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Dofetilide (Tikosyn): A new drug to control atrial fibrillation

ABSTRACT

Dofetilide, a new class III antiarrhythmic agent, selectively blocks a specific cardiac potassium channel, I_{Kr}, increasing the effective refractory period of the myocyte and thereby terminating reentrant arrhythmias. Given orally, it appears to effectively convert atrial fibrillation and atrial flutter to sinus rhythm and maintain sinus rhythm after conversion in appropriately selected patients. This paper reviews the pharmacology of dofetilide, the evidence of its effectiveness, and the appropriate precautions in using it.

KEY POINTS

Dofetilide is generally well tolerated but like other class III drugs can cause torsades de pointes. The risk is dose-dependent and can be minimized by adjusting the dosage according to creatinine clearance and QT interval, by excluding patients with known risk factors for long QT syndrome and torsades de pointes, and by starting treatment in an inpatient monitored setting for the first 3 days.

Unlike other antiarrhythmic agents, oral dofetilide did not increase the mortality rate in clinical studies in postmyocardial infarction patients or those with congestive heart failure at high risk for sudden cardiac death.

Concomitant use of drugs that increase the plasma level of dofetilide is contraindicated; these include cimetidine, ketoconazole, trimethoprim-sulfamethoxazole, and verapamil.

DOFETILIDE (Tikosyn), a new antiarrhythmic drug, can convert atrial fibrillation and atrial flutter to sinus rhythm in approximately 30% of cases and maintain sinus rhythm after electrical or pharmacologic conversion for up to 1 year in 60% to 70% of cases, without increasing the risk of sudden death in patients at high risk.

Such new drugs are needed, as many of the antiarrhythmic drugs in use up to now have actually produced higher mortality rates in clinical trials than did placebo, or cause unacceptable side effects.

This article reviews the mechanism of action, safety, effectiveness, and clinical use of dofetilide.

PROBLEMS WITH PREVIOUS DRUGS

A variety of drugs have been used to terminate or prevent atrial and ventricular arrhythmias, but their safety, efficacy, and tolerability in patients at high risk of sudden death have been disappointing.

In a meta-analysis of randomized clinical trials that ran for 3 months to 1 year,[1] Coplen et al calculated that patients who received quinidine to maintain sinus rhythm after cardioversion of atrial fibrillation had an unadjusted mortality rate of 2.9%, compared with 0.8% in control patients. Similarly, survivors of myocardial infarction (MI) with left ventricular dysfunction who received the class IC agents flecainide, encainide, and moricizine long-term in the CAST study[2] and the class III agent sotalol in the SWORD study[3] also had higher mortality rates than did those who received placebo. In addition, some of the agents have side effects such as gastrointestinal disturbances, arrhythmias, hypotension,

TABLE 1

Pharmacokinetics of dofetilide

Absorption Approximately 100%
Bioavailability 92%
Volume of distribution 3.3 L/Kg
Protein binding 65%
Time to peak plasma concentration 2.2 hours (range 1–4)
Half-life 8–10 hours
Elimination Renal 80%, hepatic 10%

and myocardial depression, which further restrict their use in specific patient populations.[4]

On the other hand, amiodarone, which is widely used to treat atrial fibrillation although not officially indicated for this purpose, has a proven safety profile in patients with structural heart disease and was not associated with increased mortality when compared with placebo in the treatment of various arrhythmias.[5] It maintains sinus rhythm in nearly two thirds of patients in up to 1 year of follow-up. However, in clinical trials, 41% of patients stopped taking amiodarone compared with 27% taking placebo. The difference was primarily due to adverse effects. Amiodarone has toxic effects on the liver, thyroid, and lungs, and its pulmonary toxicity can be life-threatening.[5]

Dofetilide does not affect cardiac output

DOFETILIDE'S MECHANISM OF ACTION

Dofetilide is a Vaughn Williams class III antiarrhythmic drug, meaning that it is a potassium channel blocker. (Other drugs in this class include sotalol and amiodarone.) Specifically, it blocks the rapid component of the major repolarizing current, the delayed rectifier (I_{Kr}).[6]

By blocking the I_{Kr} channel, dofetilide delays myocardial repolarization and increases the refractory period (FIGURE 1). This constitutes the basis of its antiarrhythmic action: if the myocytes have a longer refractory period, a reentrant arrhythmic wavefront has a greater chance of encountering refractory tissue and would therefore be suppressed or terminated.

