

Table 5a: Baseline characteristics associated with CHF-ITT

| Baseline characteristics | Dofetilide N=762(%) | Placebo N=756(%) |
|---------------------------------|---------------------|------------------|
| Number of Previous MI | | |
| 0 | 373(49) | 366(46.4) |
| 1 | 256(33.6) | 233(30.6) |
| 2 | 61(10.6) | 101(13.4) |
| 3 | 58(3.0) | 21(4.1) |
| >3 | 14(1.6) | 23(3.5) |
| Number of cardiac arrests | | |
| 0 | 736(96.6) | 716(94.7) |
| 1 | 23(3.0) | 36(4.6) |
| 2 | 3(0.4) | 4(0.3) |
| Ischemic Heart Disease | | |
| Yes | 509(66.6) | 508(67.2) |
| No | 233(33.2) | 248(32.8) |
| Wall Motion Index | | |
| <0.8 | 231(30.3) | 229(30.3) |
| >=0.8 - 1.2 | 531(69.7) | 627(69.7) |
| >1.2 | 0 | 0 |
| Median | 0.9 | 0.9 |
| Range | 0.8, 1.2 | 0.8-1.2 |
| Number of complications | | |
| Thrombolytic treatment | 10 (1.5) | 25(3.0) |
| Reinfarctions | 0 | 1(0.1) |
| Cardiac arrests | 1(0.1) | 2(0.3) |
| Arrhythmias requiring treatment | 139 (20.9) | 154(17.7) |
| Others | 315(41.1) | 311 (41.1) |

Table 5b: Baseline characteristics associated with CHF-ITT

| Baseline characteristics | Dofetilide (N=762) | Placebo (N=756) |
|-------------------------------|--------------------|-----------------|
| NYHA at Baseline | | |
| I | 16(2.1) | 17(2.5) |
| II | 266(33.4) | 297(39.3) |
| III | 425(56.0) | 365(31.5) |
| IV | 49(6.3) | 32(6.9) |
| Not done | 0 | 1 |
| Not available | 6 | 4 |
| Killip class | | |
| I | 195(23.6) | 171(22.6) |
| II | 425(56.0) | 439(61.1) |
| III | 112(14.6) | 107(14.2) |
| IV | 10(1.3) | 14(1.9) |
| Missing | 7 | 5 |
| Creatinine clearance (ml/min) | | |
| <20 | 5(0.4) | 3(0.7) |
| 20-40 | 195(23.3) | 196(26.1) |
| 40-80 | 274(36.1) | 273(36.6) |
| >=60 | 266(36.0) | 275(36.6) |
| Missing | 4 | 3 |
| Mean | 36.9 | 37.0 |
| Std | 23.4 | 24.5 |

Table 5c: Baseline characteristics associated with MI-ITT

| | Dofetilide | Placebo |
|------------------------|------------|------------|
| Number (%) of subjects | 749 (%) | 761 (%) |
| Chest pain | | |
| Present | 695 (92.8) | 713 (93.7) |
| Absent | 54 (7.2) | 48 (6.3) |
| ECG changes-Anterior | | |
| Present | 466 (62.7) | 477 (63.2) |
| Absent | 277 (37.3) | 278 (36.8) |
| Missing | 6 | 6 |
| ECG changes -Inferior | | |
| Present | 218 (29.3) | 212 (28.1) |
| Absent | 526 (70.7) | 542 (71.9) |
| Missing | 5 | 7 |
| ECG changes-Non-Q wave | | |
| Present | 120 (16.1) | 142 (18.8) |
| Absent | 624 (83.9) | 614 (81.2) |
| Missing | 5 | 5 |
| ECG changes -Others | | |
| Present | 143 (100) | 149 (100) |
| Missing | 606 | 612 |
| Elevated Enzymes | | |
| Present | 746 (99.6) | 758 (99.6) |
| Absent | 3 (0.4) | 3 (0.4) |

Age, Sex, and Race

Demographic data for both CHF and MI studies are presented in Tables 6 and 7. The distribution of patients by age, sex, weight and height between treatment groups appear almost symmetrical except in the numbers and age of females. Twenty seven percent (27%) of randomized patients was female, and the age range was 19-98 and 26-94 years, with a mean of 70 and 69 years for CHF and MI, respectively (Tables 6 and 7). The distribution of females was slightly different between treatment groups, 28% randomized to Dofetilide group compared to 25% randomized to placebo, and the age distribution of females was also different, 20% in the Dofetilide CHF group were within the age range 45 - 64 years compared to 15% in the placebo group (Table 6). The demographics of the "screened only" population were not very different from the randomized population.

The population recruited to DIAMOND CHF were, in general terms, elderly and seriously handicapped by their disease. In the randomized population, 70% were aged 65-84 years and 4% were 85 years or over (Table 6). There were 991 (65%) patients in the randomized population in the DIAMOND MI studies aged between 65-84 years, and 53 (3.5%) patients were 85 years and over (Table 7). The majority (>99%) of the randomized population was white. There were very few blacks and other ethnic populations (<0.5%) in the populations screened and randomized.

Table 6: Demographics - CHF - ITT

| | Dofetilide | | | Placebo | | |
|-----------------------------------|------------|------------|-----------|-----------|------------|-----------|
| | Males | Females | Total | Males | Females | Total |
| N (%) of pts. | 546 | 216 | 762 | 568 | 188 | 756 |
| Age(yrs) | | | | | | |
| <18 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18-44 | 12(2.2) | 1(0.5) | 13(1.7) | 10(1.8) | 1(0.5) | 11(1.5) |
| 45-64 | 147(26.9) | 44(20.4) | 191(25.1) | 151(26.6) | 29(15.4) | 180(23.8) |
| 65-84 | 374(68.5) | 153(70.8) | 527(69.2) | 394(69.4) | 138(73.4) | 532(70.4) |
| >=85 | 13(2.4) | 18(8.3) | 31(4.1) | 13(2.3) | 20(10.6) | 33(4.4) |
| Age Range (yrs) | 26-90 | 35-94 | 26-94 | 32-92 | 37-92 | 32-92 |
| Mean Age(yrs) | 69 | 72 | 70 | 69 | 73 | 70 |
| Race | | | | | | |
| White | 544(99.6) | 216(100.0) | 760(99.7) | 567(99.8) | 188(100.0) | 755(99.9) |
| Black | 1(0.2) | 0 | 1(0.1) | 0 | 0 | 0 |
| Other | 1(0.2) | 0 | 1(0.1) | 1(0.2) | 0 | 1(0.1) |
| Weight Range(kg) | 44-134 | 34-119 | 34-134 | 43-135 | 38-111 | 38-135 |
| Mean weight(kg) | 78 | 66 | 75 | 79 | 65 | 75 |
| Height Range(cm) | 155-196 | 145-180 | 145-196 | 156-196 | 148-178 | 148-196 |
| Mean Height(cm) | 174 | 162 | 170 | 174 | 162 | 171 |
| Alc. consumption (units /week) | | | | | | |
| Median values | 2 | 0 | 1 | 2 | 0 | 1 |
| Not known | 13 | 1 | 14 | 11 | 2 | 13 |

Table 7: Demographics - MI - ITT

| | Dofetilide | | | Placebo | | |
|-----------------------------------|------------|-----------|-----------|-----------|-----------|-----------|
| | Males | Females | Total | Males | Females | Total |
| N (%) of patients | 542 | 207 | 749 | 569 | 192 | 761 |
| Age(yrs) | | | | | | |
| <18 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18-44 | 12(2.2) | 0 | 12(1.6) | 16(2.8) | 2(1.0) | 18(2.4) |
| 45-64 | 194(35.8) | 35(16.9) | 229(30.6) | 179(31.5) | 28(14.6) | 207(27.2) |
| 65-84 | 321(59.2) | 165(79.7) | 486(64.9) | 357(62.7) | 148(77.1) | 505(66.4) |
| >=85 | 15(2.8) | 7(3.4) | 22(2.9) | 17(3.0) | 14(7.3) | 31(4.1) |
| Age Range (yrs) | 34-88 | 46-89 | 34-89 | 33-92 | 41-91 | 33-92 |
| Mean Age(yrs) | 67 | 72 | 68 | 67 | 73 | 69 |
| Race | | | | | | |
| White | 541(99.8) | 207(100) | 748(99.9) | 567(99.6) | 192(100) | 759(99.7) |
| Black | 1(0.2) | 0 | 1(0.1) | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 2(0.2) | 0 | 2(0.1) |
| Weight Range(kg) | 45-130 | 40-108 | 40-130 | 46-154 | 40-102 | 40-154 |
| Mean weight(kg) | 78 | 65 | 75 | 79 | 64 | 75 |
| Height Range(cm) | 150-194 | 142-196 | 142-196 | 155-195 | 145-176 | 145-195 |
| Mean Height(cm) | 174 | 162 | 170 | 174 | 162 | 171 |
| Alc. consumption (units /week) | | | | | | |
| Median values | 2 | 0 | 1 | 3 | 0 | 1 |
| Not known | 17 | 5 | 22 | 19 | 1 | 20 |

NYHA classification

At baseline, the majority of CHF patients [(808 (54%))] had NYHA class III, and the majority of MI patients [773(54%)] had NYHA class II (Tables 8 and 9). The relatively higher frequency of NYHA class II patients in the MI group may have contributed to a higher frequency of completers in the MI study compared to CHF study (Table 16).

