Rationalizing the heart failure trials: from theory to practice

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It is 10 years since the CONSENSUS I study showed that ACE inhibitors improved mortality in heart failure.

This finding has been confirmed in numerous trials, for example SOLVD, SAVE. Indeed, in the intervening 10 years, many other potential therapies have been examined in mortality trials, but so far no other therapy has had as good effect on mortality as ACE inhibitors.

The other therapies which have been examined are digoxin, amlodipine, beta-blockers, amiodarone, etc. Despite ACE inhibitors being a very effective therapy for heart failure, there is still remarkable under-use of them in clinical practice. The reason for this needs to be explained further, but fear of hypothermia and renal dysfunction appear to be major factors.

Key Words: Chronic heart failure, angiotensin converting enzyme inhibitors.

Drugs used in heart failure trials

Chronic heart failure is a disease which is common, costly, disabling and also very deadly for the patient — but the important thing is that chronic heart failure is also very treatable. There have been many clinical trials recently so that we now know a lot more about how best to treat chronic heart failure than we knew even 4 years ago (Table 1).

Diuretics

The initial treatment in chronic heart failure is diuretics which improve symptoms in the patients, although we do not know what effect diuretics have on survival. We probably never will know this because diuretics are so good at relieving symptoms that no mortality trial will ever be done with diuretics alone.

ACE inhibitors

The next class of drugs which should be given to all patients with heart failure is the angiotensin-converting enzyme inhibitors (the ACE inhibitors). Recent trials have shown unequivocally that they improve both symptoms and survival. The evidence shows clearly that all patients with chronic heart failure should be treated with an ACE inhibitor. In the 1990s there can be no doubt about this procedure. The first-ever trial in this area was the CONSENSUS 1 trial, now 10 years old[1]. In it enalapril was found to reduce the death rate in severe grade 4 heart failure by about 50%. The next study was the SOLVD Treatment study which investigated patients with mild to moderate heart failure. Again an ACE inhibitor reduced mortality, this time by 20–30%. The third large-scale trial was the SOLVD Prevention trial which investigated patients with asymptomatic left ventricular dysfunction[2]. Again the ACE inhibitor reduced important end-points such as death or hospitalization.

Hydralazine with isosorbide dinitrate

After ACE inhibitors, the next treatment which has been shown to improve mortality is a combination of hydralazine and isosorbide dinitrate. This was originally
shown in the VHeFT 1 trial in which hydralazine and isosorbide dinitrate were shown to reduce the mortality rate\(^3\). In a subsequent trial (the VHeFT 2 trial) hydralazine and isosorbide dinitrate were compared with enalapril and in this enalapril was superior to hydralazine with isosorbide dinitrate at improving mortality. For that reason an ACE inhibitor is preferable to all other vasodilators in patients with heart failure.

**Digoxin**

The next treatment to consider is digoxin, but there are very recent data on use of digoxin. The most recent trial (DIG trial) showed that digoxin had a neutral effect on mortality. It was neither beneficial nor harmful. However, we do know from earlier trials that digoxin does improve the symptoms of patients with heart failure and we are therefore left knowing now that digoxin improves symptoms but has a neutral effect on mortality.

**β-blockers**

The next group of drugs which tend to be indicated in chronic heart failure are the β-blockers. Clearly this is a complete turnaround from what we used to believe but there is evidence now accumulating to suggest that β-blockers delay progression of the disease. However, this issue is not clear-cut and there are numerous questions still to be answered about β-blockers. In one of the β-blocker trials (the MDC trial) patients with dilated cardiomyopathy were randomized to placebo or metoprolol. Death itself did not seem to be significantly altered but the need for a cardiac transplant was remarkably reduced by metoprolol and this is consistent with the idea that β-blockers slow down the rate of progression of the disease. In another trial (the CIBIS trial) patients were randomized to bisoprolol or placebo and there was a non-significant trend towards a benefit with bisoprolol\(^4\). One might have thought that β-blockers would be particularly beneficial in heart failure patients who had previously had myocardial infarctions. However, in the CIBIS trial exactly the opposite was found in that the patients who tended to benefit most from bisoprolol were those who had no history of a myocardial infarction. This is obviously a surprising observation which has not yet been explained.

As well as the MDC and the CIBIS trials, there have been several smaller trials. In a meta-analysis of these two large trials together with the smaller trials, there was a non-significant trend towards benefit with β-blockers against mortality. However, the concept of β-blockers has been thrown into disarray by the recent U.S.A. Carvedilol trial\(^5\). Carvedilol is a unique β-blocker because it is a non-selective β-blocker which is also an α-blocker and which also has antioxidant activity which makes it special pharmacologically. The recently published trial from the U.S.A. showed a marked reduction in mortality in patients given carvedilol. Although the absolute reduction in mortality in the carvedilol trial is low, the relative reduction in mortality is the largest ever seen in any heart failure trial. The mortality rate was 7-8% in placebo and 3-2% with carvedilol, which is a 65% reduction in risk. There has never been such a large reduction in relative risk in any previous heart failure trial, although the absolute reduction is small. Therefore, we are a little unclear over β-blockers. Large question marks hang over β-blockers and we require further data before β-blockers should be used in a more widespread fashion.

