Dofetilide for the treatment of atrial fibrillation in patients with congestive heart failure

Both atrial fibrillation and congestive heart failure occur more commonly in older age groups. As the world population ages, the prevalence of both atrial fibrillation and congestive heart failure will increase\[1,2\]. When the two conditions are both present, mortality is very high\[3\]. Atrial fibrillation is also a frequent reason for worsening of heart failure requiring hospitalization. Currently the only available medication that can be used to achieve sinus rhythm in the setting of heart failure is amiodarone\[4,5\], which is associated with frequent and occasionally serious side effects\[6\].

In recent years, the use of pure class III drugs for the treatment of re-entrant arrhythmias has received increasing attention. One such drug is dofetilide, which, as a pure blocker of the delayed rectifier potassium current (\(I_{Kr}\)), prolongs cardiac action potential and the QTc interval. Dofetilide has been demonstrated to be effective both in converting atrial fibrillation to sinus rhythm and for the long-term maintenance of sinus rhythm after conversion\[7\]. As with most other drugs which prolong the action potential, dofetilide carries a risk of proarrhythmia; in particular torsade de pointes ventricular tachycardia. In patients receiving dofetilide, torsade de pointes tachycardia is most frequently observed shortly after initiation of treatment, and all clinical trials have utilized in-hospital initiation with continuous electrocardiographic monitoring. The use of antiarrhythmic drugs is known to carry a particular risk of life threatening proarrhythmia in the setting of congestive heart failure\[8–10\]. Only amiodarone\[4,5\], digoxin\[11\] and beta-blockers\[12,13\] have been proven in large trials to be safe in patients with congestive heart failure, whereas a number of class I drugs\[8,14\] as well as the class III drug d-sotalol\[10\] have been shown to increase mortality in various patient populations.

The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) studies were designed to evaluate the efficacy and safety of dofetilide in patients with congestive heart failure or a recent myocardial infarction accompanied by left ventricular dysfunction. The two DIAMOND studies were conducted concurrently in 37 Danish cardiology units, and the DIAMOND CHF study has recently been reported\[15\]. Patients admitted to hospital with a diagnosis of congestive heart failure who had been in NYHA class III or IV heart failure at some time within the preceding month were eligible for DIAMOND CHF. For inclusion, severe left ventricular dysfunction, corresponding to a left ventricular ejection fraction below 35%, was required, as determined by echocardiography in a core laboratory. The study exclusion criteria, which were kept to a minimum, included severe diseases unrelated to heart failure and conditions associated with a prolonged QTc interval. Patients with a myocardial infarct within the last 7 days were excluded and considered for the DIAMOND myocardial infarct study (unpublished).

In order to determine if the patients enrolled were representative of patients usually seen in clinical practice, all centres participating in DIAMOND CHF were required to screen consecutive patients admitted to their department with congestive heart failure. A total of 5548 patients with heart failure were screened, 46% of whose ejection fraction was below 35%. Of the latter group, 60% were included in the study, with 762 patients receiving dofetilide and 756 receiving placebo.

The dose of dofetilide used in the trial was 0.5 mg twice daily. If the patient’s calculated creatinine clearance was below 60 ml . min\(^{-1}\) or if the patient had atrial fibrillation at baseline, the dose was reduced to 0.25 mg twice daily (or 0.25 mg once daily for patients with clearance 20–40 ml . min\(^{-1}\)). If the calculated creatinine clearance was below 20 ml . min\(^{-1}\) the patient was excluded from the study.

The minimum treatment period in DIAMOND CHF was 1 year. Recruitment took place over 2 years, giving a 1–3 year period of follow-up. The primary end-point in DIAMOND CHF was all-cause mortality, for which no difference was seen between dofetilide and placebo\[15\]. Since the patients in DIAMOND CHF were carefully selected to be representative of patients with moderate or severe congestive heart failure, the mortality as anticipated was high, with 311 deaths in the dofetilide group and
317 in the placebo group. As would be predicted with this high event rate, the confidence intervals around the observed result were narrow, supporting the interpretation that DIAMOND CHF was truly neutral with respect to mortality. The risk ratio associated with dofetilide treatment was 0.95, with 95% confidence limits of 0.81–1.11.

