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.

The letter may be a short table or a small figure.

Please send a copy of your letter on disk. Full instructions to authors appear in the January 1997 issue of Heart (page 89).

K+ channel opening: a new drug principle in cardiovascular medicine

Sir,—Nielsen-Kudsk JE et al recently reviewed K+ channel openers, addressing their clinical usefulness as vasodilatory and cardioprotective drugs.1 They eluded to electrophysiological aspects of these drugs and stated that two of them, pinacidil and nicorandil, had been given to thousands of patients without reports of adverse arrhythmias. They also mentioned that repolarisation abnormalities in terms of ST segment and T wave changes were a common finding in the electrocardiogram following administration of pinacidil. However, we feel there is cause for some concern regarding the potential proarrhythmic effects of these drugs, and we encourage prescribers to be very observant regarding arrhythmias in their patients.

It is known that augmentation of ATP regulated potassium current IATP by pinacidil increases dispersion of repolarisation to the ventricular tissue enough to induce extrasystolic activity (phase 2 reentry) due to a marked abbreviation of the action potential in the epicardium. This electrical heterogeneity can be abolished by 4-aminoypyridine, which may also prevent development of ST segment elevation induced by pinacidil or coronary artery occlusion in dogs. Under conditions where the action potential is significantly abbreviated, IATP is diminished or even blocked resulting in decline of contractility function and oxygen consumption. Such electrophysiological modulation of the ventricular conduction is most likely the effect underlying the cardioprotective mechanism of K+ channel openers. The question is, however, whether a desired cardioprotective benefit from K+ channel openers could lead to arrhythmic events? Until more information is available, we would hesitate to accept that repolarisation abnormalities induced by pinacidil are benign in all patients. As we have seen with many drugs in the past, the initial experience may look very promising but extended use may later disclose serious side effects. Promising results have been obtained, however, when IATP and ICa,L blockers have been administered simultaneously to rats. Coronary flow was increased and fibrillatory activity decreased during acute myocardial ischaemia.1,3

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

Sir,—We agree with Drs Gussak and Bierregaard that the cardiac electrophysiological effects of K+ channel openers is an important issue. As stated in our review, pharmacological activation of ATP sensitive K+ channels (KATP) in the heart has the potential to produce both proarrhythmic and antiarrhythmic effects. Theoretically, shortening of the action potential duration (APD) in an acute myocardium induced by KATP channel openers would pre-dispose to reentry ventricular tachyarrhythmias, resulting from a reduction in the refractory period and regional differences in repolarisation and K+ accumulation. On the other hand, repolarisation by KATP channel opening is expected to inhibit arrhythmias due to triggered activity (early and delayed afterdepolarisations) and abnormal automaticity. These novel drugs might be useful in the treatment of long QT related arrhythmias.1 In the setting of acute myocardial ischaemia, the contribution and interplay between different arrhythmia mechanisms is complex and incompletely understood. As a consequence, there are some experimental data showing proarhythmic and other antiarrhythmic effects of KATP openers depending on species, dose, and model of ischaemia.1 The ability of KATP channel activators to reduce ischaemia injury will tend to reduce the susceptibility to arrhythmias.

Although APD shortening followed by inhibition of Ca2+ influx, acceleration of cardiac contractile arrest, and preservation of ATP in the ischaemic myocardium is an attractive theory to explain the cardioprotective effects of KATP channel openers, the underlying mechanism is unsettled.1 Recent studies indicate that cardioprotection can be achieved at doses which do not reduce APD and that there is a lack of correlation between the APD shortening and cardioprotective effect of KATP openers.1,4 Thus, the question whether KATP channel activators in clinically relevant doses might be proarrhythmic or antiarrhythmic is still undecided and unresolved.5 To our knowledge, there are no clinical reports of proarrhythmic effects in patients treated by KATP openers as antihypertensive or antiischaemic agents. As with any new drug, we agree to be observant and to report any suspected adverse effect.

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Prophylactic replacement of Björk-Shiley convexo-concave heart valves: an easy-to-use tool to aid decision-making in individual patients

Sir,—Steyerberg et al1 presented an attractive model to facilitate decision-making in individual patients considering convexo-concave prostheses. Based on admittedly idealised risks for surgical and non-surgical strategies, they have indicated how patients can maximise their chances of living a normal life span, that is, life expectancy if the valve prosthesis were not prone to breaking up. The example given, briefly, is of a 40 year old man who would be expected to live 25 years with a Björk-Shiley valve and 32 years with a convexo-concave prosthesis. Maximising his odds of reaching the age of 65 should, according to the authors, direct the decision-making process. This is, in my opinion, not correct, and they should stick back with their admission that “Most patients are risk averse and attaching more value to nearby years than to years in the distant future” is not something they need to negate their thesis. Certainly the quality of life to be expected between the ages of 40 and 50 is greater than that to be expected between the ages of 55 and 65. Moreover, the probability of living to the age of 65 is one thing, but when you die, if you die before then, is another. In spite of almost identical

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expected survival to age 65 for a surgical and a non-surgical strategy, the surgical survival curve is close to a right angle, with a small sharp drop in survival periperioperatively, whereas the non-surgical curve will be more linear since cases of strut fracture will be evenly distributed over time. Although the two curves meet near age 65, the non-surgical curve lies above the surgical one at every point in time before then. The estimated outcomes with and without surgery must favour surgery to a greater extent than in the planned case if surgery is to be recommended to the patient.