Table 8: NYHA by drug group - CHF

| NYHA Class | Dofetilide | Placebo | Total |
|------------|--------------|--------------|-------------|
| I | 16 | 17 | 33 |
| II | 268 (35%) | 297 (40%) | 565 (37.5%) |
| III | 423 (56%) | 385 (51%) | 808 (54%) |
| IV | 49 | 52 | 101 |
| Total | 756 | 751 | 1507* |

*11 patients (6 Dof; 5Plcbo) had no NYHA classification

Source: Reviewer

Table 9: NYHA by drug group - MI

| NYHA Class | Dofetilide | Placebo | Total |
|------------|------------|--------------|-----------|
| I | 80 | 82 | 162 |
| II | 383 (54%) | 390 (53%) | 773 (54%) |
| III | 215 (30%) | 233 (32%) | 448 (31%) |
| IV | 34 | 27 | 61 |
| Total | 712 | 732 | 1444* |

*66 (37Dof; 29 Placebo) patients had no NYHA classification

Source: Reviewer

8.4 Randomization by NYHA

All randomized patients had NYHA classification at baseline except 77 patients (66 CHF and 11 MI) with no baseline data (Tables 8 and 9). In the CHF group, there were relatively small differences between the treatment groups in the NYHA classification at baseline, Dofetilide having a lower percentage of patients in Class II compared to placebo (35% versus 40%), and slightly more in Class III (56% versus 51%) (Table 8). In the MI study, the percentage of patients in class III was slightly lower in Dofetilide group (30% compared to 32%) whereas there was no difference in class II (Table 9).

Randomization by WMI

The frequency distribution of LVEF as measured by WMI in both studies and in both treatment groups is presented in Tables 10 and 11. The majority of randomized patients had baseline WMI data except 422/5812 (7.3%) screened CHF patients with no baseline data and 402/8893(4.5%) screened patients in the MI group (Tables 10 and 11). There was no significant imbalance between the treatment groups.

Table 10: WMI by drug group-CHF

| WMI | Dofetilide | Placebo | Total |
|-----------|------------|---------|--------|
| <0.8 | 231 | 229 | 460 |
| >0.8-<1.2 | 531 | 527 | 1058 |
| <0.8 | - | - | 269* |
| >0.8-<1.2 | - | - | 3603* |
| Unknown | - | - | 422* |
| Total | | | 5812** |

*Screened but not randomized.**Some patients had multiple screening and WMI estimates Source: Reviewer

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Table 11: WMI by drug group-MI

| WMI | Dofetilide | Placebo | Total |
|-----------|------------|---------|--------|
| <0.8 | 61 | 49 | 110 |
| >0.8-<1.2 | 688 | 712 | 1400 |
| <0.8 | - | - | 83* |
| >0.8-<1.2 | - | - | 6698* |
| Unknown | - | - | 402* |
| Total | | | 8893** |

screened but not randomized. **Some patients had multiple screening and WMI estimates. Tables 7-10 Source : Reviewer

8.5 Duration of treatment and drug exposure

Duration of treatment and drug exposure are summarized in Tables 12 and 13 below. This calculation of drug exposure in subject-days may not reflect the actual amount of drug exposure because of dose adjustments during the study (Table 13).

Table 12: Treatment duration in DIAMOND CHF/MI

| | CHF | | MI | |
|-------------------------------|------------|----------|------------|----------|
| | Dofetilide | Placebo | Dofetilide | Placebo |
| | N=762 | N=756 | N=749 | N=761 |
| Duration of treatment in days | | | | |
| Median (days) | 383 | 371 | 454 | 458 |
| Range (days) | (1-1099) | (1-1093) | (1-1300) | (1-1293) |

See Appendix Figures 1-8

Table 13: Total drug exposure time-ITT-CHF/MI

| | Dofetilide | Placebo |
|------------------------------------|------------|---------|
| Subjects-days of Drug Exposure-CHF | 296881 | 291690 |
| Subjects-days of Drug Exposure-MI | 344943 | 363848 |

8.6 Disposition of randomized patients

The disposition of randomized patients and the final status of randomized patients at the end of the studies are summarized in Tables 14 and 15. A total of 1417 patients completed the studies. In the CHF study, 324 (42.5%) and 308 (40.7%) patients completed the study in the Dofetilide and placebo groups, respectively. In the MI study, 388 (51.8%) and 397 (52%) patients completed the study in the Dofetilide and placebo groups, respectively.

Enumeration of patients-Diamond-CHF and MI

Accounting for all randomized patients the reviewer considered the submitted data adequate for both trials. 3028 patients (1518 for CHF and 1510 for MI) were randomized to both studies. 1417 (632 for CHF and 785 for MI) completed the study and were censored $3028 - 1417 = 1611$ patients were not censored and had to be accounted for.

A total of 527 patients were censored and included in analysis (For reasons see Table 15) $1611 - 527 = 1084$ patients to be accounted for. 647 died before the last clinic visit date $1084 - 647 = 437$ to be accounted for. 437 died before the end of study; $437 - 437 = 0$. The final status of all randomized patients is summarized in Table 14. The distribution of the censored and dead patients by treatment groups is summarized in Table 15 and the reasons for discontinuations is presented in Table 16. The duration of the follow-up of the discontinued patients is summarized in Appendix Tables 2 and 3. There are no survival data on the non-randomized patients, 10,792 (4030 for CHF and 6762 for MI), as specified in the protocol.

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Table 14: Disposition of randomized patients - CHF/MI

| Disposition of subjects | CHF(N=5812) | | MI(N=8693) | |
|----------------------------------|-------------|-------------|------------|-------------|
| | Dofetilide | Placebo | Dofetilide | Placebo |
| Total no. of patients screened | 5548* | | 8272* | |
| Screened non-randomized patients | 4030 | | 6762 | |
| Randomized | 762 | 756 | 749 | 761 |
| Completed study | 324 (42.5%) | 308 (40.7%) | 388 (51%) | 397 (52.2%) |
| Discontinued | 438(57.5%) | 448(59.3%) | 361(48.2%) | 364(47.8%) |
| For analyses | | | | |
| ITT | 762 | 756 | 749 | 761 |
| Safety | 762 | 756 | 749 | 761 |
| Laboratory data | 762 | 756 | 749 | 761 |

*There were multiple screenings for some patients

Table 15: Final status at last clinic visit - CHF/MI

| Final Status of patients at last clinic visit date | Number of patients | | | |
|--|--------------------|----------|------------|-------|
| | *C / D | Censored | Deaths EOS | Total |
| Completed study | 1417 | - | - | 1417 |
| Patient died | 647 | | | 647 |
| Adverse events | | 175 | 183 | 358 |
| Asked to be withdrawn | | 211 | 163 | 374 |
| Protocol violation | | 19 | 6 | 25 |
| QT/QTc prolongation | | 28 | 11 | 39 |
| Lost to follow up | | 10 | 6 | 16 |
| Laboratory abnormality | | 17 | 11 | 28 |
| Did not meet selection criteria | | 0 | 2 | 5 |
| Other | | 64 | 55 | 119 |
| Unknown status | | 0 | 0 | 0 |
| Total Randomized Patients | 2064 | 527 | 437 | 3028 |

* C= Completers; D = Deaths by last clinic visit date; EOS=End of study Source: Reviewer

