Review Article

Primary Prevention of Sudden Cardiac Death: Apart From the Defibrillator, What Is Important in Patients with Myocardial Infarction or Heart Failure?

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Sudden cardiac death (SCD) continues to be one of the most important health problems worldwide. It is responsible for around 400,000 deaths annually in the USA, equivalent to around 63% of cardiovascular deaths.[1,2] Episodes of ventricular tachycardia or ventricular fibrillation are its most common electrical substrate, while 80% of its victims have coronary artery disease.[1-3] Conversely, patients with a history of myocardial infarction or heart failure are at increased risk of SCD, usually because of ventricular tachyarrhythmias.[1-3] Indeed, the likelihood of SCD increases by 4-6 times in patients with myocardial infarction, and by 6-9 times in those with heart failure.[2]

Prevention of sudden cardiac death

The use of implantable defibrillator devices in the primary prevention of SCD has contributed significantly to a reduction in mortality among high risk patients, including post-infarction patients with left ventricular dysfunction and patients with heart failure.[4-10] Large randomised studies have shown that these devices have reduced the incidence of SCD and improved the prognosis of selected high risk patients by terminating life-threatening ventricular tachy-arrhythmias.[4-10] On the other hand, the reduction in mortality found in these large randomised studies of primary prevention was the same as in studies of secondary prevention of SCD.[4-10]

Not all post-infarction patients have an indication for defibrillator implantation, according to the entry criteria of the above studies; furthermore, these devices have not been found to reduce mortality in the immediate post-infarction period, when the risk of SCD is higher.[11] Thus, the benefits of these devices are an addition to those of the optimum drug therapy that all post-infarction patients should receive.[4-10]

What is important apart from defibrillators?

Apart, then from defibrillators, optimisation and reinforcement of the pharmaceutical therapy delivered is considered to be of vital importance, and is often our only choice in attempting to reduce the overall mortality from SCD and to improve the prognosis of post-infarction patients or those with heart failure.

During the last decades, randomised clinical studies have attempted to evaluate the role of various drugs in the primary prevention of SCD and the reduction of overall mortality in high risk patients. However,

the first results were not encouraging, because while defibrillators improved survival, the standard antiarrhythmic agents failed to reduce, and in certain cases even increased SCD incidence or overall mortality. The publication of the Cardiac Arrhythmia Suppression Trial (CAST) helped us to become aware that in practice class I antiarrhythmics increase mortality, mainly because of an increase in arrhythmological deaths, when they are given to patients with coronary artery disease.[12]

Among the standard antiarrhythmic drugs, amiodarone is the only agent for which there are signs that it reduces mortality from SCD and at least does not increase the overall mortality of patients with coronary artery disease or heart failure. Indeed, amiodarone did not significantly reduce total or cardiovascular mortality in the CAMIAT trial, even though it significantly reduced the incidence of SCD in the CAMIAT and EMIAT studies and in a subsequent meta-analysis.[13-15] Its beneficial effect on arrhythmological mortality appears to be neutralised by the increase in deaths from causes other than SCD and by the high rate of therapy interruption because of side effects.[13-15] In addition, retrospective analyses have shown that the greatest, if not the only benefit of amiodarone comes when it is administered together with β-blockers.[16] Dofetilide and azimilide also do not appear to have a negative effect on prognosis and are considered as alternatives to amiodarone in cases where the latter drug is not tolerated or is ineffective.[17,18]

In general, standard antiarrhythmic drugs have only a limited place in the treatment of ventricular arrhythmias in patients with coronary artery disease or heart failure, and should only be used in the following circumstances:

1. Benign, non-sustained ventricular arrhythmias causing intense and continuous symptoms that are not tolerated by the patients and cannot be controlled with β-blockers.

2. As supplementary therapy to a defibrillator for the control of ventricular tachyarrhythmias in order to reduce device discharges.

3. In patients with potentially lethal ventricular arrhythmias who are not candidates for a defibrillator or who do not wish to undergo device implantation.

However, a significant reduction in cardiovascular mortality, including SCD, and an improvement in the prognosis of post-infarction patients and those with heart failure has been achieved through the use of β-blockers and other "non-antiarrhythmic" drugs (drugs without main, direct electrophysiological ef-

fects on the myocardium or on the special stimulus conduction network), such as converting enzyme inhibitors, angiotensin receptor inhibitors, statins, spironolactone, and perhaps ω-3 fatty acids.

The benefit of β-blockers is the result of various, well-established drug properties, such as an increase in the density and sensitivity of cardiac β-adrenergic receptors, a decrease in neurohormonal activation and catecholamine cardiotoxicity, a reduction in heart rate and myocardial oxygen demand, a reduction in blood pressure, an improvement in cardiac structure and function, and a reduction in oxidative stress and apoptosis of myocardial cells.[19] As a result, β-blockers improve symptoms and hospitalisation rate, reduce the risk of further myocardial necrosis and reinfarction, and reduce the contribution of ischaemia to the occurrence of severe arrhythmias, thus contributing to a reduction in SCD and an improved prognosis in patients with coronary artery disease and/or heart failure.[19]

Recommendations for the administration of β-blockers after myocardial infarction were based on their ability to improve prognosis and reduce the recurrence of infarction in a large number of clinical studies.[19] Among 201,752 infarction patients in the Cooperative Cardiovascular Project, those who received β-blockers had lower two-year mortality compared with those who did not.[20] As early as the 1980s it became apparent that the improvement of survival in these patients was due to a significant degree to a reduction in SCD.

