

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_{ATP} channel, while the hypoglycaemic action of sulphonylureas is mediated by closure of these channels within the membrane of β cells in the islets of Langerhan. The authors suggest that it may be simply a case of "adding a potassium channel opener along with insulin during [myocardial infarction] MI" 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_{ATP} channels within cardiac myocytes. Evidence is emerging that it is the mitochondrial and not the cell membrane K_{ATP} channels that initiates the cardioprotective effects of preconditioning. This conclusion is based on recent work from Marban's group.²⁻⁴ These investigators show that diazoxide, an agonist that opens mito K_{ATP} channels > 1000-fold more potently than their surface counterparts in heart cells, cardioprotects at concentrations that only open the mito K_{ATP} channels. In addition, at this low concentration of diazoxide a specific mito K_{ATP} channel blocker abolishes myocyte protection.

Although nicorandil opens membrane K_{ATP} channels, to our knowledge it is not known whether it activates the mitochondrial K_{ATP} channel. Indeed its efficacy in treating patients with symptomatic coronary artery disease may equally relate to the fact that nicorandil is a nitrate.

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

inflatons. The author cites Tomai *et al*'s paper⁵ as evidence that the K_{ATP} 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 inhibit vasodilatation in vascular smooth muscle and could therefore be preventing coronary collateral recruitment. Glibenclamide also has direct electrophysiological effects, as opening of membrane K_{ATP} 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_{ATP} 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 randomly assigned to sulphonylurea, insulin or diet alone.⁶ Over a 10 year follow up the outcome of these treatments were compared and no difference was found in the rate of myocardial infarction or diabetes related death between participants assigned sulphonylurea or insulin treatment.

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, Rayne Institute,
St Thomas's Hospital, London SE1 7EH, UK

- 1 Connaughton M, Webber J. Diabetes and coronary artery disease: time to stop taking the tablets. *Heart* 1998;80:108-9.
- 2 Sato T, O'Rourke B, Marba, E. Modulation of mitochondrial ATP-dependent K^+ channels by protein kinase C. *Circ Res* 1998;83:110-14.
- 3 Jaburek M, Yarov-Yarvovoy V, Paucck P, *et al*. State-dependent inhibition of the mitochondrial K_{ATP} channel by glyburide and 5-hydroxydecanoate. *J Biol Chem* 1998;273:13578-82.
- 4 Liu Y, Sato T, O'Rourke B, *et al*. Mitochondrial ATP-dependent potassium channels novel effectors of cardioprotection. *Circulation* 1998;97:2463-9.
- 5 Tomai F, Crea F, Gaspardone A. Ischaemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K^+ channel blocker. *Circulation* 1994;90:700-5.
- 6 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

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 valuable and 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 proves sooner or later to be an oversimplification. We would certainly acknowledge that current understanding of the biology of the K_{ATP} channel is incomplete, as signalled by the very recent reporting of a mitochondrial K_{ATP} 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 carried significant qualifications. 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 stable and unstable angina,¹ and its 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 when considering prognosis 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 main purpose of our speculations was to stimulate debate, and we find it gratifying that Marber's group and ourselves have come to similar conclusions from rather different directions.

- 1 Patel DJ, Purcell H, Wright C, *et al*. Nicorandil reduces myocardial ischaemia and tachyarrhythmias in unstable angina: results of a randomised placebo-controlled multicentre study [abstract]. *Eur Heart J* 1997;18(suppl):P1043.

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

EDITOR.—Rao and Joseph's correspondence in *Heart*¹ highlighted the reduction in time to administration of thrombolytic therapy by 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 administered²

- (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 with ischaemic ST segment changes.³ 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) v 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.¹ In addition, the overall "pain to needle time" is important in reducing infarct size and improving survival. Koren *et al's* study⁴ 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.⁵

Therefore, greater use of ECG telephonic transmission and reporting, and prehospital bolus administration of thrombolytics may be significant in reducing infarct size and

improving survival⁶ as they might shorten the "pain to needle time".

S COCCOLINI
A MARESTA

Department of Cardiology,
S. Maria delle Croci Hospital,
via Missiroli n.10—48100 Ravenna, Italy

M S GOTSMAN
A T WEISS

Department of Cardiology,
Hadassah University Hospital,
POB 12000—91120 Jerusalem, Israel

- 1 Rao AC, Joseph SP. Reduction in time delays in administering thrombolytic treatment [correspondence]. *Heart* 1998;79:422.
- 2 Pell ACH, Muller HC, Robertson CE, *et al*. Effect of "fast track" admission for acute myocardial infarction on delay to thrombolysis. *BMJ* 1992;304:83-7.
- 3 Coccolini S, Berti G, Maresta S, *et al*. The diagnostic impact of prehospital field-transmitted 12 leads electrocardiography in acute ischemic syndromes [abstract]. *Giorn Ital Cardiol* 1998; 28(suppl 2):67.
- 4 Koren G, Weiss AT, Gotsman MS, *et al*. Prevention of myocardial damage by early treatment with intravenous streptokinase. *N Engl J Med* 1985;313:1384-9.
- 5 Coccolini S, Dondi M, Maresta A, *et al*. A randomized pilot study of continuous infusion versus double bolus administration of rTPA: influence on infarct size and function [abstract]. *J Heart Failure* 1997;4(suppl 1):106.
- 6 Rawles J. Magnitude of benefit from earlier thrombolytic treatment in acute myocardial infarction: new evidence from Grampian region early anistreplase trial (GREAT). *BMJ* 1996;312:212-16.