Table 16: Enumeration of subjects -CHF/MI by treatment groups

| Final Status of patients | Number of patients (N) | | | | | | | Total N | |
|------------------------------------|------------------------|---------|----------------|---------|--------------------|-----|-------|---------|------|
| | CHF | | MI | | Total Censored EOS | | | | |
| | Dofetilid e | Placebo | Dofetilid e | Placebo | | | | | |
| Completed study | 324 | 308 | 388 | 397 | | | | 1417 | |
| Patient died | 174 | 184 | 143 | 146 | | | | 647 | |
| | | | | | CHF | MI | Total | | |
| Adverse event | 57 | 48 | 38 | 40 | 88 | 87 | 175 | 358 | |
| Asked to be withdrawn | 43 | 55 | 28 | 38 | 93 | 118 | 211 | 374 | |
| Protocol violation | 2 | 3 | 0 | 1 | 13 | 6 | 19 | 25 | |
| QT/QTc prolongation | 2 | 1 | 8 | 0 | *14 | *14 | 28 | 39 | |
| Lost to follow up | 1 | 2 | 2 | 1 | 4 | 6 | 10 | 16 | |
| Laboratory abnormality | 5 | 4 | 3 | 1 | 13 | 4 | 17 | 28 | |
| Did not meet selection criteria | 1 | 0 | 1 | 0 | 2 | 1 | 3 | 5 | |
| Other | 20 | 16 | 5 | 11 | 42 | 22 | 64 | 119 | |
| Subtotal | 131 | 129 | 85 | 92 | 269 | 258 | 527 | - | |
| Total Randomized Pt. | 260 | | 177 | | 527 | | | 2064 | 3028 |

EOS= End of study ; * 25/28 (89%) patients with QT/QTc prolongation were on Dofetilide. Source-Reviewer

8.7 Discontinuations

Primary analyses showed 438 (57.5%) and 448 (59.3%) permanently discontinued CHF patients for the Dofetilide and placebo groups, respectively. In the MI study, 361 (48.2%) and 364(47.8%) permanently discontinued patients were in the Dofetilide and placebo groups, respectively (Table 17). The reasons for discontinuations are presented in Table 17. The sponsor presented analyses of discontinuations on the basis of drug relatedness but the reviewer does not see any justification for this separation since this could not be ascertained or proved.

Table 17: Discontinuations - ITT-CHF/MI

| | CHF | | MI | |
|---|------------|-----------|------------|-----------|
| | Dofetilide | Placebo | Dofetilide | Placebo |
| Total No of Subjects (%) | 762(100) | 756(100) | 749(100) | 761(100) |
| Total Number of discontinuations | 438(57.5) | 448(59.3) | 361(48.2) | 364(47.8) |
| Adverse events | 109(14.3) | 84(11) | 83(11) | 82(10.8) |
| Laboratory abnormality | 11(1.5) | 7(1.5) | 5(0.6) | 1(0.1) |
| Patient died | 174(22.8) | 184(24.3) | 143(19.1) | 146(19.2) |
| QT/QTc prolongation | 14(1.8) | 3(0.4) | 19(2.5) | 3(0.4) |
| Protocol Violation | 7(0.9) | 11(1.5) | 5(0.6) | 2(0.3) |
| Lost to follow up | 3(0.4) | 4(0.5) | 6(0.8) | 3(0.4) |
| Other | 30(3.9) | 48(6.3) | 17(2.3) | 24(3.2) |
| Does not meet randomization criteria | 1(0.1) | 2(0.3) | 0(0) | 2(0.3) |
| Withdrawn consent | 89(11.7) | 101(13.4) | 83(11) | 101(13.3) |

Patient Died includes death and cardiac arrest with resuscitation. Source-Sponsor

8.8 Duration of follow-up of patients for mortality - CHF/MI

Only 3 patients were physically seen by the investigators at the end of study dates, because all other patients were seen at the last clinic visit date. The Events Committee and the CRO periodically (monthly±) reviewed the Danish Central Personal Register for deaths and subsequently notified the investigators. A 100% follow-up on mortality, however, was achieved including patients lost to follow up and patients seen during the 3 months preceding the end of study (Table 18).

Table 18: 1101 Deaths observed by Investigators (INV) and CPR

| | Dofetilide | | | | Placebo | | | |
|-------------------|----------------------------------|-------|------------------------------|-------|----------------------------------|-------|------------------------------|-------|
| | Discontinued subjects from study | | Subjects who completed study | | Discontinued subjects from study | | Subjects who completed study | |
| | Deaths (INV/CPR) | Total | Deaths (INV/CPR) | Total | Deaths (INV/CPR) | Total | Deaths (INV/CPR) | Total |
| CHF-dates | | | | | | | | |
| Before 09/11/96 | 297 (274/23) | 429 | 0 | 12 | 309 (292/17) | 442 | 1 (1/0) | 14 |
| 09/11/96-10/10/96 | 3 (3/0) | 5 | 4 (3/1) | 109 | 2 (2/0) | 4 | 2 (2/0) | 95 |
| 10/11/96-11/10/96 | 1 (1/0) | 3 | 2 (2/0) | 80 | 2 (2/0) | 2 | 1 (1/0) | 87 |
| 11/11/96-12/10/96 | 1 (1/0) | 1 | 3 (1/2) | 123 | 0 | 0 | 0 | 112 |
| Total | 302 (279/23) | 438 | 9 (6/3) | 324 | 313 (296/17) | 448 | 4 (4/0) | 308 |
| Overall CHF | 311(285/26)762 | | | | 317(300/17)756 | | | |
| MI-dates | | | | | | | | |
| Before 04/02/97 | 219 206/13 | 352 | 0 | 5 | 237 (225/12) | 355 | 0 | 4 |
| 04/02/97-05/01/97 | 3 (3/0) | 4 | 1 (0/1) | 113 | 1 (1/0) | 4 | 1 (1/0) | 108 |
| 05/02/97-06/01/97 | 2 (2/0) | 3 | 3 (2/1) | 119 | 3 (3/0) | 3 | 1 (1/0) | 142 |
| 06/02/97-07/01/97 | 1 (1/0) | 2 | 1 (1/0) | 151 | 0 | 2 | 0 | 143 |
| Total | 225 (212/13) | 361 | 5 (3/2) | 388 | 241 (229/12) | 364 | 2 (2/0) | 397 |
| Overall MI | 230(215/15)749 | | | | 243(231/12)761 | | | |

INV=Deaths identified by Investigator and CPR; CPR=Deaths identified by CPR review only. (302+225+9+5+313+241+4+2 =1101 total deaths followed up); 17 deaths retrieved from CPR only + 1084 [(1081 (Table 18) +3 dead patients seen at EOS) = (647+437) Tables 15 and 16] =1101.

The numbers of patients, mean duration and the range of duration (in days) of follow-up among randomized patients according to reasons for discontinuations are presented in Appendix Tables 2-3.

8.9 Protocol violations - CHF/MI

The commonest protocol violation in the CHF study was incorrect concomitant drug treatment (Table 19). The discontinuations for incorrect allocation of subjects or incorrect diagnoses were about the same in both studies and did not impact the analyses of their primary endpoints.

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Table 19: Protocol Violations-CHF/MI

| Final status of patients | CHF | | MI | |
|--|---------------|---------------|---------------|---------------|
| | Dofetilide | Placebo | Dofetilide | Placebo |
| Number of subjects | 762 | 756 | 749 | 761 |
| Number (%) of subjects with at least one violation | 115 (15.1) | 108 (14.3) | 132 (17.6) | 125 (16.4) |
| Reasons for Protocol violation: * | | | | |
| Incorrect CHF/MI allocation | 7(0.9) | 4(0.5) | 10(1.3) | 9(1.2) |
| Incorrect consent date | 0 | 2(0.3) | 0 | 1(0.1) |
| Medical history | 6(0.8) | 5(0.7) | 0 | 4(0.5) |
| Incorrect concomitant drug | 33(4.3) | 43(5.7) | 24(3.2) | 22(2.9) |
| Incorrect CHF/MI diagnosis | 0 | 2(0.3) | 20(2.7) | 17(2.2) |
| Wall Motion Index | - | - | 1(0.1) | 2(0.3) |
| Inclusion/exclusion criteria | 26(3.4) | 22(2.9) | 21(2.8) | 22(2.9) |
| High QTc at baseline | 13(1.7) | 11(1.5) | 10(1.3) | 8(1.1) |
| Alcohol consumption | 18(2.4) | 18(2.4) | 22(2.9) | 15(2.0) |
| Laboratory abnormalities | 22(2.9) | 12(1.6) | 19(2.5) | 15(2.0) |
| Elevated enzymes | - | - | 18(2.4) | 18(2.4) |
| Scheduled surgical procedures | - | - | 2(0.3) | 3(0.4) |

* Subjects may have more than one violation.

Statistical Analysis

9.0 Data analyzed - Mortality DIAMOND TRIALS

The data analyzed include 3028 randomized patients (1518 and 1510) up to the end of the last clinic visit date and also to the end of each study date (December 10 1996 for CHF and July 1 1997 for MI). For analysis of primary endpoint, only the last visit date (LVD) was specified in the protocol. Events during the period between LVD and EOS were accounted for by the reviewer using the CRFs. All the patients who died during this period were treated as ITT in the primary analysis. Four randomized CHF patients were censored on the dates they had heart transplants, 2 receiving Dofetilide and 2 placebo. One randomized MI patient to Dofetilide was censored on the date of heart transplant.