Propranolol administration led to a significant reduction in all-cause and cardiovascular mortality, SCD, and the incidence of coronary events in patients with myocardial infarction.[21] Patients with heart failure reaped the greatest benefit. Similarly, the reduction in total mortality after the long-term administration of metoprolol was mainly due to a 40% reduction in SCD.[22] Recent randomised clinical studies have confirmed the beneficial effects of β-blockers on the prognosis of patients with myocardial infarction and/or heart failure. In the CAPRICORN trial, carvedilol further reduced the high mortality among patients with myocardial infarction and left ventricular dysfunction, also lowering the incidence of sustained ventricular tachyarrhythmias by more than 70%.[23,24] Finally, the added benefit of β-blockers in post-infarction patients with defibrillators was shown by a post hoc analysis of MADIT II, in which β-blockers reduced device discharges for ventricular tachyarrhythmias and improved survival in the patients who were taking the largest doses.[25]

Recently, the highly significant contribution of the renin-angiotensin-aldosterone system to cardiac diseases has been recognised and extensive research is under way into the possible clinical benefit of medications that block it in various clinical situations.

Angiotensin converting enzyme inhibitors lower the concentration of angiotensin II that is available to connect with its receptors, thus achieving partial blockade of the system.[26] These drugs have been used with impressive results in arterial hypertension, asymptomatic and symptomatic left ventricular dysfunction, heart failure, and myocardial infarction.[26] The use of these medications in patients with myocardial infarction has improved their survival and contributed to a reduction in fatal cardiovascular complications.[26,27] The benefit is greater in high risk patients, such as those with signs of heart failure and/or left ventricular systolic dysfunction. Various clinical studies have confirmed their efficacy and safety and have shown a significant reduction in mortality, both all-cause and from SCD. A recent meta-analysis showed that they reduce all-cause mortality by 17%, cardiovascular mortality by 15%, and SCD by 20%.[27]

Angiotensin II receptor blockers also contribute to the pharmaceutical blocking of the renin-angiotensin-aldosterone system via a different route. They reduce afterload, increase cardiac output, and prevent left ventricular remodelling after myocardial infarction. Studies have demonstrated the contribution of these drugs to a reduction in mortality in patients with heart failure and myocardial infarction.[28,29] In general, angiotensin II receptor blockers are given to patients who do not tolerate the converting enzyme inhibitors, although the two medications can be coadministered.[28,29] In a suitable dosage they might be equally as effective as converting enzyme inhibitors in reducing SCD, although further studies will be needed to confirm this.[28,29]

Despite treatment with angiotensin II receptor blockers and converting enzyme inhibitors, aldosterone levels often remain high in patients with heart failure or myocardial infarction. In two recent studies of patients with heart failure and myocardial infarction, aldosterone blockade with spironolactone and eplerenone led to a reduction not only in total mortality, but also in SCD. In the RALES study, spironolactone administration was associated with a 30% reduction in total mortality, which was the result of a reduction in deaths from heart failure by 34% and from SCD by 29%.[30] In the EPHESUS trial, eplerenone significantly reduced total mortality, almost exclusively as the result of a reduction in cardiovascular deaths.[31] At least half of the benefit

was credited to a reduction in SCD.[31] The mechanisms of the beneficial effects of aldosterone blockade on the survival and prognosis of high risk patients with myocardial infarction and/or heart failure have not been fully elucidated. Apart from the beneficial action on electrolytes and intravascular volume, it is likely that these drugs reduce inflammation in the coronary vascular net, inhibit interstitial fibrosis, improve endothelial function, and limit sympathetic stimulation.

Statins administered to patients with myocardial infarction have brought about a significant reduction in mortality. At least a part of this positive effect seems to be due to a reduction in SCD. Studies of patients with defibrillators have shown that statins reduce the frequency of appropriate treatment discharges.[32] In MADIT II, patients who were taking statins had a lower incidence of SCD. Although their antiarrhythmic mechanism is not clear, there are indications that they reduce myocardial ischaemia, ventricular dilatation, and myocardial fibrosis.[33]

It also appears that ω-3 fatty acids have a beneficial effect in patients with myocardial infarction and/or heart failure. These substances are claimed to improve endothelial function, stabilise cell membranes, prevent platelet accumulation, and inhibit the proliferation of smooth muscle fibres. In addition, there are indications that they prevent excessive intracellular calcium concentrations, stabilising the function of L-type calcium channels in periods of stress and inhibiting voltage-gated sodium channels. Recent studies of patients with myocardial infarction have shown that ω-3 fatty acids contribute to a reduction in mortality, mainly through a reduction in SCD.[34,35]

Conclusions

SCD continues to be one of the most important and intractable health problems, despite the progress that has been made in understanding its pathophysiological mechanisms and the improvements and developments in methods for its management. SCD has a particularly high incidence among patients with myocardial infarction and/or heart failure.

In spite of the reduction in mortality among high risk patients, and the parallel reduction in SCD, from the use of implantable defibrillator devices, drug treatment continues to be an indispensable and irreplaceable component of therapy.

Of all the antiarrhythmic drugs, only β-blockers, and perhaps amiodarone, especially when coadministered with β-blockers, have a proven ability to reduce

SCD apart from a reduction in total mortality. It is important to keep in mind, however, that the drugs used in the standard treatment of patients with myocardial infarction and/or heart failure bear a large degree of responsibility for the improvement in these patients' prognosis, and thus contribute to the reduction in all-cause mortality and in SCD.

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