Dofetilide prolongs the refractory period in the atria to a greater extent than in the ventricles. Dose for dose, the increase in the atrial effective refractory period is double that of the ventricular effective refractory period.[7] Perhaps for this reason, dofetilide is more effective in treating atrial arrhythmias than in ventricular arrhythmias.

PHARMACODYNAMICS OF DOFETILIDE

Dofetilide is a cardioselective I_{Kr} blocker. At recommended doses, it has no effect on other potassium channels (I_{Ks}, I_{K1}), sodium channels, calcium channels, or beta receptors.[6] Therefore, it has a selective effect of prolonging the action potential duration and the refractory period in myocardial tissue.

On the electrocardiogram, dofetilide selectively prolongs the QT interval but has no effect on the PR, QRS, AH, or HV intervals.[8] It does not significantly affect the function of the sinus node (cycle length or recovery time).

HEMODYNAMIC EFFECTS OF DOFETILIDE

By virtue of its pure class III antiarrhythmic action, dofetilide does not depress myocardial function, unlike nonspecific class III agents such as amiodarone or sotalol.[9] When it was given to patients with congestive heart failure and compromised ventricular function (in New York Heart Association class II or III and with left ventricular ejection fractions < 35%), their mean cardiac output was maintained despite a small reduction in mean heart rate.[10]

PHARMACOKINETICS OF DOFETILIDE

Absorption and distribution. After an oral dose, dofetilide is almost 100% absorbed (TABLE 1) and reaches a peak plasma concentration in approximately 2 hours (range 1–4 hours), irrespective of dose.[11] However, food nearly doubles the time to peak plasma concentration.[12] Dofetilide is widely distributed in the body.

Elimination is mainly through renal excretion via passive glomerular filtration and cationic tubular secretion. Approximately 80% of a dose is excreted in the urine.[13] The

How class III antiarrhythmic drugs work

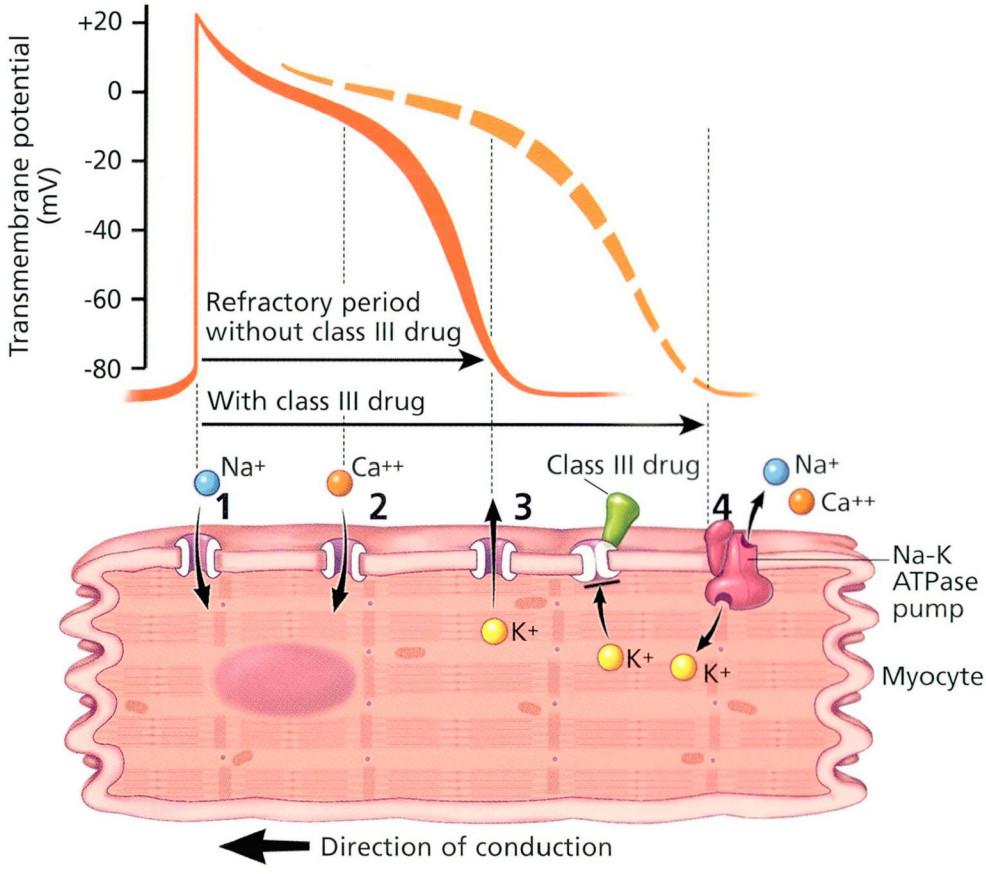
The action potential of a heart cell (electrical activity required for contraction) depends on ions moving in and out of the cell through specific ion channels that open and close in a specific sequence.

