfusion arrhythmias, effects that can be reproduced with bradykinin infusion and negated by bradykinin B$_2$ receptor antagonism$^{[9]}$.

In clinical studies ACE inhibition also reduces ventricular arrhythmias during myocardial ischaemia and reperfusion in acute myocardial infarction, particularly if given early$^{[10]}$. The AIRE study demonstrated a significant reduction in QT dispersion with ramipril post myocardial infarction$^{[11]}$, a factor that may have contributed to the reduced all-cause mortality and sudden death achieved as well as beneficial effects on arrhythmogenic factors in heart failure such as left ventricular dysfunction, raised catecholamines and hypokalaemia.

However, as the findings of Jeron et al.$^{[5]}$ are independent of left ventricular dysfunction other mechanisms must be involved. Myocardial ischaemia results in the release of various vasoactive substances from coronary vascular endothelial cells, some of which, such as bradykinin, appear to be protective. Indeed, bradykinin infusion exerts a cardioprotective effect during ischaemia, protects against reperfusion arrhythmias, and is associated with improved myocardial energy metabolism with increased glyco gen stores and energy-rich phosphates, and a reduction in lactate and infarct size$^{[6]}$. Bradykinin stimulates nitric oxide (NO) release from the endothelium, significant in view of the loss of antiarrhythmic effect from ACE inhibitors or bradykinin when the NO pathway is blocked pharmacologically. The ACE DD genotype is associated with increased conversion of infused angiotensin I to angiotensin II in humans$^{[12]}$ and a
significant increase in bradykinin degradation\textsuperscript{13}. Attenuated bradykinin degradation is a potential candidate in the antiarrhythmic role of ACE inhibitors and in the reduced QT dispersion seen in the absence of homozygosity for the ACE D allele.

Although a role for ACE inhibition in preventing coronary events now seems clear, the association of the I allele (as a marker of lower ACE activity) with reduced coronary risk is much less clear. As the authors highlight, several studies have shown that the D allele of the ACE genotype is associated with a greater risk of myocardial infarction (and several have not), as well as increased neurohumoral activation, cardiac dilatation and poorer prognosis post myocardial infarction. There is also evidence of an association of the D allele with sudden cardiac death both in a general\textsuperscript{14} and specific population\textsuperscript{15} and the authors highlight the increased risk of malignant ventricular arrhythmias in association with the angiotensin II type 1 CC genotype with the ACE DD genotype. However, analysis of the large ISIS study cohort\textsuperscript{16} has suggested a substantially lesser association between the DD genotype and myocardial infarction (and no predictive value on future survival) than was previously thought. The evidence from ISIS-3 would appear fairly condemning, although the strategy of targeting younger patients may not be the most revealing in respect to the ACE genotype.

Identification of high-risk patients post myocardial infarction has proved a confounding factor in improving mortality rate. The selection of appropriate patients and the development of new agents remains highly desirable, partly due to the risk of some of the interventions currently being evaluated. Safe agents could be widely employed. Does the identification of increased QT dispersion with the DD genotype, and therefore higher ACE, the beneficial effects of ACE inhibitors post myocardial infarction, including a reduction in QT dispersion and sudden cardiac death, suggest a new high risk group to be treated? Or, in the shadow of ISIS-3, with no effect of the ACE polymorphism on prognosis post myocardial infarction, are we simply reminded of a potential mechanism by which these safe drugs need evaluating further in the reduction of arrhythmia and sudden cardiac death post myocardial infarction in all patients? Considering the average age in HOPE, and in this study by Jeron et al\textsuperscript{5}, was considerably greater than that in the ACE genotype study of ISIS-3, were the subjects too young to demonstrate an effect of the D allele in mortality rate post myocardial infarction? Was the reduced cardiovascular mortality rate in the HOPE study not only due to effects on vascular smooth muscle cell proliferation, plaque rupture, endothelial function, left ventricular hypertrophy and fibrinolysis the authors allude to, but also perhaps reduced myocardial fibrosis with a concomitant reduction in QT dispersion and the inducibility of ventricular arrhythmias? Sadly, on average the patients studied by Jeron et al\textsuperscript{5} were 5.5 years post myocardial infarction. To develop a therapeutic strategy using ACE inhibitors as novel antiarrhythmics we must first know what a prospective study tells us about the ACE genotype, its relation to prolonged QT dispersion acutely post myocardial infarction, and crucially any effect on ventricular arrhythmias, sudden cardiac death and mortality rate. Perhaps in the meantime we should ensure that all patients who would currently benefit from an ACE inhibitor are receiving them, and at a dose proven in the large trials to be efficacious.

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Radioactive stents to reduce restenosis: time for an epitaph?

See page 669 for the article to which this Editorial refers

Stents are playing an increasingly important role in percutaneous coronary interventions and they seem to be here to stay. They are easy to implant, safe with new antiplatelet agents and have been shown to reduce restenosis, by eliminating local recoil of the vessel wall, mainly in large vessels and in discrete lesions. However, they have created the new problem of in-stent stenosis, exclusively due to neointimal hyperplasia, and some concern still exists regarding the late arterial wall response, as potentially favourable positive remodelling is also prevented by stents.

The dream of all interventional cardiologists is, one day, to have stents without restenosis. During more than 20 years, the pathobiology of restenosis has stimulated, continuously and extensively, basic and clinical research. Much is already known but the process is, unfortunately, very complex, with too many players involved with iatrogenic aggression to the atherosclerotic plaque and the different components of the arterial wall. To complicate the issue, restenosis varies from place to place, within the same coronary artery or the same patient, and in spite of the same degree of aggression, for instance, the same stent delivery pressure.

The battle against restenosis, particularly in-stent restenosis, continues and is the focus of all our attention. Stimulated by researchers, this battle is also a formidable challenge to the industry, forced to respond to the needs of clinicians and to save the ‘golden egg’ represented by stents.

Ionizing radiation has emerged in the last few years as a potentially important way of reducing restenosis. It provides non-specific breaks in chromosomal DNA and is an effective and potent antiproliferative, when cells are actively dividing at the time of exposure. The concept is simple and radiation therapy appears to be ideally suited for in-stent restenosis[1].

Catheter-based intravascular brachytherapy, mainly from gama and beta sources, based on results in animal models of restenosis demonstrating inhibition of smooth muscle cell proliferation and neointimal hyperplasia, is being clinically used. After careful dose-response studies, which engaged a multidisciplinary clinical research team including radiation oncologists and physicists, results of recent multicentre randomized trials have shown its safety and efficacy[2–4]. Some drawbacks have already been revealed, however, such as late vessel thrombosis requiring more aggressive and extended antiplatelet therapy and the so-called ‘geographic miss’, producing edge stenosis due to inadequate radiation.

Within the context of vascular radiation, the idea of a radioactive stent is, indeed, attractive. Stents would now be used as a platform for local radiation delivery, and they would control the intimal hyperplastic response. In opposition to catheter-based methods, radioactive stents would be simpler, quicker and safer, because of lower radiation activity and lack of dosimetry constraints.