**Amiodarone**

The next drug which has been assessed in mortality trials is amiodarone. The data are again mixed with one trial showing a mortality benefit and one showing a neutral effect. The first trial was the GESICA trial in Argentina where amiodarone was found to significantly reduce mortality\(^6\). Interestingly, in this trial amiodarone reduced mortality due both to sudden death and to progressive heart failure. The benefit with amiodarone was interestingly seen in those with and in those without apparent ventricular tachycardia, which suggests the possibility that amiodarone was working through some other mechanism other than its antiarrhythmic effect. However, a second study was performed in the U.S.A. (the CHFSTAT trial) and there no difference was found between amiodarone and placebo\(^7\). One interesting finding was that amiodarone only seemed to have beneficial effect if you looked at patients with non-ischaemic heart failure i.e. those with cardiomyopathies. Therefore, the findings are inconsistent in relation to amiodarone. There was a beneficial mortality in the GESICA trial and interestingly, in the GESICA trial most of the patients had cardiomyopathies. In the U.S.A. CHFSTAT trial there was no overall mortality benefit although there did appear to be a benefit in patients who had cardiomyopathies. We can perhaps conclude, therefore, that amiodarone is of value in patients with cardiomyopathies but is not of any mortality benefit in patients with ischaemic heart failure. However, this whole area of class III antiarrhythmias has been put into even greater disarray by the recent SWORD trial in which D-sotalol was found surprisingly to increase mortality in patients with left ventricular dysfunction after a myocardial infarction\(^8\). D-sotalol is an interesting drug because it is not a β-blocker. Instead, it is a class III antiarrhythmic drug as is amiodarone and therefore D-sotalol has some similarities to amiodarone. It is, therefore, somewhat worrying that a drug similar to amiodarone appears to increase mortality in patients recovering from a myocardial infarction, such a finding makes many physicians rather hesitant about using amiodarone except where there are symptomatic arrhythmias necessitating treatment.
**Amlodipine**

The remaining drug that has been studied in a mortality trial is amlodipine. The rationale behind this is that vasodilators are of benefit in heart failure and calcium antagonists are obviously vasodilators, so that it seemed natural to find out whether amlodipine would have any beneficial effects on mortality in the same way as hydralazine and isosorbide dinitrate had. Therefore, the PRAISE study was performed\[10\]. In this study, amlodipine was found to have no significant effect on mortality; it neither improved nor deteriorated mortality. However, the PRAISE study had another interesting finding: amlodipine did have a significant beneficial effect in patients with cardiomyopathies, whereas amlodipine had no beneficial effect in patients who had heart failure due to ischaemic disease. A smaller study with felodipine (the VHeFT 3 trial) also found no overall effect on mortality with felodipine.

**Overall indications**

Therefore we now know quite a lot about which drugs should be used and what drugs should not be used in heart failure. The clear message is that all patients with heart failure should be on an ACE inhibitor and perhaps a diuretic if they need it. This message has come through repeatedly from all the mortality trials and yet it is surprising to discover that in the U.K. only 33% of patients with heart failure actually receive an ACE inhibitor drug\[10\]. There can be no real excuse for this and it is shameful that 67% of patients with heart failure are being denied treatment that would improve their symptoms and their survival. Why? What possible justification can there be for patients with heart failure not receiving treatment which has been shown to improve their symptoms and their survival?

**General problem**

The main reason for patients being denied effective treatment is that doctors have an unreasonable concern about the side effects of ACE inhibitors. Doctors are worried about the fall in blood pressure and about renal dysfunction. We will try to put those concerns in perspective in the figures from the CONSENSUS 1 trial of the number of patients who had to have the drug withdrawn because of side effects. As far as hypotension is concerned, this amounted to seven patients out of 126 who had to have their drugs stopped because of renal dysfunction. We will try to put those concerns in perspective in the figures from the CONSENSUS 1 trial of mortality in the case of a β-blocker may even improve the rate of progression of heart failure over time. Finally, if there is concern about first-dose hypotension then perindopril could be the ACE inhibitor of choice.

**Conclusion**

In conclusion, all patients with heart failure should receive an ACE inhibitor and most patients should receive a diuretic. If an ACE inhibitor is not tolerated for any reason then hydralazine and isosorbide dinitrate can be substituted for the ACE inhibitor. If the patient is still symptomatic, despite the correct dose of diuretic and an ACE inhibitor, then digoxin can be added to their regime or hydralazine and isosorbide dinitrate can be added to their regime. Both of these will help improve their symptoms. If a patient has symptomatic arrhythmias, amiodarone is worth adding to their drug regime but there seems little justification for using amiodarone in all patients unless they have documented arrhythmias. Further, if the patient has coincidental angina, which is quite common in heart failure, then it seems safe to use a β-blocker or amlodipine as these drugs will not have any harmful effect on mortality in heart failure — and in the case of a β-blocker may even improve the rate of progression of heart failure over time. Finally, if there is concern about first-dose hypotension with an ACE inhibitor, then perindopril is a reasonable choice because uniquely it does not appear to reduce systemic BP.

**References**


