Toward Preventing Coronary Death from Ventricular Fibrillation

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SUMMARY

Sudden coronary death from ventricular fibrillation is the biggest and possibly the most remediable of the major public health problems at the moment. Most of those liable to sudden death can be identified and it is possible that by the use of beta-adrenergic blocking or other antiarrhythmic drugs, by reducing the consumption of cigarettes and perhaps, by different therapies for hypertension, a substantial proportion of coronary deaths might be prevented or, at least, postponed.

SUDDEN CORONARY DEATH is an outstanding therapeutic problem in North America and Western Europe. Ventricular fibrillation, which is responsible for the majority of sudden deaths, is, under favorable circumstances, both treatable and preventable. Those who are saved from dying from this cause inevitably remain at risk from underlying coronary artery disease, but several years of productive life may be gained by postponing their demise.

It has been estimated that there are probably some 300,000 sudden deaths from coronary disease in the United States each year.1 I would like to examine the hypothesis that this death toll could be reduced or postponed in say 100,000 persons, by 1978, if we applied knowledge which is either currently available or could be acquired readily.

If an impact of this magnitude is to be made so soon, it must depend upon the recognition and treatment of those at risk. Fortunately, although death by this means is often unexpected, it is not entirely unpredictable as three-quarters of those dying suddenly have previously been recognized as having hypertension, heart disease or diabetes.2

Three possible strategies suggest themselves. First, one could correct the known primary risk factors for coronary heart disease, particularly those associated with sudden death. Secondly, one could identify patients with manifest coronary heart disease and so modify its progression that the conditions which favor the development of ventricular arrhythmias would be minimized. Finally, one could specifically prevent ventricular fibrillation itself by antiarrhythmic therapy.

Correction of Risk Factors

Much information is now available about the risk factors associated with coronary heart disease. Kannel et al.3 have recently analyzed the Framingham and Albany data to determine those which are particularly associated with sudden death. These workers conclude that the risk factors for sudden death are the same as they are for coronary heart disease as a whole (hyperlipidemia, hypertension, cigarette smoking, excessive weight, lack of physical activity and left ventricular hypertrophy on ECG). It appears, however, that there is a particularly strong relation to cigarette smoking.2

Hyperlipidemia

Hyperlipidemia seems to be no more associated with sudden death than it is with coronary heart attacks in general. It has appeared from some trials that the coronary death rate as a whole may be reduced by diet4,5 and clofibrate6,7 and in one study, sudden death was thought to be specifically reduced.8 However, the failure of several antihyperlipidemic therapies in the Coronary Drug Project Research Group study9 suggests that this form of treatment is unlikely, at least in the short term, to produce a major effect on death from coronary disease.

Hypertension

There is no evidence at present that the treatment of hypertension reduces mortality from acute coronary heart attacks but the duration of the major controlled studies to date may have been too short to show a favorable result. It is possible, however, that the antihypertensive agents used in these studies had detrimental effects which negated the potential beneficial consequences of lowering blood pressure insofar as preventing heart attacks is concerned. Stewart10 has undertaken an uncontrolled but prospective study of two apparently similar groups of hypertensive patients, one of which received propranolol and the other, antihypertensive drugs without beta-adrenergic blocking characteristics. Myocardial infarction occurred significantly less frequently in the propranolol-treated group. Lambert11 has made similar observations on patients with the combination of hypertension and angina. The possible protective effect of beta-adrenergic blocking drugs requires confirmation by large-scale controlled studies, as it has important implications in the choice of therapy for hypertension.

Smoking

Unlike the inconclusive evidence with regard to treating hyperlipidemia or lowering blood pressure, stopping smoking seems to have a beneficial effect on reducing the incidence of heart attacks. Wilhelmsson et al.12 from Göteborg have shown that the stopping of smoking after myocardial infarction appears to reduce the risk of death in the succeeding two years.
Modifying the Course of Coronary Artery Disease

There are at least three promising ways of so modifying the course of coronary artery disease that the risk of ventricular fibrillation could be reduced: coronary artery bypass graft surgery, the recognition and treatment of unstable angina (often regarded as a "pre-heart attack" condition), and interventions in the course of myocardial infarction to limit the area of damage.

Coronary Artery Bypass Graft Surgery

There is a widespread belief, particularly among surgeons, that coronary artery bypass graft surgery will have an important impact on the mortality from coronary artery disease. A report from the Cleveland Clinic suggests that, particularly in three-vessel and left main coronary artery disease, surgery is associated with substantial reduction in the mortality over the succeeding five years. As Ross has pointed out, however, there is as yet no evidence that coronary artery surgery itself reduces mortality. Even if the studies from the Cleveland Clinic proved correct, a vastly increased amount of coronary artery surgery would be required to reduce the mortality in the community by 100,000 per annum — perhaps between 500,000-2,000,000 operations a year would be necessary to achieve this effect. Not until the studies now being conducted in the Veterans Administration Hospitals and by the European Coronary Artery Surgery Trial are available will the beneficial prognostic effect of surgery, if any, be known but it seems improbable in community terms that it will have a major impact.

