Can drug effects on mortality in heart failure be predicted by any surrogate measure?

Introduction

In chronic heart failure, the impact of the drug therapy on mortality is a crucial issue that can best be answered by large expensive mortality trials. The need for these large expensive trials can act as a hindrance towards novel drug development. Indeed, the daunting prospect of such an expensive trial may explain why the pharmaceutical industry has produced 20 different ACE inhibitors rather than 20 novel compounds all acting via different mechanisms. There are, however, surrogate markers which might help circumvent this problem. These non-invasive surrogate markers could help in two ways. Firstly, it may be possible for a marker to give a reasonably accurate indication of what effect the proposed new drug would have in any subsequent large mortality trial. We would then be able to select out promising drugs for these mortality studies from a large range of candidate novel therapies and avoid the current situation where financial pressures may stifle novel drug development indiscriminately. Secondly, successful markers of mortality might themselves be potential targets for future drug development in the expectation that some of these markers represent key processes leading to mortality.

However, in order for these markers to be accepted as surrogates for cardiac mortality, there must be sufficient evidence to show that drug therapy which alters mortality also causes a corresponding change in the surrogate. Not too long ago ejection fraction was considered a potential surrogate end-point for survival in patients with heart failure. However, its positive predictive value for sudden death is low and inotropic drug therapy such as milrinone, which improved ventricular function, had the opposite, adverse effect on mortality1'1. Hence, surrogates other than ejection fraction will need to be considered. Recent compelling evidence linking the autonomic nervous system and cardiac mortality including sudden death2'-3), suggests to us that parameters such as heart rate variability, baroreceptor sensitivity and ventricular repolarization characteristics (QT dispersion) may well serve this purpose as potential surrogate markers. However, the predictive value of many of these autonomic markers is at present, uncertain.

The objective of this article is to assess how accurate these potential surrogate markers actually are at predicting drug effects on mortality in chronic heart failure. We have attempted to do this by reviewing the different drugs that have had an impact on mortality in heart failure and to see what their effects are on various potential surrogate markers. The markers that we have looked at include heart rate and its variability, baroreceptor sensitivity, QT dispersion, arrhythmias, late potentials and neurohormones.

The effect of drug therapy on various surrogate markers in chronic heart failure (see Table 1)

Drugs that have a favourable effect on mortality

ACE inhibitors

The mortality benefits of ACE inhibitors have been attributed to both neurohormonal suppression and vasodilatation6). Furthermore, it has been shown that the effect of ACE inhibitors on mortality reduction was greater in those with a high baseline circulating norepinephrine level or an activated renin angiotensin system7). This reduction in mortality is paralleled by changes in various markers of autonomic tone, including a decreased heart rate8), increased heart rate variability9'-11), increased baroreceptor sensitivity12'-14), decreased QT dispersion15) and a reduction in malignant ventricular arrhythmias16'-18). In summary therefore, all potential surrogates are favourably altered by ACE inhibitors, which correspond with their favourable effect on mortality6'-8,19).

Hydralazine-isosorbide dinitrate

The vasodilator combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality in the V-HeFT I study20). It has no impact on arrhythmic events in patients with left ventricular dysfunction and a history of inducible ventricular tachycardia21). However, unlike ACE inhibitors, the hydralazine plus isosorbide dinitrate combination is associated with a small but significant rise in heart rate and an increased plasma norepinephrine concentration during the first year of follow-up6). However, the impact on autonomic markers such as heart rate...
variability and baroreceptor sensitivity is not known. In summary, unlike the situation with ACE inhibitors, there is a discrepancy here between their favourable effects on mortality and their unfavourable effects on heart rate and neurohormones.

**Beta-blockers**

In addition to heart rate reduction,[22,23] beta-blockers have consistently improved heart rate variability,[10,24,25] and plasma neurohormones (e.g. ANP, catecholamines)[26,27]. Beta-blockers have also been reported to reduce ventricular tachyarrhythmias[28,29]. The reports on the effects of beta-blockers on baroreceptor sensitivity are, however, conflicting[30,32]. With regard to QT dispersion, beta-blockers have also been shown to reduce QT dispersion in the long QT syndrome[33,34]. This has been demonstrated by Napolitano et al.[33] who found that beta-blockers caused a greater reduction in those with higher baseline values. Sotolol also reduces QT dispersion in post-myocardial infarction patients[35].

In chronic heart failure, the corresponding data on mortality are not entirely clear, although favourable effects are likely. Metoprolol[22] and bisoprolol[23] have produced favourable but not statistically significant data on mortality. However, more recently, carvedilol[36], a second generation beta-adrenergic antagonist with \( \alpha_1 \)-blocking effects, has been shown to reduce mortality by 65% when compared to placebo in chronic heart failure. Therefore as far as beta-blockers are concerned, there is good consensus between their effects on mortality and their effects on all surrogates.

**Drugs that have no overall impact on mortality**

**Digoxin**

Until recently the use of digoxin therapy in chronic heart failure and sinus rhythm has been controversial. Digoxin has been shown to reduce heart rate significantly in some studies[37,38] but not in others[39]. Furthermore, it has also been shown to have favourable autonomic modulating properties; it restores heart rate variability[37,38], improves baroreceptor sensitivity[40] and reduces circulating catecholamines[37,41,42]. However despite these promising signs, digoxin had no impact on mortality in the DIG trial[43] or on arrhythmic events in the DIMT study[44].