Inconclusive messages from equivalence trials in thrombolysis

EDITOR.—Since the mid-80s a series of large scale randomised clinical trials has progressively proved the effectiveness of thrombolytic treatment in acute myocardial infarction but, despite prodigious efforts, the superiority of intensive strategies based on tissue-type plasminogen activator (tPA) over the standard regimen with streptokinase has not been

proved.¹ The certainty of the benefit has fuelled the search for new thrombolytic agents for a guaranteed market; however, the uncertainty of further benefits from new drugs has suggested testing their equivalence rather than superiority in impracticable trials. This approach has given poor results as demonstrated if one assesses the additional benefits (deaths avoided) and risks (excess of strokes) produced by single steps in the search for better or equivalent thrombolytic agents. We compared indirectly the efficacy and safety of tPA, reteplase, and saruplase by combining the results of studies assessing these agents and streptokinase, as well as streptokinase and no thrombolytic agent (fig 1).²

Based on the results of the equivalence trials INJECT³ and COMPASS,⁴ the minimum expected effect of reteplase and saruplase on mortality compared to prethrombolysis controls is smaller than the minimum effect attained with standard thrombolytic treatment (seven fewer deaths would be avoided by using reteplase or saruplase compared with tPA). Likewise, the maximum expected excess of strokes with reteplase or saruplase is greater than with current thrombolytic agents (13 more strokes would occur with reteplase and 11 with saruplase compared with streptokinase). This means that reteplase and saruplase may be worse than the worst expected effect of effective thrombolytic strategies, such as those based on streptokinase (in GISSI-I and ISIS-2) or on tPA (in GISSI-2, ISIS-3, and GUSTO-I).¹

The GUSTO-III trial,⁵ 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.