Unstable Angina

There has been considerable interest in recent years in unstable angina as a predictor of heart attacks and, in particular, of sudden death. The fact that 60-70% of patients who present in hospital with myocardial infarction give a history of new or worsening angina has led many to suppose that sudden death might also be preceded by warning symptoms which would permit prophylactic action. A further encouragement to this view was the finding by Kuller, Cooper and Perper that 38% of patients dying suddenly had seen a physician in the preceding two weeks. Similar findings have been reported from a number of centers. However, Kienlen suggested that patients who died suddenly were less liable to have had prodromal symptoms than those who had sustained a myocardial infarction.

With these ideas in mind we embarked on a study of unstable angina in a community in the hope that one would be able to predict a substantial proportion of the patients who would go on to develop an acute heart attack.

In one part of the study, complete information on all acute heart attacks was obtained from general practitioners in a defined population of approximately 25,000 males between the ages of 35 and 69. During the period of this part of the study, 87 patients died suddenly (i.e., without symptoms or within one hour of the onset of symptoms) and 104 patients sustained a myocardial infarction. Only ten (12%) of those who died suddenly had consulted their doctor because of new or worsening anginal pain compared with 34 (33%) of those who subsequently sustained a myocardial infarction. A further point of interest was that of the 87 cases of sudden death, 40 (46%) had seen a doctor within the preceding four weeks. However, of these only ten had mentioned symptoms of unstable angina; the remainder had seen him for a variety of reasons including fainting attacks, indigestion, trauma, influenza, and routine check-ups for chronic disease.

In a further study from the same population but lasting 2½ years, general practitioners were asked to refer to cardiologists in a special clinic all patients who had symptoms suggestive of unstable angina. Of 251 patients enrolled in the clinic during this period, only 10% proceeded to definite myocardial infarction, a further 2% to possible myocardial infarction, and 3% died suddenly in the succeeding six months. It would seem, therefore, that although myocardial infarction and, to a lesser extent, sudden death are often preceded by unstable angina, only a small proportion of patients complaining of new or worsening angina proceed to sudden death.

The prediction of sudden death on the basis of symptoms other than chest pain is of a very low order. Thus, Kuller reports that 70% of patients who died suddenly had given a history of fatigue prior to the event, compared with 20% of a control series in the general population. If Kuller's figures were to be applied to our community of 25,000 middle-aged males, 60 patients would complain of fatigue as a prodromal symptom of sudden death; a further 4,000 would have the same symptoms without doing so. Fatigue is therefore not a useful discriminator.

It would appear that although new and worsening angina is associated with an increased risk of proceeding to myocardial infarction and sudden death and therefore justifies vigorous treatment, whether this be by drug therapy or surgery, only a small proportion of deaths in the community could be prevented by identifying such cases.

Myocardial Infarction

Great interest is now being shown in the possibility of limiting the size of a myocardial infarction by a variety of interventions. It is to be hoped that these methods will be shown to be as effective in humans as they are in a dog preparation. They are likely to have little impact on the incidence of ventricular fibrillation as a manifestation of acute myocardial infarction because ventricular fibrillation usually occurs at a time before such intervention can be applied. Nonetheless, the implications of such work have great importance for the long-term prognosis of the patients affected, because the size of infarction is undoubtedly an important factor in determining the risk of sudden death, months or years after an initial attack.

Ventricular Anti-arrhythmic Therapy

Ventricular fibrillation appears in a number of different contexts in ischemic heart disease, the most familiar one being its development in mobile or hospital coronary care. Considerable success has been achieved in correcting ventricular fibrillation, especially in the pre-hospital phase, but it is less certain that it can be effectively prevented. Early in the history of coronary care units, the concept developed that there were premonitory arrhythmias for ventricular fibrillation. The detection of such arrhythmias...
became the major preoccupation of coronary care unit personnel following Lown’s claim that ventricular fibrillation was not unheralded and that failure to prevent it was due to inadequate observation and treatment of the patient. The apparent fall in hospital mortality and the reduction in the incidence of ventricular fibrillation made those involved in coronary care confident that real progress had been made. However, many units continue to encounter primary ventricular fibrillation. Why should this be so?

