LETTERS TO THE EDITOR

Scope
Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation
Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figure. Please send a copy of your letter on disk. Full instructions to authors appear in the January 1999 issue of Heart (page 104).

Diabetes and coronary artery disease: time to stop taking the tablets

EDITOR—We write in response to the editorial “Diabetes and coronary artery disease: time to stop taking the tablets”1. The authors highlight previous studies where diabetic patients treated with sulphonylureas have an excess cardiovascular mortality during myocardial infarction compared with diabetic patients treated by other means. As Connaughton and Webber point out ischaemic preconditioning has refocused our attention on these trials. The profound protective effects of ischaemic preconditioning are thought to be mediated by opening of a K<sub>ATP</sub> channel, while the hypoglycaemic action of sulphonylureas is mediated by closure of these channels within the membrane of β cells in the islets of Langheran. The authors suggest that it may be simply a case of “adding a potassium channel opener along with insulin during [myocardial infarction] MI”2 to improve outcome in diabetics presenting with infarction. However, recent findings suggest this is an oversimplification and probably incorrect.

One problem is that, there are at least two different K<sub>ATP</sub> channels within cardiac myocytes. Evidence is emerging that it is the mitochondrial and not the cell membrane K<sub>ATP</sub> channels that initiate the cardioprotective effects of preconditioning. This conclusion is based on recent work from Marban’s group.3,4 These investigators show that diazoxide, an agonist that opens mitoK<sub>ATP</sub> channels >1000-fold more potently than their surface counterparts in heart cells, cardioprotects at concentrations that only open the mitoK<sub>ATP</sub> channels. In addition, at this low concentration of diazoxide a specific mitoK<sub>ATP</sub> channel blocker abolishes myocyte protection.

Although nicorandil opens membrane K<sub>ATP</sub> channels, to our knowledge it is not known whether it activates the mitochondrial K<sub>ATP</sub> channel. Indeed its efficacy in treating patients with symptomatic coronary artery disease may equally relate to the fact that nicorandil is a K<sub>ATP</sub> channel opener.

Coronary angioplasty is thought to be a surrogate model of ischaemic preconditioning in man. It has been shown by several groups that the first balloon inflation can protect the myocardium against ST depression in subsequent inflations. The author cites Tomai et al’s paper1 as evidence that the K<sub>ATP</sub> channel is pivotal in protection in this model. They demonstrated that pretreatment with glibenclamide abolished the protection afforded during angioplasty. However, this model has its limitations; first, the preconditioning may not be caused by endogenous adaptation but rather opening of myocardial collateral vessels during the initial ischaemia. Glibenclamide is also known to mimic vasodilatation in vascular smooth muscle and could therefore be preventing coronary collateral recruitment. Glibenclamide also has direct electrophysiological effects, as opening of membrane K<sub>ATP</sub> channels shortens the action potential, causing ST segment shift, the index of depth of ischaemia in this study. As Connaughton and Webber point out, the concentrations of sulphonylureas required to activate cardiac K<sub>ATP</sub> channels is between 100 and 1000 times higher than those required to induce pancreatic insulin release. These observations raise serious doubts as to whether glibenclamide used to treat diabetes will block ischaemic preconditioning.

In conclusion, Connaughton and Webber suggest the need for clinical trials to support the theoretical superiority of insulin. Such a trial has now been published—3867 newly diagnosed diabetics were assigned to insulin therapy (as an agnostic that opens mitoK<sub>ATP</sub> channels) or diet therapy (as opening of membrane K<sub>ATP</sub> channels >1000-fold more potently than their surface counterparts). These investigators show that diazoxide, an ATP-sensitive mitochondrial K<sub>ATP</sub> channel blocker, abolishes myocyte protection.

We agree with Connaughton and Webber that the time to stop taking the tablets is therefore “not yet”. R J EDWARDS R D RAKHIT M S MARBER Department of Cardiology, UMDS, Royal Institute, St Thomas’s Hospital, London SE1 7EH, UK


This letter was shown to the authors, who reply as follows:

We are grateful to Edwards et al for drawing attention to studies pertinent to our editorial that have been published since it was written. The report of the UK prospective diabetes study is especially pertinent. It answers one arm of a hypothesis we considered, finding no difference in long term cardiovascular outcome between diabetic patients treated with insulin or sulphonylureas. This provides strong evidence against our speculation that diabetic patients with coronary disease should not be treated with sulphonylureas.