1. Sodium floods into the cell via sodium channels as it rapidly depolarizes.

2. Calcium slowly enters the cell via calcium channels.

3. Potassium is allowed to leave the cell via potassium channels as it repolarizes. Class III drugs such as amiodarone, sotalol, and dofetilide block potassium efflux and extend the refractory period of the cell, making it less likely to depolarize in response to electrical stimuli.

4. Sodium and calcium are exchanged for potassium via the sodium-potassium ATPase pump.



In the atria, class III antiarrhythmic drugs decrease the refractory gap

Re-entrant circuit, encountering excitable cells (**left**), can stimulate them to depolarize and perpetuate the arrythmia; with a class III drug (**right**), the re-entrant circuit is more likely to encounter a gap of refractory cells and be terminated.

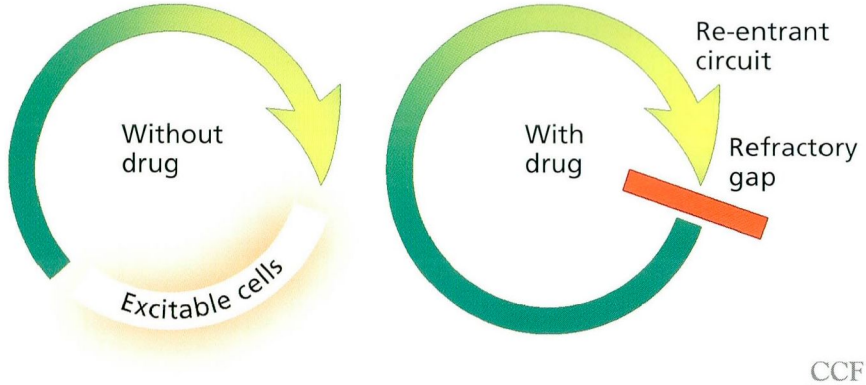


FIGURE 1

TABLE 2

Dofetilide drug interactions

These drugs increase the plasma level of dofetilide:
Cimetidine*
Ketoconazole*
Megestrol
Prochlorperazine
Trimethoprim-sulfamethoxazole*
Verapamil*

These drugs have no effect on dofetilide:
Antacids
Amlodipine
Glyburide
Hormone replacement therapy
Omeprazole
Phenytoin
Ranitidine
Theophylline

Dofetilide has no effect on:
Digoxin
Hormone replacement therapy
Propranolol
Phenytoin
Theophylline
Warfarin

*Concomitant use contraindicated

Do not start dofetilide if the creatinine clearance is < 20

remainder is excreted in the feces (< 10%) or metabolized in the liver, predominantly by the cytochrome P4503A4 family, into inactive metabolites.[14]

The elimination half-life is 8 to 10 hours in patients with normal renal function. The steady-state plasma concentration is attained by the third day of a twice-daily dosing regimen.

In hepatic dysfunction the pharmacokinetic profile of dofetilide is not significantly different from that in matched controls, and no dosage adjustment is required.[15]

In renal impairment, patients have lower drug clearance, higher plasma concentrations, and an increased elimination half-life. The dose should therefore be adjusted according to the patient's renal function.

In special populations. Elderly patients develop higher dofetilide concentrations, primarily because of reduced renal function. Women tend also to have higher plasma concentrations than men even after correcting for body weight and creatinine clearance. Smoking or coronary artery disease do not affect the disposition of dofetilide.[16]

DRUG INTERACTIONS

Dofetilide has significant interactions with certain drugs that interfere with either its hepatic metabolism or renal excretion (TABLE 2). It has no known effects on any laboratory tests.

EFFECTIVENESS IN ATRIAL FIBRILLATION

Atrial fibrillation, one of the most common arrhythmias, occurs in 5.9% of patients older than 65 years[17] and is an independent risk factor for thromboembolism and stroke.[18]

In three randomized, double-blind, placebo-controlled studies,[19–21] patients who received dofetilide had higher rates of conversion to sinus rhythm, higher rates of staying in sinus rhythm after conversion, and, for patients with sinus rhythm at baseline, lower rates of developing atrial fibrillation than did patients who received placebo. However, the final results of two of these studies are not yet published,[19,20] and in the third,[21] conversion of atrial fibrillation was only a secondary end point.