9.1 Analysis of Total Mortality - Primary endpoint

Analysis of total mortality was based on ITT analysis (Tables 20-21), and the time to death was compared between treatment groups using the log rank test at the 5% level (2 sided), stratified for WMI and center (Table 22, Figures 3 and 4).

Out of 1518 randomized patients to the CHF study, 628 (41.5%) patients died from both treatment arms, and 890 (58.5%) survived. Dofetilide treated patients in the CHF and MI studies had fewer all cause deaths than placebo (311 versus 317 for CHF and (230 versus 243 for MI) (Table 20). The differences, though in favor of Dofetilide, are not statistically significant ($p=0.557$ and $p=0.226$). The probability of survival at 12 months and at the end of both studies shows no difference between treatment groups (Figures 3 and 4) (Tables 22-24).

Table 20: Mortality CHF/MI - ITT, OT, and OT+30 days

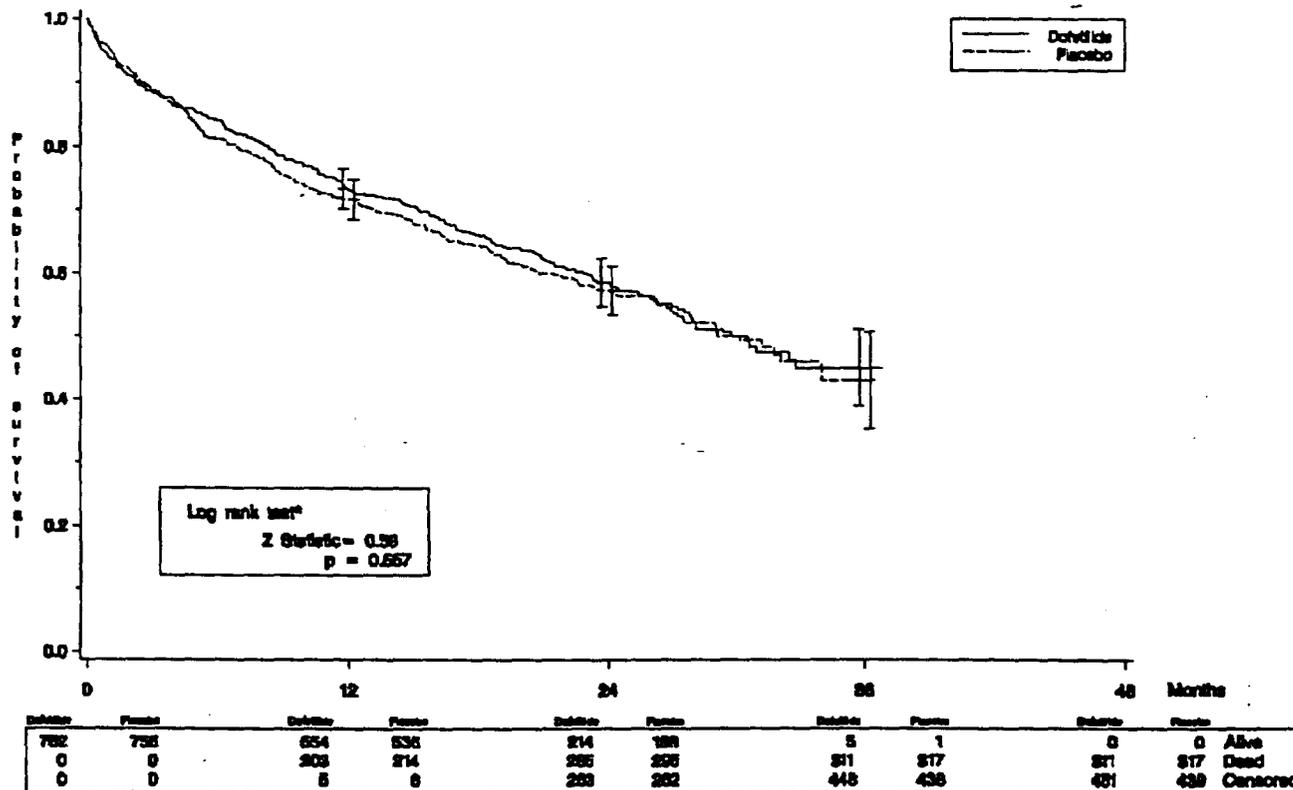
| Mortality | CHF | | | MI | | |
|-------------------------------|-------------------|----------------|-------|-------------------|----------------|-------|
| | Dofetilide(N=762) | Placebo(N=756) | p** | Dofetilide(N=749) | Placebo(N=761) | p** |
| End of Study - ITT | 311 (41%) | 317 (42%) | 0.557 | 230 (31%) | 243 (32%) | 0.226 |
| Probability of survival-1 yr. | 0.73 | 0.72 | | 0.79 | 0.77 | |
| On-Treatment (OT) | 82 (11%) | 92 (12%) | 0.539 | 69 (9%) | 83 (11%) | 0.280 |
| Probability of survival-1 yr. | 0.89 | 0.89 | | 0.91 | 0.90 | |
| OT + 30 days | 211 (28%) | 213 (28%) | 0.872 | 171 (23%) | 188 (25%) | 0.325 |
| Probability of survival 1 yr. | 0.78 | 0.76 | | 0.81 | 0.79 | |

**Log rank test for differences in survival times over the entire period. Significance at the 5% level-Sponsor

**Log rank test for Total Mortality for CHF p-value 0.57; for MI p value 0.224 at the 5% level - See Reviewers analysis in Table 21 that reflects difference in number of patients followed up for 360 days.

Figures 3 (Table 22) CHF- Total Mortality

DOFETILIDE PROTOCOL 400 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
 KAPLAN MEIER PLOT OF TOTAL MORTALITY (95% CI): CHF STUDY - INTENT-TO-TREAT POPULATION



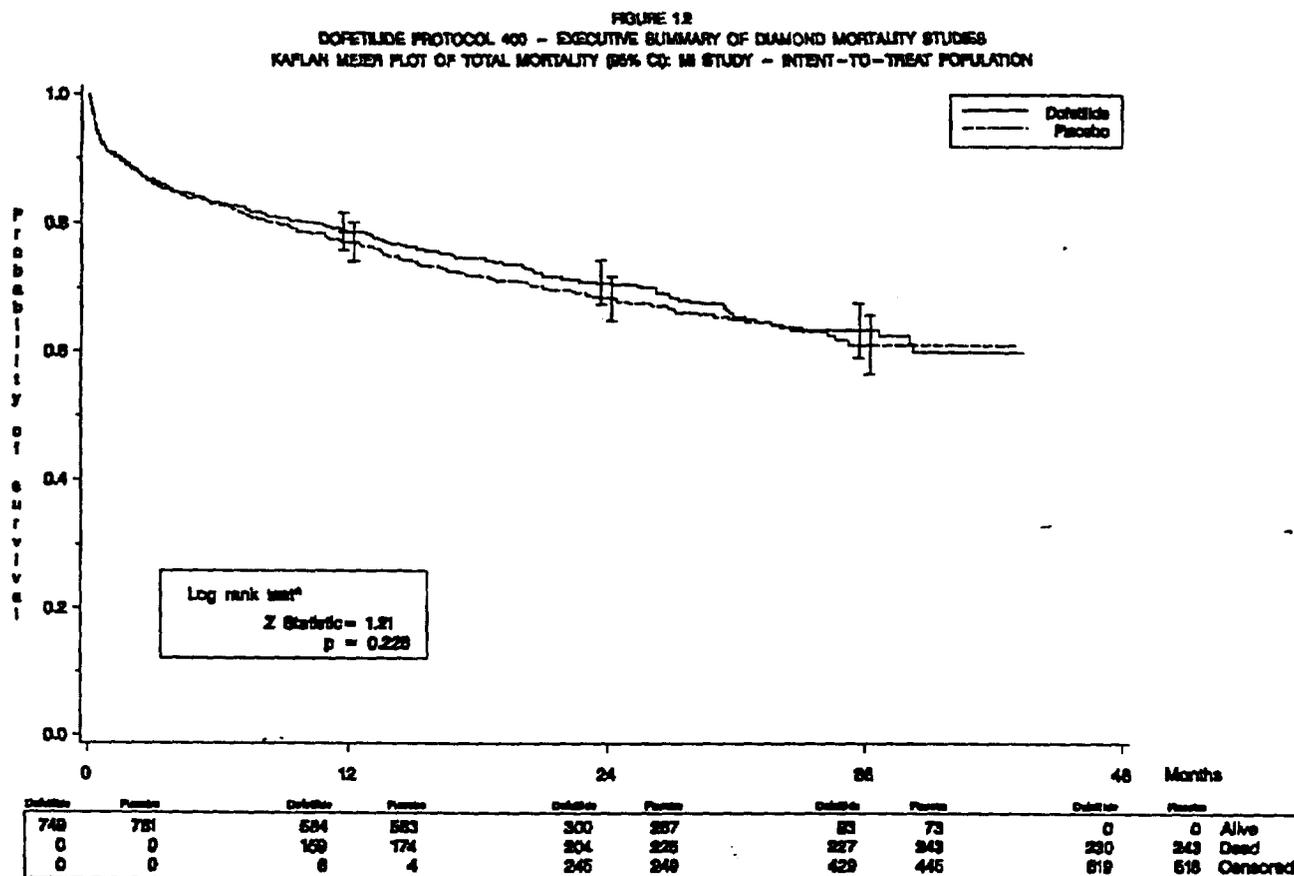
D: 16APR1997 - 09MAY1997

T: 27NOV97(18:03)