We also suggested that adding a potassium channel opener to insulin treatment in the setting of acute myocardial infarction might be beneficial. Edwards and colleagues suggest this rationale is based on an oversimplification, and is therefore probably incorrect. This conclusion does not necessarily follow from their premise. It is virtually a truism that any conjecture in science is open to being an oversimplification. We would certainly acknowledge that current understanding of the biology of the K<sub>ATP</sub> channel is incomplete, as signalled by the very recent reporting of a mitochondrial K<sub>ATP</sub> channel, to which Edwards et al allude. They are likewise justifiably cautious about drawing inferences from models of preconditioning such as human coronary angioplasty, and we made it plain that our assessment of such evidence was qualified. It would nonetheless be a mistake to confuse the limitations of current understanding with attempts to find improved treatment strategies. Nicorandil is effective in both diabetes and unstable angina, and the underlying mode of action may be important in endogenous myocardial protection against ischaemia. Its antagonists can block such protection in animal and human models, and have been shown to be inferior to insulin, or to improve the subclinical setting after myocardial infarction. It therefore continues to seem reasonable to us to investigate nicorandil’s effect in diabetic patients who have a high incidence of coronary disease and worse than average consequences from this.

It may indeed be oversimplistic—or even wrong—to suggest that opening potassium channels in myocardial ischaemia or infarction is a good thing, and closing them is a bad thing. This does not mean that such a hypothesis cannot stimulate a useful clinical study, and it was this for which we argued. As Edwards and colleagues are no doubt aware, the way to support or refute a clinical hypothesis is to do the study rather than to predict its outcome from other data. A major purpose of our speculation was to stimulate debate, and we find it gratifying that Marber’s group and ourselves have come to similar conclusions from rather different directions.


Reduction in time delays in administering thrombolytic therapy in acute myocardial infarction

EDITOR—Rao and Joseph’s correspondence in Heart highlighted the reduction in time to administration of thrombolytic therapy in direct admission of patients with suspected acute myocardial infarction to the coronary care unit (CCU) by ambulance staff who had been trained in reading ECGs.

There are four models for admission to hospital of patients with suspected acute myocardial infarction:

1. The patient is evaluated in the A&E department where the first ECG is recorded, then the patient is admitted to CCU where thrombolytic therapy is administered.
2. The patient is admitted to the A&E department, the ECG is recorded and thrombolytic therapy administered.
(3) The patient is admitted directly to the CCU after out-of-hospital ECG recording by paramedics or general practitioners.

(4) ECG is recorded before hospital admission (at home or in the ambulance) by paramedics and transmitted immediately by “telephone” to the receiving CCU where the attending cardiologist can analyse it; thrombolytic therapy may be administered before admission to the A&E department.

The last model is quite novel and does not consume additional resources as large numbers of ambulance personnel will not require training in reading ECGs and the A&E department does not need to evolve a system for admitting suitable patients directly to the CCU. The ECG diagnostic accuracy in one study was 92% in the typical chest pain group.

The time to ECG recording was shorter when done in the prehospital setting than when done after admission to the A&E department (mean (SD) 8 (6) vs 21 (12) minutes; p < 0.001).

Other factors may influence the delay to thrombolytic treatment and the method of administration is important as bolus administrations needs less time than an infusion. In addition, the overall “pain to needle time” is important in reducing infarct size and improving survival. Koren et al’s study first demonstrated that early administration of thrombolytics provided a gain in terms of left ventricular (LV) function and necrotic tissue mass if the “time to needle” was less than 90 minutes. The delay in administering thrombolytics, by infusion or bolus, was not as important as overall “pain to needle time” in reducing infarct size and ameliorating LV function.

Therefore, greater use of ECG telephonic transmission and reporting, and prehospital bolus administration of thrombolytics may be significant in reducing infarct size and improving survival as they might shorten the “pain to needle time”.

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The GUSTO-III trial,1 which assessed the superiority of reteplase over alteplase in a larger population than INJECT, provides a better—although not definitive—estimate of the risk-benefit profile of reteplase. As with streptokinase and tPA, further studies might have indicated at least whether reteplase did not differ substantially from standard thrombolytics.

Deaths avoided per 1000 patients treated with

<table>
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<tr>
<th>Thrombolytic</th>
<th>Worst result expected with tPA</th>
<th>Worst result expected with streptokinase</th>
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<tbody>
<tr>
<td>Streptokinase</td>
<td>16</td>
<td>-3</td>
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<tr>
<td></td>
<td>22</td>
<td>0</td>
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<tr>
<td></td>
<td>27</td>
<td>+5</td>
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<tr>
<td>tPA</td>
<td>18</td>
<td>0</td>
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<tr>
<td></td>
<td>25</td>
<td>+5</td>
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<tr>
<td></td>
<td>31</td>
<td>-12</td>
</tr>
<tr>
<td>Reteplase</td>
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<td>-1</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>38</td>
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<tr>
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<td></td>
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Figure 1 Absolute number of deaths avoided and absolute excess of strokes/1000 patients treated with different thrombolytic agents compared to prethrombolytic era on the basis of the results of the respective superiority or equivalence trials. Numerical data indicate point estimates and limits of 95% confidence intervals (horizontal bars). Mortality and stroke rate were assumed to be 10% and 1.5%, respectively, in patients not treated with thrombolytic agents.
Nurse led, multidisciplinary intervention in chronic heart failure