The EMERALD study

The EMERALD study (European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide)[19] enrolled 671 patients who had been in atrial fibrillation for 1 week to 2 years (median 3 months) and randomly assigned them to receive one of the following regimens:

- Dofetilide groups: 125, 250, or 500 µg twice daily
- Sotalol 80 mg twice daily
- Placebo.

At a dosage of 500 µg twice daily, dofetilide was significantly more effective than either placebo or sotalol in both conversion to and maintenance of normal sinus rhythm. The probability of remaining in normal sinus rhythm after either pharmacologic or electric cardioversion was 0.71 at 6 months and 0.66 at 12 months in the dofetilide 500 µg twice-daily group, compared with 0.57 at 6

TABLE 3

Effect of dofetilide on atrial fibrillation: three studies

STUDY	NO. OF PATIENTS	REGIMEN	CONVERSION RATE, %	PROBABILITY OF OF MAINTAINING NORMAL SINUS RHYTHM		HAZARD RATIO VS PLACEBO AND 95% CI
				6 MO.	12 MO.	
EMERALD[19]	671	Placebo	1	0.26	0.21	
		Sotalol 80 mg twice daily	5	0.57	0.49	0.45 (0.31–0.64)
		Dofetilide 500 µg twice daily	29*	0.71	0.66	0.29 (0.19–0.44)
SAFIRE-D[20]	325	Placebo	1	0.37	0.25	
		Dofetilide 500 µg twice daily	32*	0.62	0.58	0.44 (0.26–0.73)
DIAMOND-CHF[21]	391	Placebo	1	NR†	0.33	
		Dofetilide (individualized dosage)	12‡	NR	0.61	0.35 (0.22–0.57)

*At 3 days (conversion phase)
†NR = not reported
‡At 1 month

months and 0.49 at 12 months in the sotalol group and 0.26 and 0.21 in the placebo group. The 250 µg twice-daily dosage of dofetilide was approximately as effective as sotalol 80 mg twice daily.

The conversion rate to normal sinus rhythm was 29% with dofetilide (all dosages combined) vs 1% with placebo in the first 3 days of treatment—the "conversion phase" (TABLE 3). Of the patients who converted pharmacologically with dofetilide, 70% did so within the first 24 hours of treatment. Further dosage adjustments for either renal impairment or QT prolongation did not affect treatment efficacy. Efficacy was also consistent regardless of age, gender, or target arrhythmia (atrial fibrillation or atrial flutter).

The SAFIRE-D study

The SAFIRE-D study (Symptomatic Atrial Fibrillation Investigation and Randomized Evaluation of Dofetilide)[20] included 325 patients with atrial fibrillation of 2 weeks' to 6 months' duration, who were randomized to receive dofetilide 125, 250, or 500 µg twice daily or placebo.

The results were similar to those in the EMERALD study. In the first 3 days of treatment, 32% of patients taking dofetilide 500 µg twice daily achieved normal sinus rhythm, compared with 1% of patients receiving placebo. The probability of staying in sinus rhythm at 6 and 12 months was also higher with dofetilide 500 µg twice daily than with placebo (TABLE 3).

Adjust the dose for renal function and QTc

The DIAMOND-CHF study

In the DIAMOND-CHF study (Danish Investigations of Arrhythmia and Mortality on Dofetilide),[21] 1,518 patients with congestive heart failure were randomized to receive dofetilide (with doses adjusted for the corrected QT interval and creatinine clearance) or placebo.

The primary end point of the study was mortality; conversion to sinus rhythm was only a secondary end point. Nevertheless, 391 patients were in atrial fibrillation on entry, and when followed-up at 1 month and 12 months, those receiving dofetilide had higher rates of spontaneous conversion to sinus rhythm than those in the placebo group (TABLE 3).