Source: CHF study - Main Body Table 6.1, Appendix 8A Table 1.1.1

* Stratified by severe and mild motion index category

Figure 4 (Table 24) MI-Total Mortality



D: 29OCT1997 - 29OCT1997

T: 27NOV97(2:09)

Source: MI study - Main Body Table 8.1, Appendix 8A Table 1.1.1

* Stratified by centre and wall motion index category

Using the database in the electronic submission, the reviewer found that in the CHF and MI studies (Drug/Placebo), 315/304 and 383/395 patients respectively, were classified as completers (Appendix Table 2). Of the completers, 12 patients were followed for less than 360 days (range 342-359 days). In the CHF study, there were 7 such patients (4 Dofetilide and 3 Placebo), and in the MI study, there were 5 patients (2 Dofetilide and 3 Placebo). As a result, 12 patients were not followed for the minimum requisite number of 360 days but were included in analysis of primary endpoint. Excluding these 12 patients did not affect the primary analysis (Tables 21 and 22). The probability of survival at 1, 2 and 3 years for both primary studies and also for the secondary endpoints shows no statistical difference between the treatment groups (Tables 22-25). These 12 patients were included in the sponsor's primary efficacy analysis.

Table 21: Total Mortality CHF/MI - ITT Comparison between Sponsor and Reviewer

| | CHF | | | | | MI | | | | |
|-----------------|--------------------|-----------------|--------------------|-----------------|------|--------------------|-----------------|--------------------|-----------------|------|
| | Sponsor | | Reviewer | | Diff | Sponsor | | Reviewer | | Diff |
| Total Mortality | Dofetilide (N=762) | Placebo (N=756) | Dofetilide (N=758) | Placebo (N=753) | 7 | Dofetilide (N=749) | Placebo (N=761) | Dofetilide (N=747) | Placebo (N=758) | 5 |
| EOS - ITT | 311(41%) | 317(42%) | 311(41%) | 317(42%) | | 230(31%) | 243(32%) | 230(31%) | 243(32%) | |
| Probability | 0.73 | 0.72 | 0.74 | 0.73 | | 0.79 | 0.77 | 0.79 | 0.77 | |
| p-value | 0.557 | | 0.57 | | | 0.226 | | 0.225 | | |

Diff=Difference between number of patients followed up for 360 days. No significant difference in p-value; Source: Reviewer

Table 22: Total mortality: Survival data CHF-ITT-OT

| | Alive at | Cumulative Dead by | Cumulative Censored by | Probability of Survival | 95% Confidence Interval | |
|----------------|----------|--------------------|------------------------|-------------------------|-------------------------|-------|
| | | | | | Lower | Upper |
| Dofetilide | | | | | | |
| Baseline | 762 | 0 | 0 | | | |
| 1 year | 421 | 63 | 278 | 0.890 | 0.864 | 0.916 |
| 2 years | 137 | 78 | 547 | 0.841 | 0.806 | 0.876 |
| 3 years | 1 | 82 | 679 | 0.801 | 0.747 | 0.855 |
| EOS(1099 days) | 0 | 82 | 680 | 0.801 | 0.747 | 0.855 |
| Placebo | | | | | | |
| Baseline | 756 | 0 | 0 | | | |
| 1 year | 398 | 62 | 296 | 0.890 | 0.864 | 0.916 |
| 2 years | 137 | 86 | 533 | 0.811 | 0.772 | 0.850 |
| 3 years | - | - | - | - | - | - |
| EOS(1093 days) | 0 | 92 | 664 | 0.738 | 0.661 | 0.816 |

Log Rank Test**: Z statistic=-0.6149; p=0.54. ** Tests for a difference in survival times between the two treatment groups, after allowing for center and WMI category. Significance at the 5% level.

Table 23: Total mortality + 30 day lag period CHF ITT-OT

| | Alive at | Cumulative Dead by | Cumulative Censored by | Probability of Survival | 95% Confidence Interval | |
|----------------|----------|--------------------|------------------------|-------------------------|-------------------------|-------|
| | | | | | Lower | Upper |
| Dofetilide | | | | | | |
| Baseline | 762 | 0 | 0 | | | |
| 1 year | 430 | 146 | 186 | 0.775 | 0.742 | 0.807 |
| 2 years | 151 | 196 | 415 | 0.642 | 0.598 | 0.686 |
| 3 years | 2 | 211 | 549 | 0.531 | 0.465 | 0.598 |
| EOS(1129 days) | 0 | 211 | 551 | 0.531 | 0.465 | 0.598 |
| Placebo | | | | | | |
| Baseline | 756 | 0 | 0 | | | |
| 1 year | 410 | 152 | 194 | 0.761 | 0.728 | 0.795 |
| 2 years | 149 | 203 | 404 | 0.628 | 0.584 | 0.672 |
| 3 years | 1 | 213 | 542 | 0.541 | 0.473 | 0.610 |
| EOS(1123 days) | 0 | 213 | 544 | 0.541 | 0.473 | 0.610 |

Log Rank Test**: Z statistic=-0.1607; p=0.8724. ** Tests for a difference in survival times between the two treatment groups, after allowing for center and WMI category. Significance at the 5% level.

Table 24: Total mortality: MI- ITT

| | Alive at | Cumulative Dead by | Cumulative Censored by | Probability of Survival | 95% Confidence Interval | |
|-------------------|----------|--------------------|------------------------|-------------------------|-------------------------|-------|
| | | | | | Lower | Upper |
| Dofetilide | | | | | | |
| Baseline | 749 | 0 | 0 | | | |
| 1 year | 584 | 159 | 6 | 0.788 | 0.758 | 0.817 |
| 2 years | 300 | 204 | 245 | 0.709 | 0.674 | 0.743 |
| 3 years | 93 | 227 | 429 | 0.633 | 0.590 | 0.676 |
| EOS(1320 days) | 0 | 230 | 519 | 0.600 | 0.546 | 0.655 |
| Placebo | | | | | | |
| Baseline | 761 | 0 | 0 | | | |
| 1 year | 583 | 174 | 4 | 0.771 | 0.741 | 0.801 |
| 2 years | 287 | 225 | 249 | 0.684 | 0.649 | 0.719 |
| 3 years | 73 | 243 | 445 | 0.611 | 0.564 | 0.657 |
| EOS(1308 days) | 0 | 243 | 518 | 0.611 | 0.564 | 0.657 |

LogRank Test**:ZStatistic=1.2109; p=0.23. ** Tests for a difference in survival times between the two treatment groups, after allowing for center and wall motion index category. Significance at the 5% level.

Table 25: Total mortality + 30day lag period: ITT-OT - MI

| | Alive at | Cumulative Dead by | Cumulative Censored by | Probability of Survival | 95% Confidence Interval | |
|-------------------|----------|--------------------|------------------------|-------------------------|-------------------------|-------|
| | | | | | Lower | Upper |
| Dofetilide | | | | | | |
| Baseline | 749 | 0 | 0 | | | |
| 1 year | 452 | 131 | 166 | 0.806 | 0.775 | 0.836 |
| 2 years | 222 | 157 | 370 | 0.745 | 0.709 | 0.781 |
| 3 years | 65 | 169 | 515 | 0.691 | 0.647 | 0.736 |
| EOS(1320 days) | 0 | 171 | 578 | 0.656 | 0.592 | 0.720 |
| Placebo | | | | | | |
| Baseline | 761 | 0 | 0 | | | |
| 1 year | 473 | 148 | 140 | 0.791 | 0.761 | 0.821 |
| 2 years | 223 | 178 | 360 | 0.724 | 0.687 | 0.760 |
| 3 years | 59 | 188 | 514 | 0.666 | 0.616 | 0.716 |
| EOS(1308 days) | 0 | 188 | 573 | 0.666 | 0.616 | 0.716 |

LogRank Test**:ZStatistic=0.9842; p=0.3250** Tests for a difference in survival times between the two treatment groups, after allowing for center and WMI index category. Significance at the 5% level.