During the 3 days of continuous monitoring at initiation of therapy, 19 cases of torsade de pointes tachycardia were observed in the dofetilide group and none in the placebo group. There was also an excess of five cardiac arrests requiring electrical cardioversion in the dofetilide group. These important observations make clear the necessity for the 3 days of initial monitoring that were mandated in this study. However, the mortality outcome in DIAMOND CHF would also have been seen to be neutral if all cases of torsade de pointes tachycardia and resuscitated cardiac arrest had been added to the death count. The rate of proarrhythmia in patients with congestive heart failure is small compared to the overall mortality. This fact is important when comparing dofetilide with drugs where the benefit of in-hospital initiation has not been demonstrated, but also has not been looked for.

The study had a number of secondary end-points related to death, such as cardiovascular death and presumed arrhythmic death, and all of these endpoints were neutral for the comparison between dofetilide and placebo.

One important morbidity end-point, the time to hospitalization for worsening heart failure (defined as hospitalization during which the treatment of heart failure was intensified) showed a beneficial effect of dofetilide. As thus defined, worsening of heart failure was reduced by 25% in the dofetilide group. To understand the possible reason for this finding, it is useful to examine the effect of dofetilide in a predefined subgroup of patients in the study: the group of all patients with atrial fibrillation present at baseline. The efficacy of dofetilide in restoring sinus rhythm in these patients with atrial fibrillation was surprisingly good. Of 391 patients with atrial fibrillation at the time of randomization, at 1 month 12% of those treated with dofetilide had spontaneously converted to sinus rhythm as compared with 1% of those treated with placebo. After 1 month in the study, investigators were encouraged to electrically cardiovert patients still in AF. A total of 17% of atrial fibrillation patients in the dofetilide group had converted spontaneously to sinus rhythm after 1 year as contrasted with 13% in the placebo group. The total conversion rate at 1 year for atrial fibrillation patients was therefore 61% in the dofetilide group and 33% in the placebo group. Dofetilide was also very efficacious in maintaining sinus rhythm after cardioversion: for atrial fibrillation patients who converted, the probability of being in sinus rhythm at 1 year was 78% on dofetilide compared with 43% on placebo.

In patients who were in sinus rhythm at the time of randomization, dofetilide also helped to prevent the development of AF. Of the 556 such patients who received dofetilide, 11 subsequently experienced AF, as contrasted with 35 of the 534 who received placebo.

The two DIAMOND studies are among the studies that formed the basis for the recent approval of dofetilide in the United States and Europe for the treatment of patients with atrial fibrillation. Dofetilide is effective in ventricular arrhythmias, but the place of dofetilide in the treatment of ventricular arrhythmias is at present unclear.

The implication of the DIAMOND CHF study is that dofetilide can safely be used to convert atrial fibrillation to sinus rhythm in patients with heart failure as well as to maintain them in sinus rhythm after spontaneous or electrical conversion. Since there was no mortality benefit in DIAMOND CHF the antiarrhythmic properties of dofetilide do not vindicate a general prophylactic indication in CHF patients. In patients with heart failure and atrial fibrillation, dofetilide may be used as an alternative to amiodarone for maintaining sinus rhythm. For such patients, when rate control cannot be accomplished with drugs of proven safety, there is at present a clear indication for the use of dofetilide or amiodarone in order to achieve and maintain sinus rhythm, with or without electrical conversion. For those patients in whom adequate rate control can be achieved, it is unknown whether treatment to achieve sinus rhythm carries any advantage. The results of the DIAMOND CHF study suggest that a reduction in hospitalizations with heart failure may be a benefit of such a strategy. Until now, an adequate comparison between rate control and the maintenance of sinus rhythm has not been possible in atrial fibrillation patients with congestive heart failure due to the lack of safe and effective drugs. We believe dofetilide to be sufficiently safe and effective to justify its use for such a comparison in the future.

The DIAMOND CHF study demonstrates that it is indeed feasible to develop antiarrhythmic drugs that are safe and effective. The results of the DIAMOND studies should alleviate some of the
pessimism that has inevitably occurred as a response to the findings of CAST\cite{9} and SWORD\cite{10}. The search for better antiarrhythmic drugs should continue.

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\textbf{References}