Once cardioversion had occurred by either pharmacologic or electrical means, the likelihood that sinus rhythm would be maintained was significantly higher in the dofetilide group than in the placebo group (hazard ratio 0.35, 95% CI 0.22–0.57; FIGURE 2). Furthermore, in patients who were in sinus rhythm at the time

DIAMOND-CHF study: After cardioversion, dofetilide increases the chance of staying in sinus rhythm

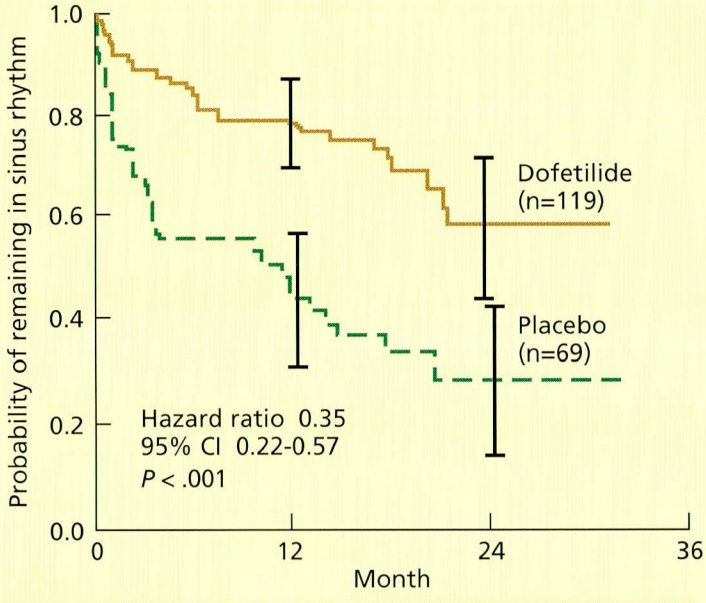


FIGURE 2. Kaplan-Meier estimate of the probability of remaining in sinus rhythm over time after successful cardioversion (electrical or pharmacological) in patients with atrial flutter or atrial fibrillation at baseline in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND-CHF) study.

FROM TORP-PEDERSEN C, MOLLER M, BLOCH-THOMSEN PE, ET AL. DOFETILIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION. N ENGL J MED 1999; 341:857–865.

of enrollment, dofetilide reduced significantly the incidence of new-onset atrial fibrillation (7% with placebo vs 2% with dofetilide; $P < .001$), suggesting that dofetilide is also effective in preventing atrial fibrillation and atrial flutter in these patients. In patients with paroxysmal atrial fibrillation, there was only a trend in prolongation of time to recurrence of paroxysmal atrial fibrillation in the dofetilide-treated patients as compared with placebo.[21]

EFFECTS ON SUPRAVENTRICULAR TACHYCARDIA

Dofetilide is better than placebo in prolonging the time to an attack of supraventricular tachycardia. In a double-blind, randomized study, dofetilide was superior to placebo and equal to propafenone in preventing recurrences of supraventricular tachycardia.[10]

EFFECTS ON VENTRICULAR TACHYCARDIA

Sotalol is the only oral agent to be approved for the treatment of ventricular arrhythmias since the CAST study,[2] mostly because it proved superior to other antiarrhythmic agents demonstrated in the ESVEM (Electrophysiologic Study versus Electrocardiographic Monitoring) study.[22]

Dofetilide may have some effect on ventricular tachycardia. In a placebo-controlled study in patients with life-threatening ventricular arrhythmias who had an implantable defibrillator with data storage capability,[10] there was no significant decrease in the time to the first defibrillation for life-threatening ventricular arrhythmia. However, the median number of events requiring defibrillations (adjusted for the patient's time in the study) tended to be lower in the dofetilide group than in the placebo groups.

Dofetilide has little effect on asymptomatic premature ventricular contractions or nonsustained ventricular tachycardia. In patients with dilated or hypertrophic cardiomyopathy, dofetilide was not as effective as amiodarone in suppressing premature ventricular contractions or nonsustained ventricular tachycardia as assessed by Holter monitoring. In the DIAMOND study,[21] there was no significant difference in the incidence of polymorphic ventricular tachycardia (not torsades de pointes), monomorphic ventricular tachycardia, or ventricular fibrillation and no difference in suppression of asymptomatic premature ventricular contractions or nonsustained ventricular tachycardia in the dofetilide group as compared with the placebo group.