Total mortality and treatment duration-CHF/MI

In order to evaluate the possible effect of treatment duration on early QT/QTc prolongation and its relation to total mortality, the reviewer carried out an analysis based on recent data submitted by the sponsor in July 1998. There is a slight increase in mortality in CHF and MI Dofetilide- treated group compared to placebo during the first 45 days of therapy but no significant difference in total mortality between the treatment groups from 45 days of treatment to the end of study (Table 26). The choice of 45 days as a cut off point is arbitrary but represents roughly the average number of days for month 1 visit date (range 28-59 days). Analyses of treatment duration by duration of follow-up in patients who died before end of study showed no statistically significant difference in mortality between the treatment groups.

Table 26: Total mortality and treatment duration - CHF and MI

| CHF (N=628) | | | MI (N=473) | | |
|-------------------------|---------------------|------------------|-------------------------|----------------------|------------------|
| Treatment Duration(dys) | Dofetilide n=311 | Placebo n=317 | Treatment Duration(dys) | *Dofetilide n=230 | Placebo n=243 |
| 1-45 | 108/311(34.7%) | 105/317(33.1%) | 1-45(days) | *118/230(51.3%) | 108/243(44.4%) |
| 46-End of study | 203/311(65.3%) | 212/317(66.9%) | 46-End of study | 112/230(48.7%) | 135/243(55.6%) |

* p=0.142 (Statistics by Dr K. Majoob) for Dofetilide versus Placebo MI study. NS for MI and CHF.
(NS=Not significant)

Source: Reviewer - See Appendix Figures 1-8; pages 101-105

Total mortality-CHF/MI study - CHF-ITT

The sponsor claims that TIKOSYN would appear to have no effect on mortality in this population with structural heart disease. While this may be supported by the lack of increased mortality compared to some other anti-arrhythmics, Dofetilide did not reduce mortality compared to placebo in the presence of structural heart disease.

Total mortality - CHF-ITT-OT

Out of 1518 randomized patients, 174 (11.5%) patients died while receiving study medication. Of the 174 patients, 82/762 died while receiving Dofetilide and 92/756 died while on placebo. There was no significant difference between treatment groups during the entire study period (p=0.539) (Table 20).

Total mortality -MI-ITT-OT

Out of 1510 randomized patients, 152 (10.1%) patients died while receiving study medication. Of the 152 patients, 69/749 died while receiving Dofetilide and 83/761 died while on placebo. There was no significant difference between treatment groups during the entire study period (p=0.280) (Table 20)

9.2 Total mortality-combined CHF and MI with AF/AFl

Analysis of combined data on all cause mortality and survival probability for CHF/MI population, including patients with AF/AFl at baseline, show no statistically significant mortality benefit between treatment groups (Table 27). The sponsor expects some clinical benefit following Dofetilide therapy on patients with supraventricular tachyarrhythmias. This should be mediated by conversion and maintenance of SR which in turn should have a favorable effect on morbidity and mortality (Tables 28a and 28b). Although there were fewer deaths among the Dofetilide-treated patients in both studies, the probability of survival was not statistically significant between treatment groups (p=0.63).(CI for Dofetilide was 0.141-0.555 compared to 0.309-0.514 for placebo @95% level). In conclusion, there is no mortality benefit in CHF or MI patients with and without AF/AFl at baseline (Figures 5 and 6). The curves for the patients in the AF/AFL substudy are flawed (See review of 115-400AF).

Table 27: Survival probability - Combined CHF/MI and AF/AFL - ITT

| | Alive at | Cumulative Dead by | Cumulative Censored by | Probability of Survival | 95% Confidence Interval | |
|----------------|----------|--------------------|------------------------|-------------------------|-------------------------|-------|
| | | | | | Lower | Upper |
| Dofetilide | | | | | | |
| Baseline | 249 | 0 | 0 | | | |
| 1 year | 170 | 77 | 2 | 0.691 | 0.633 | 0.748 |
| 2 years | 62 | 104 | 83 | 0.541 | 0.472 | 0.610 |
| 3 years | 7 | 110 | 132 | 0.464 | 0.380 | 0.548 |
| EOS(1320 days) | 0 | 111 | 138 | 0.348 | 0.141 | 0.555 |
| Placebo | | | | | | |
| Baseline | 257 | 0 | 0 | | | |
| 1 year | 175 | 81 | 1 | 0.685 | 0.628 | 0.742 |
| 2 years | 72 | 108 | 77 | 0.545 | 0.479 | 0.612 |
| 3 years | 6 | 116 | 135 | 0.412 | 0.309 | 0.514 |
| EOS(1308 days) | 0 | 116 | 141 | 0.412 | 0.309 | 0.514 |

LogRank Test**:ZStatistic=-0.0818; p=0.93 ** Tests for a difference in survival times between the two treatment groups, after allowing for center and WMI category. Significance at 5% level.

Total mortality CHF/MI with AF/AFL

Out of a total of 506 patients in the DIAMOND studies, 391(77.3%) were from the CHF study, and 115 (22.7%) from the MI study (Tables 28a-b). The mortality data during and at the end of studies are presented in Tables 28a and 28b. The morbidity frequencies (stroke and systemic embolism) are also presented in Tables 28a and b, and show no significant differences between the treatment groups. There is no significant difference in the morbidity event rates (Stroke and Systemic embolism) between the treatment groups. The survival curves for both treatment groups are graphically presented in Figures 5, 6a and 6b. It is evident that there are no significant differences in mortality between the two treatment groups in the main study(p=0.63), but there is a significant difference in mortality in the substudy (p=0.04) (Figure 5).

Table 28a: Morbidity and mortality in AF/AFL at baseline - CHF

| | Dofetilide | Placebo |
|--|------------|----------|
| Total number of subjects | 762 | 756 |
| Number of subjects with AF at baseline | 190 | 201 |
| Number (%) of Deaths: During Study | 45(23.7) | 50(24.9) |
| Total Deaths | 84(44.2) | 88(43.8) |
| Stroke | 7(3.7) | 6(2.99) |
| Systemic embolism | 2(1.1) | 2(1.0) |

Table 28b: Morbidity and mortality in AF/AFL at baseline - MI

| | Dofetilide | Placebo |
|--|------------|----------|
| Total number of subjects | 749 | 761 |
| Number of subjects with AF at baseline | 59 | 56 |
| Number (%) of Deaths: During Study | 16(27.1) | 14(25.0) |
| Total Deaths | 27(45.8) | 28(50) |
| Stroke | 2(3.4) | 2(3.6) |
| Systemic embolism | 1(1.7) | 0 |

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Figure 5: Mortality studies CHF/MI +AF DIAMOND(n=506) and Substudy AF(n=177)

