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.

This is not a 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 electrocardiographic 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 I_ATP by pinacidil increases dispersion of repolarisation to some 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-aminoptyridine (a concentration highly selective to block calcium independent transient outward current I_to) or by a blocker of the ATP regulated potassium channels, glyburide.2 This may also prevent development of ST segment elevation due to pinacidil or coronary artery occlusion in dogs.3 Under conditions where the action potential is significantly abbreviated, I_ATP 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. Provocative studies have been obtained, however, when I_ATP and I_to blockers have been administered simultaneously to rats. Coronary flow was increased and fibrillatory activity decreased during acute myocardial ischaemia.4,5


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

Sir,—We agree with Drs Gussak and Bierrejgaard that the cardiac electrophysiological effects of K+ channel openers is an important aspect. As stated in our review, pharmacological activation of ATP sensitive K+ channel (I_ATP) in the heart has the potential to produce both proarrhythmic and antiarrhythmic effects. Theoretically, shortening of the action potential duration (APD) in an apical region of myocardium induced by I_ATP channel openers would pre-dispose to reentry ventricular tachyarrhythmias, resulting from a reduction in the refractory period and regional differences in repolarisation and A_K+ accumulation. On the other hand, repolarisation by I_ATP 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 interaction between different arrhythmia mechanisms is complex and incompletely understood. As a consequence, there are some experimental data showing proar-rhythmic and other antiarrhythmic effects of K_ATP openers depending on species, dose, and model of ischaemia.4,6 The ability of K_ATP 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 and proarrhythmic effects of K_ATP channel openers, the underlying mechanism is unsettled.7 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 K_ATP openers.8 Thus, the question whether K_ATP channel activators in clinically relevant doses might be proarrhythmic or antiarrhythmic is far from being answered and unresolved.9 To our knowledge, there are no clinical reports of proarrhythmic effects in patients treated by K_ATP openers as anti-hypertensive or anti-anginal agents. As with any new drug, we advise that prescribers be observant and report any suspected adverse effect.


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 the elective replacement of Björk-Shiley 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 15 years more in the future if he is treated with his own valve. 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 the authors step back with their admission that “Most patients are risk averse and attach more value to nearby years than to years in the distant future” is not good enough 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. More importantly, 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
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 perioperatively,
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 with-
out surgery must favour surgery to a greater
extent than in the presented case if surgery is
to be recommended to the patient.

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1 Steyerberg EW, van der Meulen JHP, van
Herwerden LA, Habbema JDF. Prophylactic
replacement of Böhrer-Stille convexo-
conave heart valves: an easy-to-use tool
to aid decision-making in individual patients.
Heart 1996;76:264-8.

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

Sir,—Decision-making in Böhrer-Stille
convexo-concave heart valves essentially
requires a weighing of short term surgical
risks (mortality, morbidity, hospital admis-
sion) against cumulative long term risks of
strut fracture. We tried to compare the mor-
tality 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-effec-
tiveness analyses, usually with a correction
for the quality of life in different possible
health states.1,2 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.3

The interpretation of the life expectancy,
is therefore an important issue for many
decision analyses and cost-effectiveness
analyses. Life expectancy reflects the num-
ber of years that a patient may expect to live,
and is calculated as the area under the sur-
vival 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

**Survival curves for a 40 year old male patient**
with a Böhrer-Stille 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 (LE surg and LEsurg), with or
without discounting (dLE and LE).

40 year old male, are shown in the figure.
These curves are constructed with our deci-
sion analytical model that incorporates fol-
low up results of 2303 patients.4 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 proba-
bilities of reaching the age of 65 are 50%-3% and
48-7% for surgery and no surgery, respect-
ively.

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>
<td></td>
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<td></td>
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<tr>
<td>Male</td>
<td>16-2</td>
<td>15-0</td>
<td>13-2</td>
<td>11-1</td>
<td>8-6</td>
<td>6-4</td>
<td>4-3</td>
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<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>6-8</td>
<td>4-8</td>
<td>3-2</td>
</tr>
<tr>
<td>Female</td>
<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 valua-
tion by weighing each subsequent year as—for
example, 95% of each previous year (dis-
count 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 expectancy is
discounted. 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 (dis-
counted) life expectancy are only one of sev-
eral aspects to be considered in the
decision-making process.

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LEX A VAN HERWERDEN
UD F HABBEKA

1 Van der Meulen JHP, Steyerberg EW, Van
er Graaf Y, Van Herwerden LA, Verbaan CJ,
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convexo-concave heart valves: a clinical and
2 Gold MR, Siegel JE, Russell LB, Weinstein
MC, eds. Cost-effectiveness in health and medi-
3 Mark DB, Hlatky MA, Califf RM, Naylor CD,
Lee KL, Armstrong PW, et al. Cost effective-
ness of thrombolytic therapy with tissue
plasminogen activator as compared with
streptokinase for acute myocardial infarction.

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;

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.

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http://heart.bmj.com/content/77/5/487.2.citation

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