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

Sir—Decision-making in Björk-Shiley convexo-concave heart valves essentially requires a weighing of short term surgical risks (mortality, morbidity, hospital admission) against cumulative long term risks of strut fracture. We tried to compare the mortality risks of “surgery” and “no surgery” on the same scale. To this aim, the life expectancy forms a suitable measure. Life expectancy is also often used in cost-effectiveness analyses, usually with a correction for the quality of life in different possible health states.1 The measure has not only been used in weighing short term against long term risks, but also in situations where treatments have an immediate benefit to the patient, such as thrombolytic therapy for acute myocardial infarction.1

The interpretation of the life expectancy, is therefore an important issue for many decision analyses and cost-effectiveness analyses. Life expectancy reflects the number of years that a patient may expect to live, and is calculated as the area under the survival curve. It should not be confused with the actual outcome of the patient—for example, a survival of 1, 2, 3 . . . years—not with the probability of reaching a certain age—for example, 65 years.

Survival curves for our example patient, a 40 year old male patient with a Björk-Shiley convexo-concave mitral heart valve. Top panel: basal life expectancy with or without discounting at 5% (dLE and LE). Lower panel: life expectancy with or without surgical replacement of the valve (LEsurg and LEsurg), with or without discounting (dLE and LE).

40 year old male, are shown in the figure. These curves are constructed with our decision analytical model that incorporates follow up results of 2303 patients.1 The basal life expectancy is the area under the first curve (25-0 years). The second panel shows survival with or without surgery. We adapted the scaling as the curves are hardly distinguishable. A surgical mortality of around 1% leads to an expected survival at 99% of the curves shown in the first panel. Survival including a lethal strut fracture risk of 0.18% per year leads to a higher survival during the first five years of follow up, and to a lower survival during later years. The curves cross at the age of 45-4 years, and not at 65 as assumed by Dr Amsel. The probabilities of reaching the age of 65 are 50-3% and 48-7% for surgery and no surgery, respectively.

Estimates of basal life expectancy (years), when future life-years are discounted by 5% for each subsequent year

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
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<tbody>
<tr>
<td>Aortic valve</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>16-2</td>
<td>15-0</td>
<td>13-2</td>
<td>11-1</td>
<td>9-6</td>
<td>7-2</td>
<td>4-9</td>
</tr>
<tr>
<td>Female</td>
<td>16-8</td>
<td>15-7</td>
<td>14-0</td>
<td>12-0</td>
<td>9-6</td>
<td>7-2</td>
<td>4-9</td>
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<tr>
<td>Mitral valve</td>
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<tr>
<td>Male</td>
<td>14-8</td>
<td>13-4</td>
<td>11-5</td>
<td>9-2</td>
<td>7-8</td>
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<tr>
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<td>15-6</td>
<td>14-3</td>
<td>12-4</td>
<td>10-2</td>
<td>7-8</td>
<td>5-6</td>
<td>3-7</td>
</tr>
</tbody>
</table>

Indeed, as suggested by Dr Amsel, patients may value years further away—for example, between 55 and 65, less than nearby years—for example, between 40 and 50. We may account for this valuation by weighing each subsequent year as—for example, 95% of each previous year (discount factor of 5%). This means that a life-year 20 years from now is worth only 36% of a present life-year. The discounted basal life expectancy is 13-4 years, and the net benefit for surgery is 0-12 years compared with 0-45 years without discounting. The discounting factor has to be increased to over 15% per year to favour “no surgery”.

For most patients, surgery is not likely to increase life expectancy substantially (for example, by more than 0-5 years). This is exaggerated when future life is compared with used less. We provide discounted basal life expectancies in the table, which can directly be used with our graphical decision support tool. We agree that differences in (discounted) life expectancy are only one of several aspects to be considered in the decision-making process.

EVERT W STEYERBERG
Department of Public Health, Erasmus University Rotterdam, The Netherlands on behalf of JAN HP VAN DER MEULEN
LEX A VAN HERWERDEN
DIK F HABBEMA

NOTICES

The 4th Annual Conference of the International Society for Quality of Life Research will take place at The Vienna Academy of Postgraduate Medical Education and Research, Vienna from 5-9 November. For further information please contact the Scientific and Administrative Secretariat (tel: 43/1 405 13 83 13; fax: 43/1 405 13 83 23; e-mail: medacad@via.at; homepage: http://www.via.at/medacad).

The 12th International Interdisciplinary Conference on Hypertension in Blacks will take place at the London Hilton, Park Lane, London from 20-24 July. For further information please contact Anne M Dubois at (US) tel: 001 770 516 7717; fax: 001 770 516 0180; or, Dale McFarlane at 0171 723 7228.
Prophylactic replacement of Björk-Shiley convexo-concave heart valves: an easy-to-use tool to aid decision-making in individual patients.

B. J. Amsel

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