Hotline Editorial

The amiodarone trials

The mortality of patients in the years after myocardial infarction remains high, in spite of all the advances in recent years. Numerous studies of prognosis have established left ventricular function and ventricular arrhythmias as main predictors of death[1,2], a high proportion of which are due to ventricular arrhythmias. It seemed at one time that the obvious approach to this problem was to identify those with complex or frequent arrhythmias and treat them with an anti-arrhythmic drug. The distressing finding of the Cardiac Arrhythmia Suppression Trial (CAST)[3] that sodium channel (Class I) drugs increased death (especially sudden death) in patients in whom serious arrhythmias could be suppressed led to a reconsideration of the principles behind the attack on post-infarction mortality. Was the principle wrong, or were the tragic results of CAST due to the peculiar pro-arrhythmic characteristics of Class I drugs?

Experiences with amiodarone in small post-infarction trials were encouraging but not entirely consistent[4,5]; the case for larger trials was strong. The European Myocardial Infarct Amiodarone Trial (EMIAT)[6] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[7] took different approaches to the problem. EMIAT selected only patients with poor left ventricular function after infarction (left ventricular ejection fraction of 40% or less), irrespective of whether they had symptomless arrhythmias (although these were recorded), whereas CAMIAT selected patients with frequent or repetitive ventricular premature depolarizations. The primary outcome of the two trials were also different — in EMIAT being all-cause mortality, in CAMIAT the composite of resuscitated ventricular fibrillation and arrhythmic death. Both trials were of moderate size (EMIAT 1488 patients and CAMIAT 1202), and thought by the trialists to be of sufficient size to address the primary outcome variable. As had been anticipated, a high proportion of patients discontinued their medication during the trials, but serious side-effects were few. No cases of torsades de pointes were observed, in striking contrast to the findings in the other Class III trials. The most important findings in both trials was that there was no significant reduction in total mortality, but a significant reduction in arrhythmic death and resuscitated cardiac arrest. What does this mean in practical terms? Gottlieb[8], in a withering attack on the authors' interpretation of the studies, entitled his editorial in the Lancet 'Dead is dead — artificial definitions are no substitute'. He argues that it does not matter how you die, it is death that matters. Viewed from the coffin, this may be true, but seen from Olympus the conclusion might be different. His first criticism is based on the fact that unwatched death was assumed to be arrhythmic if no alternative explanation was forthcoming. What is the answer to his criticisms? First, it is true that death in these circumstances may be due to a variety of causes such as pulmonary embolism, cardiac rupture, aortic dissection and so forth. But in the clinical context of the study, ventricular arrhythmias are the most likely mechanism of death, and it is probably only arrhythmic death that amiodarone would reduce significantly. Therefore, although Gottlieb has a point, it does not invalidate the conclusions of the authors.

Secondly, apart from beta-blockers, amiodarone is virtually unique amongst anti-arrhythmic drugs in reducing arrhythmic death without pro-arrhythmia. Therefore, while there is little evidence to support the routine use of amiodarone in the kinds of patients included in EMIAT and CAMIAT, it is not unreasonable to extrapolate the findings to patients for whom there are strong indications for anti-arrhythmic therapy. As the EMIAT authors write 'the clinician may be encouraged to consider amiodarone for patients with symptomatic or sustained and potentially dangerous arrhythmias, even after myocardial infarction'. Thirdly, each of the amiodarone trials has been relatively small, and it may well be that a meta-analysis of all the trials, as is now being undertaken, will provide more compelling evidence as to amiodarone's place in therapy.

Finally, the trials should encourage new trials that should better define the role of amiodarone or similar drugs in post-infarction patients at high risk. The criteria used for selecting patients in EMIAT and CAMIAT may not be the best available today. Improved techniques may allow us to define the groups of patients who will benefit most from this approach. Furthermore, one would hope that pharmacological research will be pursued vigorously so as to identify new agents which will have the
desirable characteristics of amiodarone without its disadvantages.

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References


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Hormone replacement therapy: current perspectives and future directions

The totality of evidence suggests that endogenous oestrogen and post-menopausal hormone replacement therapy reduce risks of cardiovascular disease. Since cardiovascular disease remains far and away the leading cause of death among women as well as men in most developed countries, hormone replacement therapy could have a substantial individual and public health impact.

More than 30 observational epidemiological studies have reported that post-menopausal women who use hormone replacement therapy have a lower risk of coronary heart disease than non-users, with risk reductions in most studies of 35% to 45%. The major mechanism of oestrogen's cardioprotective effect is its anti-atherogenic effect on the lipid profile. Specifically, hormone replacement therapy decreases low-density lipoprotein (LDL) cholesterol and increases high-density lipoprotein (HDL) cholesterol. Hormone replacement therapy also has a potential antithrombotic mechanism, resulting in decreased arterial impedance, increased production of prostacyclin and decreased production of thromboxane A2 by platelets.

In addition to cardioprotective benefits, hormone replacement therapy use is also associated with increased risks of osteoporosis, and recent studies have raised the possibility of protective effects on colon cancer, stroke and Alzheimer's disease. Any benefits, however, must be weighed against the clear increase in risk of uterine cancer with unopposed oestrogen and probable increases in breast cancer risk with all preparations, especially with long-term use.

The well-established risk of oestrogen-induced endometrial hyperplasia and neoplasia has focused attention on the effects of combined oestrogen/progestin regimens, which are increasingly prescribed for women with intact uteri. There had been concern, however, that progestin, through less favourable effects on lipid parameters, might also substantially attenuate or even abolish the cardioprotective effects of oestrogen. This question was addressed in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, which compared the effects of unopposed oestrogen, three different oestrogen/progestin regimens, and placebo on cardiovascular risk factors among 875 healthy post-menopausal women. Each hormone regimen increased HDL cholesterol levels, although oestrogen alone and a combined regimen using a cyclic micronized natural progesterone were associated with greater HDL increases than the combined regimens using continuous...