One possible explanation is that the “warning” ventricular arrhythmias are not being detected and, therefore, not being treated effectively. Mogensen25 demonstrated that many arrhythmias, particularly ventricular tachycardia, were not observed by nurses and as a consequence prophylactic therapy was not instituted. More recently, Romhilt et al.26 have shown by analysis of off-line computer studies that even in a good coronary care unit there is a low rate of arrhythmia detection by nurses. We have recently confirmed these findings in a similar study27 using an on-line arrhythmia computer.

It can be concluded that even with good standard monitoring equipment and well-trained nurses, patients with “warning arrhythmias” are not being adequately treated.

Lie et al.28 from Amsterdam have recently questioned the importance attributed to “warning arrhythmias” since a high proportion of patients have them without proceeding to ventricular fibrillation. They also found that ventricular fibrillation is frequently unheralded. They showed that by giving lidocaine in high doses by intravenous infusion they could effectively prevent the appearance of primary ventricular fibrillation.29 Impressive results have also been reported by Wyman and Hammersmith30 in uncontrolled studies.

However, in the Amsterdam study, there was a high incidence of toxic effects from the drug and the question arises as to whether other forms of therapy which do not require meticulous intravenous infusion would be safer and easier to administer.

The well-known study by Koch-Weser et al.31 demonstrated the potential prophylactic value of procainamide, but because of its toxic effects, particularly on atrioventricular conduction, it has to be used with considerable caution in the acute phase of infarction. The necessity of frequent administration also presents problems. We have, therefore, sought other drugs to use in this context and have recently completed a study on mexiletine which resembles lidocaine but is a primary amine which is effective when given orally.32, 33 In this double-blind control study34 starting within the first 12 hours following infarction, and continuing for 48 hours, there was a highly significant reduction in the incidence of R-on-T ectopic beats (from 30% to 10%) and in ventricular tachycardia (from 77% to 30%) and particularly in repetitive episodes of these events. Two (4%) of patients in the placebo group developed ventricular fibrillation; none developed in the mexiletine group. Similar results have been reported using disopyramide.34 It is certainly too early to say whether mexiletine or disopyramide are suitable drugs for routine use in the early stages of myocardial infarction but further studies are justified.

Long-Term Arrhythmia Prophylaxis

Valuable as it is to prevent ventricular arrhythmias within the context of acute myocardial infarction, long-term prophylaxis is of much greater importance because most cases of ventricular fibrillation occur without warning or with symptoms of such short duration that cardiac resuscitative measures cannot easily be applied. Much thought has been devoted to identifying groups of patients at particularly high risk to whom antiarrhythmic therapy might most appropriately be given.

One such group would be composed of those recovering from myocardial infarction. Wilhelmsson et al.35 have reported that over a period of two years the death rate of postinfarction patients treated by alpenrol was half that of those on a placebo. This protective effect of a beta-adrenergic blocking drug has been confirmed by the Multicentre practolol trial.37 In this study, more than 3,000 patients were randomized to practolol or placebo starting 7 to 28 days after sustaining a myocardial infarction. Follow-up lasted for at least one year.

A highly significant reduction in cardiac deaths but a nonsignificant reduction in nonfatal reinfarctions was found (table 1). Of particular relevance was the finding that deaths within the first two hours were substantially reduced in the practolol group compared with the placebo group; deaths after that period were not significantly reduced (table 2).

When discriminate function analysis was used, three subgroups appeared to be particularly benefited. These were those with anterior infarction as opposed to inferior infarction, those with a normal or low diastolic pressure at the time of entry compared with those of above normal pressures, and those with normal or below normal weights compared with those of above normal weights.

With regard to the association with anterior infarction, this could be partly related to the fact that patients with anterior infarction were much more likely to die in the months immediately following acute myocardial infarction than were those with inferior infarction. A significant reduction in death rate would, therefore, be shown more easily. However, a curious feature emerged as far as inferior infarctions were concerned. Although there was an apparent reduction in death in the first two hours this was not significant (although it was proportionately as great as that in

### Table 1. Practolol Postinfarction Trial: Total Deaths and Reinfarction

<table>
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<th></th>
<th>Practolol</th>
<th>Placebo</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Cardiac deaths</td>
<td>47</td>
<td>73</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Non-fatal reinfarctions</td>
<td>69</td>
<td>89</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>All cardiac events</td>
<td>116</td>
<td>102</td>
<td>&lt;0.01</td>
</tr>
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From the Multicentre International Study.27 A comparison of incidence of cardiac death and nonfatal reinfarction in patients treated with practolol and placebo.