EFFECTS ON CONGESTIVE HEART FAILURE

In the DIAMOND-CHF study, dofetilide-treated patients had a statistically significantly lower rate of hospitalization for worsening heart failure (30% vs 38%) compared with those on placebo. The overall risk of hospitalization for worsening heart failure was signifi-

DIAMOND-CHF study: In CHF with LV dysfunction, dofetilide decreases hospitalization rates

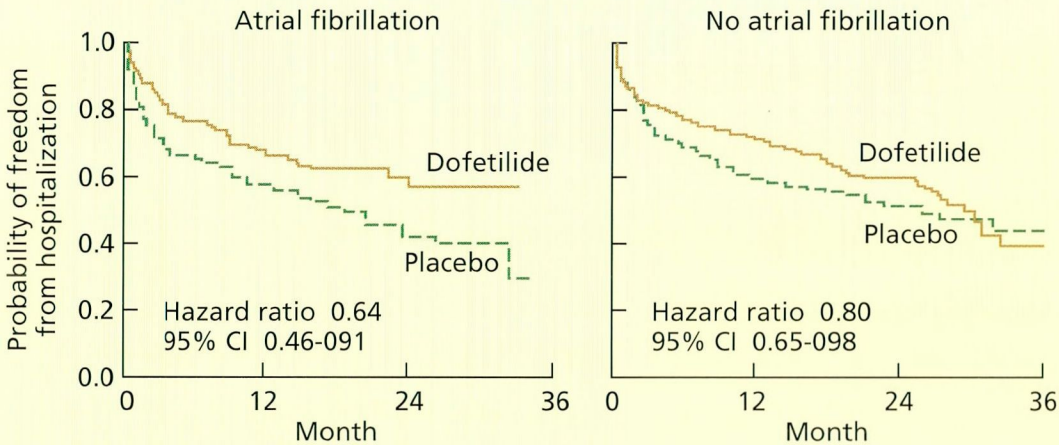


FIGURE 3. Kaplan-Meier plot of the probability of freedom from hospitalization for worsening congestive heart failure in patients with atrial fibrillation (**left**) and without atrial fibrillation (**right**) at baseline in the in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND-CHF) study.

FROM TORP-PEDERSEN C, MOLLER M, BLOCH-THOMSEN PE, ET AL. DOFETILIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION. N ENGL J MED 1999; 341:857–865.

cantly reduced in the dofetilide group regardless of the presence of atrial fibrillation at baseline (FIGURE 3).[21]

NO EFFECT ON MORTALITY

The DIAMOND trials consisted of two survival studies designed to evaluate the overall safety and efficacy of prophylactic use of dofetilide in a group of patients at high risk for sudden cardiac death. Patients with a left ventricular ejection fraction less than 35%, plus either congestive heart failure (DIAMOND-CHF; n = 1,518 patients)[21] or a myocardial infarction in the previous 2 to 7 days (DIAMOND-MI; n = 1,510 patients)[23] were randomized to receive either dofetilide 500 µg twice daily (with dose adjustments according to an algorithm) or placebo in addition to the best available medical therapy. All patients were continuously monitored on telemetry for the first 3 days of treatment.

In both studies, there was no statistical difference in mortality between the placebo and dofetilide groups. The 1-year rate of all-cause mortality with dofetilide was similar to that with placebo: 41% in patients with congestive heart failure and 31% in post-MI patients. The hazard ratio of death on treatment with dofetilide as compared with placebo was 0.94 (95% CI 0.81–1.11) in DIAMOND-CHF and 0.97 (95% CI 0.80–1.17) in DIAMOND-MI.

Therefore, although dofetilide did not decrease the mortality rate in patients with congestive heart failure and post-MI at high risk of sudden cardiac death, at least it did not increase it. There were also no differences in the rates of cardiac or arrhythmic death or reinfarction between the two groups. This is quite different from the previous experience in the CAST (Cardiac Arrhythmia Suppression Trial)[2] and SWORD (Survival with Oral D-Sotalol)[3] studies, which showed an increased risk of mortality compared with placebo when the antiarrhythmic agents flecainide, encainide, moricizine, and sotalol were used in high-risk patients. The message is that dofetilide can be used safely in certain high-risk patients with structural heart disease, provided that guidelines are followed regarding starting the drug in the hospital and adjusting the dosage appropriately.

Stop dofetilide if the QTc is > 500 after the second dose

OTHER CLASS III AGENTS

Amiodarone has been shown to have significant clinical efficacy in treating a variety of cardiac arrhythmias. However, in addition to its potassium channel-blocking properties, amiodarone possesses sodium channel-blocking, calcium channel-blocking, and beta-blocking properties and anti-ischemic effects, which may contribute to its overall efficacy.[24] Therefore, comparing it with dofetilide is difficult.