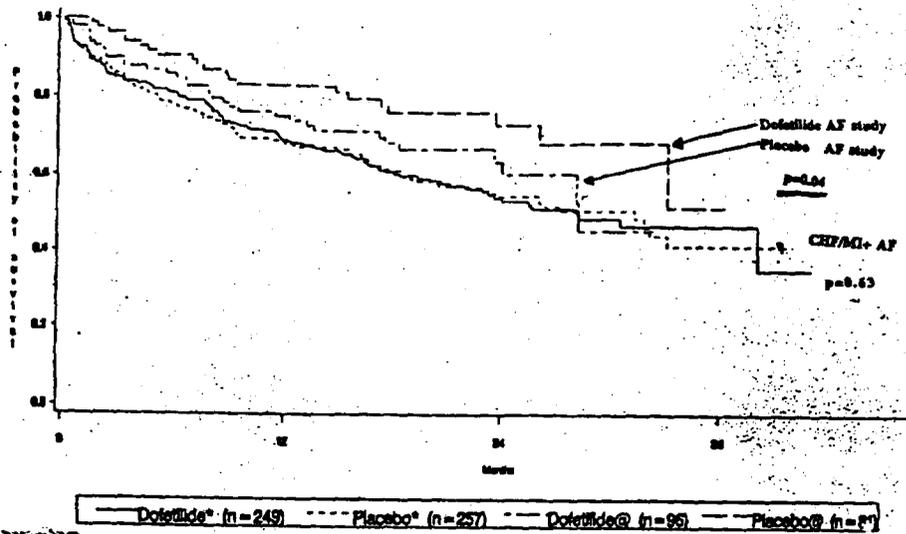
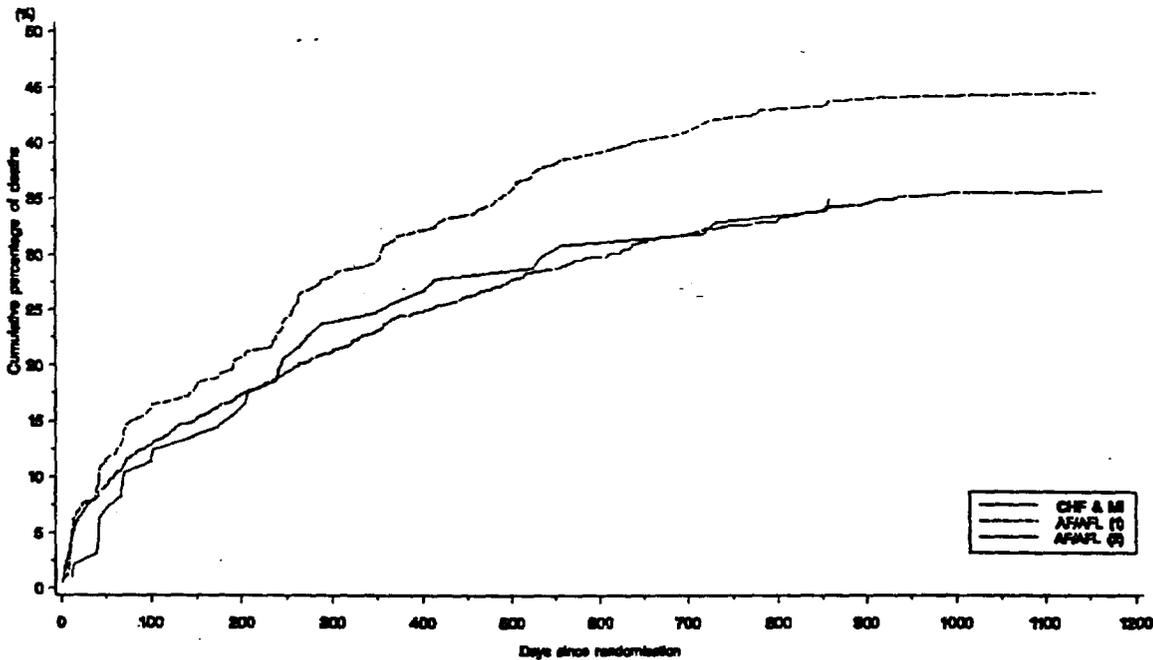


Figure 5 above is a composite of Figures 6a and 6b below. Note the relatively low survival curve of placebo group in figure 6b compared to Dofetilide in Figure 6a.

Figure 6a: Mortality studies CHF/MI +AF - Dofetilide

FIGURE 3.7
DOFETILIDE PROTOCOL 400 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
SUMMARY OF CUMULATIVE MORTALITY: SUBJECTS RECEIVING DOFETILIDE



0: 880287 - 870887
2: 870887(8:89)

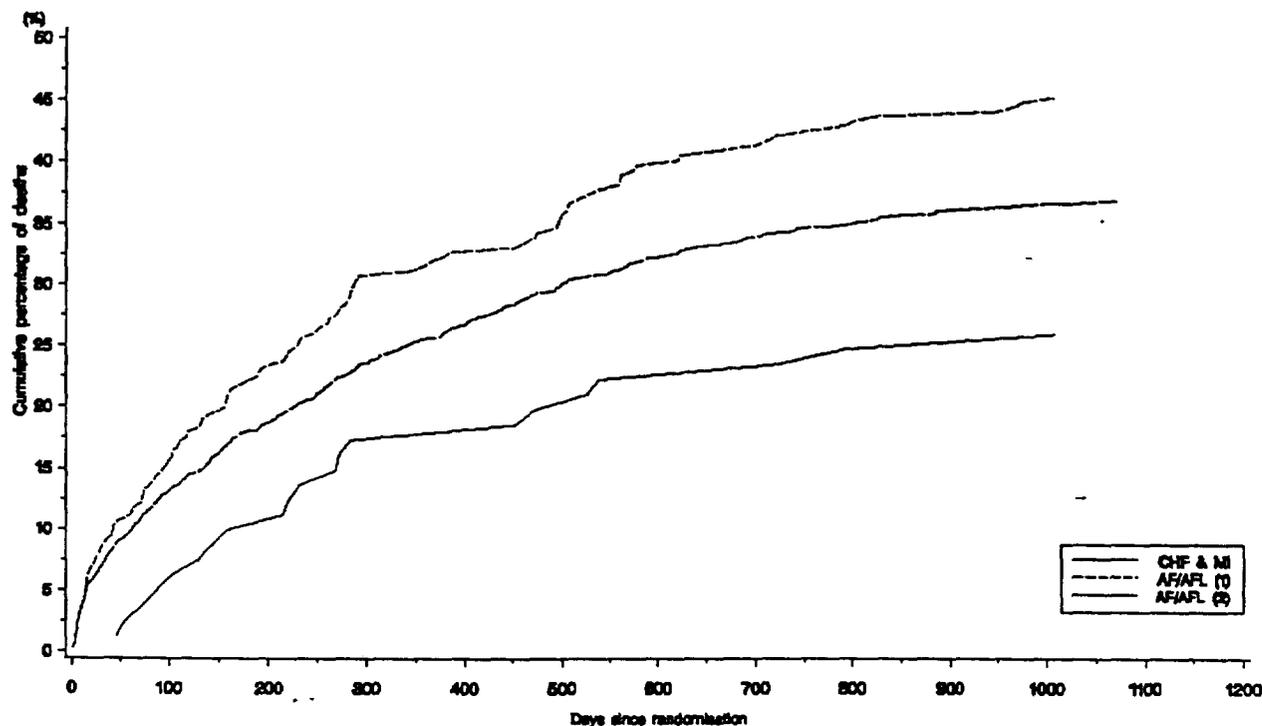
(1) = Patients with AF/AF at baseline for the CHF and MI studies.
(2) = Patients who were defined to be in the AF/AF sub-study.

Upper curve = 249 Dofetilide patients with AF; Lower curve = All 1511 patients randomized to DIAMOND Dofetilide;
Middle curve = 97 Dofetilide treated patients with AF who entered the AF substudy (see pages 70-80).

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Figure 6b: Mortality studies CHF/MI +AF - Placebo

FIGURE 3B
DOFETILIDE PROTOCOL 400 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
SUMMARY OF CUMULATIVE MORTALITY: SUBJECTS RECEIVING PLACEBO



D: 28OCT1987 - 27NOV1987
E: 27NOV1987(12:27)

(1) = Patients with AF/AFL at baseline for the CHF and MI studies.
(2) = Patients who were defined to be in the AF/AFL sub-study.

Upper curve = 257 Placebo patients with AF; Middle curve = 1517 patients randomized to DIAMOND Placebo;
Lower curve = 81 Placebo treated patients with AF who entered the AF substudy (see pages 70-80).

9.3 Prognostic factors

The distribution frequencies of WMI and mortality are presented in Table 29. The overall relative hazard of Dofetilide therapy versus placebo, having adjusted for prognostic factors (WMI and NYHA) in the CHF-ITT group is 0.94 (CI 0.81-1.11 @ 95% level), and in patients classified as CHF-ITT-OT, the relative hazard of Dofetilide versus placebo is 0.86 (CI 0.64-1.17 @95% level). The hazard ratio of WMI for MI-ITT is 0.48 whereas for CHF it was 0.71 (p values for both studies = <0.001) (Appendix Tables 6-7). The data show that although both studies had decreased hazard with increased WMI, the risk was less with MI compared to CHF. This may partly be accounted for by the higher frequencies of NYHA class II in MI patients (54%) compared to CHF (37.5%) at baseline.

Total mortality and WMI - CHF/MI

The frequency distribution of WMI, an indication of left ventricular ejection fraction, among patients who died at the end of the studies, is presented in Table 29. It is evident that there are significant differences in the NYHA class of patients in CHF study compared to MI, and claims for clinical benefits, such as hospitalization for worsening of heart failure should take these differences into account (See Table 36b, page 40).

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Out of the 311 and 317 dead patients in the CHF, respectively, 48.4% and 50.2% in the drug and placebo groups, respectively, had WMI >0.8. In contrast, out of 230 and 243 dead patients in the MI study, 79.1% and 71.6% in the drug and placebo groups, respectively, had WMI >0.8. This data suggest that mortality was relatively higher in MI patients with WMI >0.8 compared to CHF with comparable WMI, regardless of treatment.