**Calcium channel antagonists**

The use of Ca-channel blockers in heart failure has been controversial because of their potentially negative inotropic activity and their ability to activate the neurohormonal system[44]. However, recent evidence has shown that the second generation dihydropyridines (e.g. amlodipine or felodipine) possess more favourable neurohormonal effects[45,47]. They appear to have no adverse effects on plasma norepinephrine levels in either normal subjects[46] or heart failure patients[45,47]. The long-term impact of these drugs on heart rate has not been reported from large trials. Although some dihydropyridines are known to cause an acute reflexogenic rise in heart rate, there are several small studies which show that the heart rate may subside in the long term[48]. The effects of calcium antagonists on heart rate variability in chronic heart failure is not known, but felodipine has been shown to have no significant effect on heart rate variability in post-myocardial infarction patients[49]. Similarly, Cook et al.[49] could not show any effect with diltiazem in normal subjects. Only verapamil, which is not used in heart failure, has been shown to improve heart rate variability in post-myocardial infarction patients[60]. There are some data suggesting that calcium antagonists improve baroreceptor
sensitivity\textsuperscript{45,52} in heart failure. In mortality trials, amlodipine and felodipine appear overall to have a neutral effect\textsuperscript{53,54}.

**Amiodarone**

Amiodarone deserves a separate mention. Low dose amiodarone was shown to reduce total mortality (including sudden death) by 28\% over a 2 year period in the GESICA trials\textsuperscript{55}. However, controversy has arisen, as another trial, CHF-STAT\textsuperscript{56} showed no improvement in survival with amiodarone despite an improvement in LV ejection fraction. The discrepancy has not been fully explained, but may be partially accounted for by differences in doses and characteristics of the patients used in the two studies. Preliminary results from the recent EMIAT and CAMIAT trials of post-myocardial infarction patients (including those with LV dysfunction) have revealed a reduction in arrhythmic events, although total mortality was not reduced. Nonetheless, amiodarone appears to have a favourable effect on potential surrogate markers; it has been shown to reduce heart rate significantly in both the GESICA\textsuperscript{55} and CHF-STAT\textsuperscript{56} studies. Furthermore it also improves increase heart rate variability\textsuperscript{157,58} and reduces QT dispersion\textsuperscript{159,60}.

**Drugs with adverse effects on mortality**

**Dopamine Receptors Agonists (Ibopamine)**

Ibopamine is an active dopaminergic prodrug which works primarily as a vasodilator with some inotropic activity. It has no significant effects on heart rate\textsuperscript{17}. Furthermore, it does not appear to have any significant proarrhythmic effects as documented by Holter monitoring and signal-averaged ECGs\textsuperscript{45,62}. It has also been shown to modulate the autonomic tone favourably and to reduce circulating plasma neurohormones\textsuperscript{42,63}. An improvement in heart rate variability (although not statistically significant) has also been documented in both the DIMT study\textsuperscript{37}. Published long-term survival data are unavailable at present but the multicentre trial PRIME II (second Prospective Randomised study of Ibopamine on Mortality and Efficacy) has apparently been terminated due to adverse effects on mortality. Ibopamine would appear to be the most worrying example of disagreement between survival data and the results with potential surrogate markers; with the latter suggesting favourable effects which were far from reproduced in the mortality trial.

**Flosequinan**

Flosequinan is a novel vasodilator with inotropic properties, no longer in use because of its adverse effects on mortality\textsuperscript{64,65}. It caused an increase in heart rate\textsuperscript{66} and is associated with increased norepinephrine levels\textsuperscript{65}. However, the worsened mortality is inconsistent with its effects on heart rate variability, where it appears to increase parasympathetic and decrease sympathetic tone, respectively\textsuperscript{60}.

**Positive inotropic agents (milrinone)**

Despite their beneficial effects on the haemodynamics of heart failure, phosphodiesterase inhibitors such as milrinone have been shown to have adverse effects on mortality\textsuperscript{11}. They are known to activate the neuroendocrine systems, especially the renin-angiotensin system\textsuperscript{67} and predispose the myocardium to arrhythmia\textsuperscript{68}. The effects of these inotropic agents on autonomic markers such as heart rate variability are unknown.

**Anti-arrhythmic therapy**

The use of antiarrhythmic therapy in chronic heart failure is limited. Apart from amiodarone, most antiarrhythmic drugs (especially Class I) have no significant effects on baseline heart rate but are associated with proarrhythmic effects, increased mortality and a deterioration in heart rate variability\textsuperscript{57}.

**Summary**

Clearly at present, the one perfect surrogate marker for mortality remains elusive. Chronic heart failure is a complex syndrome: as such it may perhaps be too simplistic to expect any single parameter to be universally predictive of drug effects on mortality, especially when each drug works by different mechanisms.

Nevertheless, neurohormonal antagonists, such as ACE inhibitors and beta-blockers, seem to benefit both mortality and all surrogate markers of mortality. Equally, inotropic drugs and Class I antiarrhythmics appear to worsen both mortality and many surrogates. This is encouraging. However, significant discrepancies exist, particularly for digoxin, ibopamine and hydralazine-nitrates, although it is only with the latter two that diametrically opposite effects occurred, whereby favourable surrogate effects turned into unfavourable mortality effects (or vice versa). It appears appropriate to have guarded optimism about the potential use of these surrogates to predict drug effects in chronic heart failure. Given our current understanding, none of the parameters discussed above is perfect when used alone. Perhaps a battery of surrogates would be more appropriate.
rather than there being any single surrogate. The most promising surrogates are heart rate variability, QT dispersion and plasma neurohormones, the first two for sudden death and the last one for death from progressive disease.

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