Azimilide blocks both the I_{Kr} and I_{Ks} potassium channels. It has been studied for the treatment of atrial fibrillation, and it is currently under review by the US Food and Drug Administration for the maintenance of sinus rhythm in patients with atrial fibrillation.

Sotalol. The SWORD trial evaluated the effect of sotalol, another I_{Kr} blocker, on mortality in patients with left ventricular dysfunction and previous MI, somewhat similar to the patients in the DIAMOND trial. However, the trial was stopped early as treatment with sotalol was associated with increased mortality, which was presumed to be primarily arrhythmic.

Dofetilide can be safe for high-risk patients, if guidelines are followed

DOFETILIDE USED WITH DEFIBRILLATORS

Intravenous dofetilide significantly decreased defibrillation thresholds (DFTs) in patients undergoing defibrillator implantation.[25] DFTs were decreased from 6.9 ± 3.7 J at baseline to 4.6 ± 2.6 J after intravenous infusion of dofetilide ($P < .05$). This effect is similar to that of sotalol, another class III agent found to reduce DFTs, but is opposite to that of class I agents[26] and amiodarone, which increase DFTs in patients receiving implantable defibrillators. Dofetilide did not significantly change pacing thresholds in patients with permanent pacemakers.

USING DOFETILIDE SAFELY

Indications

Dofetilide is indicated for converting atrial fibrillation and flutter to sinus rhythm and for maintaining sinus rhythm after cardioversion. In high-risk patients with structural heart disease, the treatment of atrial fibrillation is currently restricted to amiodarone. Dofetilide offers a reasonable alternative in patients at no additional risk for torsades de pointes, by virtue of its efficacy in converting atrial fibrillation and maintaining normal sinus rhythm, its neutral effect on mortality in this high-risk population, and its lack of long-term multiorgan side effects.

Contraindications

The exclusion criteria from the DIAMOND study could be used to identify patients not suitable for dofetilide treatment. These include:

- Bradycardia (heart rate < 50) during waking hours
- Sinoatrial block or second- or third-degree atrioventricular block not treated with a pacemaker
- History of drug-induced torsades de pointes
- A corrected QT interval longer than 460 ms (> 500 ms in the presence of bundle branch block)
- Use of other QT-prolonging medications
- A serum potassium level less than 3.6 mmol/L or greater than 5.5 mmol/L
- A calculated creatinine clearance less than 20 mL/minute
- Serious liver dysfunction
- Concomitant use of cimetidine, verapamil, or ketoconazole (TABLE 2).

Dosage and administration

Dofetilide should be started in the hospital, with cardiac monitoring. The dosage should be individualized on the basis of creatinine clearance[27] and the corrected QT interval (see **"How to prescribe dofetilide safely,"** page 361).

Creatinine clearance. Dofetilide clearance is linearly related to the estimated creatinine clearance. Therefore, to prevent an excessive increase in plasma concentration in patients with reduced renal function, the dose should be decreased if the patient has renal impairment.

Corrected QT interval. An electrocardiogram should be obtained 2 hours after the first dose, and the dosage should be adjusted on the basis of corrected QT prolongation after the drug is started. An increase of more

How to prescribe dofetilide safely

1. **Do not use dofetilide if patient is at high risk for torsades de pointes**, ie, if he or she has any of the following:
   Bradycardia (heart rate < 50) during waking hours
   Sinoatrial block or second- or third-degree atrioventricular block not treated with a pacemaker
   History of drug-induced torsades de pointes
   A corrected QT interval more than 460 ms (> 500 ms in the presence of bundle branch block)
   Use of other QT-prolonging medications
   A serum potassium level < 3.6 mmol/L or > 5.5 mmol/L
   Calculated creatinine clearance < 20 mL/minute
   Serious liver dysfunction
   Concomitant use of cimetidine, verapamil, or ketoconazole

2. **Begin cardiac monitoring in the hospital**

3. **Check baseline corrected QT interval (QTc)**
   QTc (ms) = QT (ms) / $\sqrt{\text{R-R interval (seconds)}}$
   Do not use dofetilide if the QTc is > 440 ms (or > 500 ms if ventricular conduction abnormality is present)
   (If heart rate is < 60, use the uncorrected QT interval)

4. **Calculate creatinine clearance**
   Men: [(140 – age in years) × weight in kg] / (72 × serum creatinine in mg/dL)
   Women: Use the same formula as in men, then multiply the result by 0.85