Editor,—To complement the editorial by McMurray and Stewart,1 I present the results of a recent study from the Netherlands in which we randomised 179 patients (mean age 73 years), hospitalised with heart failure to intervention by a specially appointed nurse or to usual care. The intervention was intensive, systematised, and planned education by a study nurse about the consequences of heart failure in daily life, using a standard nursing care plan. During hospital stay, the study nurse assessed patients’ needs, provided education and support to patients (and family), gave patients a card with warning symptoms, and discussed discharge. Within one week after discharge the study nurse telephoned patients to assess potential problems and to make an appointment for a home visit. During the home visit the study nurse reinforced and continued education as warranted by the patient’s situation. If needed, home care was arranged in writing about specific patient needs. Between discharge and home visit, patients could call the study nurse in case of problems. After the home visit, the patient was advised to call their cardiologist, general practitioner or emergency heart centre in case of problems. Therefore, the intervention lasted from hospital admission to 10 days after discharge from hospital. Data were collected on resource utilisation and a trend was described (p = 0.06) towards fewer readmissions and visits to the emergency heart centre in the intervention group.

The main focus of the intervention was education and support by a nurse and follow up of the intervention was limited to 10 days after discharge. The study provides insight in the particular effect of education and support by a nurse. Our results show that this limited intervention is effective to enhance self care, but more is needed to get statistically significant results on readmission. The information is valuable in determining the required “dose” of nursing intervention. This confirms McMurray’s and Stewart’s editorial that describes the importance of determining which aspects of the intervention work. I would like to add two points to the list of issues regarding implementation and achieving optimal cost-benefit mentioned by McMurray and Stewart.

• There is a huge difference in the populations in the published studies: Rich et al and Stewart et al investigated a high risk sample for hospital readmission.1,4 This means that a specific subgroup (high risk patients) of the very heterogeneous heart failure population can benefit from that specific intervention. Other hospitalised, studied patients from a transplant clinic, which also had to be noted before generalising results to a general clinical heart failure population. Comparing all these studies in an overview as provided in the editorial can be helpful, but caution should be used when applying the results to practice.

• End points in effect studies should be standardised as much as possible. There is a great difference between studies reported in the editorial. Some authors used hospitalisation as a primary end point and others combined this with mortality. Accumulating end points to a “major” variable (such as rehospitalisation and mortality) may increase the power of studies, but it sometimes makes comparison with other studies difficult.

In addition, I would like to support the authors’ plea for inclusion of variables that explain the mechanism of (beneficial) effects of intervention (such as compliance or self care). In this way we might get more insight as to which intervention (and which “dose”) is most appropriate for which heart failure patient.

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NOTICES

Inflammation in cardiovascular disease, a conference hosted by The Royal College of Physicians of London, will be held on 22 September in London, UK. For further details, please contact Royal College of Physicians, Conference Office, 11 St Andrews Place, Regent’s Park, London NW1 4LE, UK; tel: +44 (0)171 935 1174 ext 252/300 436; fax: +44 (0)171 487 5218; email: conferences@rcplondon.ac.uk.

The world congress on non-invasive and invasive cardiology will be held in Rajkot, Gujarat, India from 24–26 December 1999. For further details visit www.cardiaccon99.com.

European conference on management of coronary heart disease will be held at the Acropolis Convention Centre in Nice, France from 17–19 April 2000 (abstract deadline 12 November 1999). For further details please contact Castle House Medical Conferences, 3 Linden Close, Tunbridge Wells, Kent TN4 6HH, UK; tel: +44 (0)1892 539666; Fax: +44 (0)1892 517773; email: conferences@castlehouse.co.uk; web site: www.castlehouse.co.uk.

Seventh world congress on heart failure—mechanisms and management will be held in Vancouver, Canada from 9–12 July 2000 under the auspices of the International Society of Heart Failure (abstract deadline 29 February 2000). For further details please contact Dr Asher Kimchi, Chair, 7th World Congress on Heart Failure, PO Box 17659, Beverly Hills, CA 90209, USA; tel: +1 310 657 8777; fax: +1 310 275 8922; email: kimedico@ucla.edu; web site: www.cardiologonline.com.