### Table 2. Practolol Postinfarction Trial: Time Between Onset and Death

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<thead>
<tr>
<th></th>
<th>Practolol</th>
<th>Placebo</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>First hour</td>
<td>27</td>
<td>47</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Second hour</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3-12 hours</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>12-24 hours</td>
<td>2</td>
<td>2</td>
<td></td>
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From the Multicentre International Study.27 Time of death after onset of recurrence of heart attack in patients on practolol and placebo.
anterior infarctions), but there was a significantly increased death rate between 2 and 24 hours (table 3). Indeed even in the anterior infarction group, no benefit could be demonstrated after two hours. These findings suggest that practolol was acting as an antiarrhythmic drug and was probably not exerting an effect in reducing infarct size and the severity of infarction, as might have been hoped from experiments on dogs. Indeed, it is possible that beta-adrenergic blocking drugs, by producing bradycardia, exert an adverse influence on the extent of myocardial damage. If this is so, it would be reasonable to suggest that patients who are on beta-adrenergic blocking drugs should be given atropine either by their physician or for self administration should they sustain a further infarction.

It is apparent from both the alprenolol and practolol studies that a beta-adrenergic blocking drug is effective in reducing mortality by 45%-50% in the one or two years after myocardial infarction. Unfortunately, the use of long-term practolol has had to be discontinued because of the side effects of the drug which included severe ocular damage and plastic peritonitis. Whether other beta-adrenergic blocking drugs will prove to have the same beneficial effects as practolol without its toxic effects remains to be shown.

The potential implications of these studies are great if we can assume — and there is no reason why we should not do so — that these drugs are as effective in preventing sudden death in patients with angina and hypertension as they are in those with previous myocardial infarction. In the United States, there are perhaps 1,000,000 patients each year recovering from myocardial infarction, approximately the same number sustaining angina for the first time and possibly 10,000,000 requiring treatment for hypertension. If a beta-adrenergic blocking drug prevented sudden death in 0.5% of those with hypertension each year, in 2% of those with angina, and in 3% of those with myocardial infarction per annum, the target figure of 100,000 could indeed be achieved.

Other Antiarrhythmic Therapy

On the basis of these reports, there are attractions in giving beta-adrenergic blocking drugs to all patients with previous myocardial infarction, angina pectoris, or hypertension, but they are potentially dangerous in respiratory disease and cardiac failure. An alternative approach would be to use the other antiarrhythmic drugs available but, unfortunately, they cannot be recommended for all patients because of their toxicity.

In this context, therefore, it is important to identify a high-risk group to whom antiarrhythmic therapy can be given. There have now been several studies that have demonstrated the relationship between ventricular ectopic activity after recovery from infarction and subsequent death.9, 20 It remains, however, unclear whether ventricular ectopic activity is related specifically to sudden death although some authors have claimed such a relationship.27, 28 Nonetheless, it would seem that those who exhibit ventricular ectopic activity, particularly of the more severe kind, are at greater risk and that it would be ethically justifiable to give antiarrhythmic therapy to such patients.

No report has yet been published showing that any particular antiarrhythmic drug is both safe and effective in this situation.41 Several new drugs — apridine, disopyramide, mexiletine and tocainide — may have some value in this field, although each of these drugs has important toxic effects.

Research on Prevention of Sudden Death

Why is it that so little has been achieved in the prevention of sudden death over the last few years when it is known that it is an outstandingly important public health problem, and that there is reason to believe that a well-organized research program could well result in a substantial impact?

The reasons may include the following:

1) Sudden death usually occurs outside the hospital. It has little emotional impact on physicians, who are not motivated to study a problem which does not present itself to them.

2) The detailed analysis of ventricular arrhythmias and the assessment of antiventricular-arrhythmic drugs is often boring. This, and the fact that little can be achieved within a one-year period, makes this field unattractive to research fellows.

3) Because much of the work in this field is promoted directly or indirectly by drug companies, it is viewed with suspicion by grant-giving research bodies.

4) The drug companies themselves are discouraged from developing new drugs because of the restrictions and bureaucracy involved in gaining clinical acceptance for their products.

It seems that there is an area where the combined and coordinated efforts of academic clinical departments, grant-aiding bodies, and the pharmaceutical industry should be harnessed to the specific end of developing and testing new drugs.

References


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**Table 3. Practolol Postinfarction Trial: Time of Deaths in Pre-entry Inferior Infarcts**

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<thead>
<tr>
<th></th>
<th>Practolol</th>
<th>Placebo</th>
<th>P</th>
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<tbody>
<tr>
<td>First 2 hours</td>
<td>11</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>2-24 hours</td>
<td>9</td>
<td>1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
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*From Multicentre International Study.*

9 Time of death after onset of recurrence of heart attack in patients on practolol and placebo who had pre-entry inferior infarcts.
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