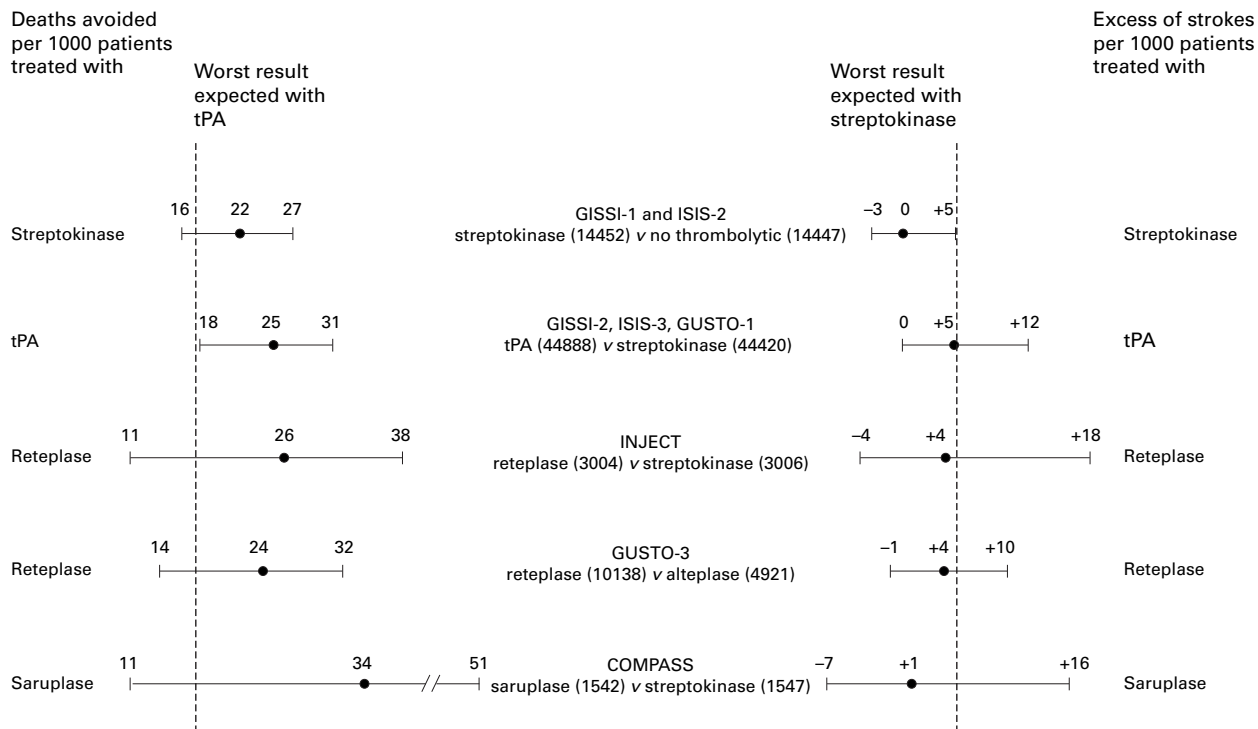


Figure 1 Absolute number of deaths avoided and absolute excess of strokes/1000 patients treated with different thrombolytic agents compared to prethrombolytic era on the basis of the result of the respective superiority or equivalence trials. Numerical data indicate point estimates and limits of 95% confidence intervals (horizontal bars). Mortality and stroke rate were assumed to be 10% and 1.5%, respectively, in patients not treated with thrombolytic agents.

The place of reteplase and saruplase in the current thrombolytic treatment of acute myocardial infarction have not been established by INJECT and COMPASS. Tests of equivalence are far less precise than superiority trials, and the efficacy–safety profile of drugs assessed in either way cannot be reliably compared. This is mainly because of the small trial populations in several equivalence studies. These small samples are not the results of the equivalence hypothesis but rest on the assumptions that: the new drug is actually more effective or safer than the standard comparator; the real aim of the study is not so much to assess the equivalence as to prove that the new drug is not inferior to the standard comparator; and that the equivalence will be proved even if the confidence interval of the difference is wide. This is difficult to accept if the study concerns “hard” outcome events that are rare in high prevalence disease, such as death in acute myocardial infarction. For example, reteplase would have been considered equivalent to streptokinase even if—on the basis that confidence intervals should not reach +1%—10 more deaths/1000 patients treated with the new drug had occurred in the INJECT trial in addition to the 95 reported with the comparator. Saruplase would also have been considered equivalent, if an excess of 30–35 deaths/1000 patients (odds ratio saruplase:streptokinase < 1.5) had been reported in the COMPASS study in addition to the 67 with streptokinase.

These devices ultimately imply that the confidence interval for estimated equivalence spans from a large benefit to a large risk. This offers no useful practical information to patients and physicians. Moreover, both the non-inferiority aim and the inconclusive results raise doubts about the ethics of randomisation in equivalence trials.

V BERTELE

V TORRI

S GARATTINI

“Mario Negri” Institute, Milan
and Consozio “Mario Negri Sud”,
S Mazia Imbaro, Italy
email: garattini@rftm.mnegr.i.it

Glossary

COMPASS, Comparison trial of saruplase and streptokinase
GISSI, Gruppo Italiano per lo studio della sopravvivenza nell’infarto
GUSTO, Global use of strategies to open occluded coronary arteries
INJECT, International joint efficacy comparison of thrombolytics
ISIS, International study of infarct survival

- Collins R, Peto R, Baigent C, *et al*. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;336:847–60.
- Early Breast Cancer Trialists’ Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992;339:1–15, 71–85.
- International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995;346:329–36.
- Tebbe U, Michels R, Adgey J, *et al*. Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: The COMPASS equivalence trial. *J Am Coll Cardiol* 1998;31:487–93.
- The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;337:1118–23.

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 informed 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.²

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.¹

- 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.^{3,4} This means that a specific subgroup (high risk patients) of the very heterogeneous heart failure population can benefit from that specific intervention. Other researchers studied patients from a transplant clinic,⁵ 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 rehospitalisation 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.

T JAARMSMA

Researcher, Department of Nursing Science,
University of Maastricht,
Netherlands Heart Foundation,
PO Box 300, 2501 CH Den Haag, Netherlands
email: T.jaarsma@hartstichting.nl

- McMurray JVV, Stewart S. Nurse led, multidisciplinary intervention in chronic heart failure [editorial]. *Heart* 1998;80:430–1.
- Jaarsma T, Halfens R, Huijter Abu Saad H, *et al*. Effects of education and support on self-care and resource utilization in patients with heart failure. *Eur Heart J* 1999;20:673–82.
- Rich MW, Gray DB, Beckham V, *et al*. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. *Am J Med* 1996;101:270–6.
- Stewart S, Pearson S, Horowitz JD. Effects of a home-based intervention among patients with congestive heart failure discharged from acute hospital care. *Arch Intern Med* 1998;158:1067–72.
- Fonarow GC, Stevenson LW, Walden JA, *et al*. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol* 1997;30:725–32.

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 8HH, UK; tel: +44 (0)1892 539606; Fax: +44 (0)1892 517773; email: cardiology@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: Klmedico@ucla.edu; web site: www.cardiologyonline.com.