5. **Initiate or adjust dofetilide dose according to creatinine clearance**

CREATININE CLEARANCE (ML/MINUTE)	DOSAGE
> 60	500 μg by mouth twice daily
40–60	250 μg by mouth twice daily
20–40	250 μg by mouth daily
< 20	Do not give

6. **Follow-up QTc during in-hospital treatment initiation**
   Measure QTc at 2–3 hours after first dose, and readjust dose accordingly
   If the QTc is increased by > 15% or if the QTc is > 550 ms, decrease dose by 50%

7. **Discontinue dofetilide if adjusted dosage is < 250 μg daily**

8. **Follow up creatinine clearance and QTc on a regular basis** and according to changing clinical situation (eg, worsening heart failure, nephrotoxic drugs) and readjust dosing accordingly
   If at any time after the second dose QTc increases to > 500 ms, dofetilide should be discontinued

ADAPTED FROM PFIZER. BRIEFING DOCUMENTS FOR TIKOSYN CAPSULES, FDA CARDIORENAL DIVISION ADVISORY COMMITTEE, JANUARY 28 1998.

than 15% from baseline or values longer than 550 ms after the first dose should prompt a decrease in the dofetilide dose.

In the DIAMOND study,[21] dofetilide was discontinued in 2% of patients because of excessive QT prolongation. The peak increase in the corrected QT interval occurred within the first 2 days of treatment.

Continue to monitor. Not only should dosage adjustments be made at baseline, but

also if the serum creatinine level should change with time. Fewer than one third of the patients were receiving 500 µg twice daily at the end of the DIAMOND study, while most were receiving 250 µg twice daily. Dofetilide should be discontinued if the dosage must be reduced below 250 µg daily.

SIDE EFFECTS AND SAFETY

Like all antiarrhythmic agents, dofetilide's most worrisome side effect is proarrhythmia, specifically torsades de pointes, in view of its class III action.

A pooled survival analysis of data from 10 randomized clinical trials involving 2,023 patients provided reassurance that dofetilide is safe in patients with supraventricular arrhythmias.[28] Oral dofetilide had no effects on overall survival compared to placebo.

In the DIAMOND-CHF study,[21] despite the exclusion of patients at high risk for torsades de pointes, 25 cases (3.3%) of torsades de pointes occurred in the dofetilide group compared to none in the placebo group. Nineteen (76%) of the 25 episodes occurred in the first 3 days of treatment while patients were being monitored, and 2 episodes were fatal. This underlines the importance of continuous cardiac monitoring during the first 3 days.

Women and CHF patients had a threefold higher rate of torsades with dofetilide

Furthermore, the incidence of torsades de pointes was higher before a protocol was adopted to adjust the dose according to renal function (4.8% vs 2.9%).[10] Up to 40% of patients receiving dofetilide had a dosage adjustment during the in-hospital initiation treatment. The dosage should be adjusted according to renal function and corrected QT interval at baseline and during follow-up, especially in patients with heart failure, in whom renal function tends to worsen with time. Even after adjusting the dosage for creatinine clearance, women and patients with heart failure had a higher rate of torsades de pointes: the odds ratio was 3.2 for women and 3.9 for patients in New York Heart Association class III or IV.

The frequency of other ventricular arrhythmias and of cardiac arrest not related to torsades de pointes was similar in the two groups. The discontinuation rate due to other side effects did not differ between the two groups. Other reported side effects include headache, muscle cramps, and sinus tachycardia. These were generally mild and transient.

HOW SUPPLIED

Dofetilide is a water-soluble powder. It is supplied for oral administration in gelatin capsules in three dosage strengths: 125 µg (orange/white), 250 µg (peach/peach), and 500 µg (peach/white).

FUTURE RESEARCH

Future studies comparing dofetilide with other currently used antiarrhythmic drugs such as sotalol, amiodarone, and flecainide would help establish its role in the treatment of atrial arrhythmias. Furthermore, blockade of the rapid component of the delayed rectifier I_{Kr} has been associated with an antifibrillatory effect in the atria but with neutral (dofetilide) or deleterious (sotalol) effects on mortality in MI survivors. Drugs that could block more than one channel are currently being developed. Azimilide is the first class III agent that blocks both the rapid and the slow component of the delayed rectifier.

Other long-term goals of antiarrhythmic therapy are to identify biochemical intermediaries and modulate the molecular and genetic substrate involved in arrhythmogenesis.

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