Table 29: Frequencies of WMI-ITT patients and mortality

| WMI | CHF(628) | | MI (473) | |
|-------|-----------------|--------------|-----------------|--------------|
| | Dofetilide(311) | Placebo(317) | Dofetilide(230) | Placebo(243) |
| 0.30 | 1 | 2 | - | - |
| 0.40 | 15 | 15 | 2 | 1 |
| 0.50 | 24 | 26 | 7 | 8 |
| 0.60 | 34 | 35 | 13 | 8 |
| 0.70 | 39 | 37 | 11 | 11 |
| 0.80 | 49 | 43 | 15 | 40 |
| 0.90 | 35 | 37 | 36 | 46 |
| 1.0 | 53 | 57 | 31 | 32 |
| 1.10 | 33 | 36 | 56 | 42 |
| 1..20 | 28 | 29 | 59 | 54 |

*One patient had WMI of 1.80 which is a violation of the inclusion criteria WMI>0.8 CHF Dof 149/311(48.4%)Plcbo159/317(50.2%); WMI >0.8 MI Dof 182/230 (79.1%) Plcbo174/243(71.6%). Source: Reviewer

10.0 Secondary Efficacy Endpoints

- ◆ Cardiac mortality
- ◆ Total arrhythmic death
- ◆ Cardiac mortality combined with resuscitated cardiac arrest
- ◆ Time to the first event of worsening heart failure requiring hospitalization,
- ◆ Time to the first event of death, worsening heart failure requiring hospitalization, or withdrawal from study treatment.

10.1 Cardiac mortality - CHF-ITT

Out of 1518 randomized patients to CHF, 506 patients died from cardiac causes in both treatment groups. A total of 255/762 (33.5%) and 251/756 (33.2%) died on Dofetilide and placebo groups, respectively (Table 30). There is no significant difference between cardiac mortality between the treatment groups (p=0.89) (Table 30), and similarly the probability of survival between both groups showed no statistical differences (p=0.1014 for MI and p= 0.8895 for CHF) (Table 31).The lack of increased mortality in the Dofetilide treated patients, in spite of its known proarrhythmic effect in the early days of exposure, is striking.

Table 30: Cardiac mortality - CHF/MI - ITT

| Mortality | CHF | | | MI | | |
|-----------------------|-------------------|----------------|--------|-------------------|----------------|-------|
| | Dofetilide(N=762) | Placebo(N=756) | p** | Dofetilide(N=749) | Placebo(N=761) | p** |
| Cardiac Mortality | 255(34%) | 251(33%) | | 191(26%) | 212(28%) | |
| *Survival Probability | 0.78 | 0.77 | 0.0889 | 0.81 | 0.79 | 0.101 |

**Log rank test for differences in survival times over the study period; See Table 31. *Probability at 1 year.

Table 31: Probability of cardiac mortality - CHF/MI - ITT

| | CHF | | | | MI | | | |
|--------|-------------|-------------------|-------------|----------------|-------------|-------------------|-------------|----------------|
| | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% |
| Year 1 | 0.775 | 0.745-0.805 | 0.766 | 0.735-0.797 | 0.813 | 0.785-0.841 | 0.793 | 0.764-0.822 |
| Year 2 | 0.643 | 0.604-0.682 | 0.643 | 0.604-0.682 | 0.752 | 0.719-0.785 | 0.719 | 0.685-0.754 |
| Year 3 | 0.511 | 0.444-0.577 | 0.520 | 0.437-0.603 | 0.696 | 0.655-0.737 | 0.652 | 0.606-0.698 |
| EOS | 0.511 | 0.444-0.577 | 0.520 | 0.437-0.603 | 0.660 | 0.604-0.716 | 0.652 | 0.606-0.698 |

LogRank Test**: Z1.638 p=0.1014 for MI Z=0.1390 =_ 0.8895 for CHF; ** Tests for a difference in survival times between the two treatment groups, after allowing for center and wall motion index category. Significance at the 5% level.

Cardiac mortality - CHF-ITT-OT

Out of 1518 randomized patients, 164 (10.8%) patients died while receiving study medication. Of the 164 patients, 79/762 (10.4%) died while receiving Dofetilide and 85/756 (11.2%) died while on placebo. There was no significant difference between treatment groups during the entire study period.

Cardiac mortality - MI - ITT

Out of 1510 randomized patients to the MI study, 411 patients died from cardiac causes ; 191/749 (26%) and 212/761 (28%) died on Dofetilide and placebo, respectively (Tables 30). There is no significant difference in cardiac mortality between the treatment groups (p=0.101), and similarly, between the probability data (Table 31). One randomized patient was censored on the date of heart transplant, and received Dofetilide.

Cardiac mortality - MI-ITT-OT

Out of 1510 randomized patients, 142 (9.4%) patients died while receiving study medication. Of the 142 patients, 63/749 (8.4%) died while receiving Dofetilide and 79/761 (10.4%) died while on placebo. There was no significant difference in cardiac mortality between treatment groups during the entire study period (p=0.223) (Table 30).

Cardiac Mortality and resuscitated cardiac arrests - CHF-ITT

Out of 1518 randomized patients to the CHF study, 346 (22.8%) had either a cardiac arrest or a resuscitated cardiac arrest from both treatment groups. A total of 178/762 (23.4%) and 168/756 (22.2%) on Dofetilide and placebo arms, respectively, had cardiac arrest or resuscitated cardiac arrest. There is no significant difference between the treatment groups (Table 32).

Cardiac Mortality and resuscitated cardiac arrests - MI - ITT

A total of 315 out of 1510 (20.9%) randomized patients to the MI study had a cardiac arrest or a resuscitated cardiac arrest. For Dofetilide and placebo groups, 157/749 (21.0%) and 158/761(20.8%) fell into this category, respectively. In the MI study, there is no significant difference in cardiac mortality between treatment groups (p=0.821).

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After adjusting for reduced creatinine clearance, the incidence of cardiac mortality in Dofetilide treated MI group is slightly less than in the placebo group (29 Dofetilide patients versus 36 placebo) (Table 33). In contrast, there were more cardiac deaths in the Dofetilide CHF patients compared to placebo group (27 Dofetilide : 18 placebo) (Tables 32-33).

Table 32: Cardiac Mortality and resuscitated cardiac arrests-CHF/MI-ITT

| Days | CHF | | MI | |
|--------------|------------------------|---------------------|------------------------|---------------------|
| | Dofetilide N=762(%) | Placebo N=756(%) | Dofetilide N=749(%) | Placebo N=761(%) |
| 1-3 | 10(1.3) | 6(0.8) | 10(1.3) | 8(1.1) |
| 4-7 | 3(0.4) | 2(0.3) | 8(1.1) | 0 |
| >7-EOS | 17(2.2) | 10(1.6) | 17(2.3) | 28(3.4) |
| Total Events | 30 | 18 | 35 | 36 |

Table 33: Cardiac Mortality and resuscitated cardiac arrests adjusted for patients with reduced creatinine clearance-CHF/MI-ITT

| Days | CHF | | MI | |
|--------------|------------------------|---------------------|------------------------|---------------------|
| | Dofetilide N=616(%) | Placebo N=756(%) | Dofetilide N=649(%) | Placebo N=761(%) |
| 1-3 | 9(1.5) | 6(0.8) | 7(1.1) | 8(1.1) |
| 4-7 | 3(0.5) | 2(0.3) | 6(0.9) | 0 |
| >7-EOS | 15(2.4) | 10(1.6) | 16(2.5) | 28(3.4) |
| Total Events | 27 | 18 | 29 | 36 |

In the combined CHF/MI data, there were more cardiac deaths among patients who had cardiac arrests in the Dofetilide treated patients (65/1511 [4.3%] compared to 54/1517 [3.56%]) in the placebo group (Table 32). During the first seven days of treatment there was a 2 fold difference in the cardiac mortality in the Dofetilide group compared to placebo 31: 16. This is possibly due to the increased QT/QTc intervals in the Dofetilide group in the early days of therapy. Downward titration of Dofetilide based on creatinine clearance still resulted in a 1.5 fold increase of cardiac arrests in the Dofetilide group compared to placebo 25:16 (Table 33). These data suggest that the risk of cardiac arrest appears greater in the Dofetilide group during the first week of treatment (<7 days), compared to placebo (Tables 32-33).

After the first week of therapy, the overall incidence of cardiac arrests appears to be similar between treatment groups in both studies. However, there were more cardiac deaths among patients who had had cardiac arrests in the Dofetilide group (30/762) compared to placebo(18/756) in the CHF study, whereas no difference was observed in the MI group.

Age and gender on Total mortality-Hazards ratio

Secondary analysis of total mortality, using age and gender as variables showed that there were more deaths in patients > 70 years in both CHF and MI studies compared to patients < 70 years old. There was no significant difference in total mortality among males and females in both studies (Table 33b). Hazards ratio are presented in Appendix Tables 4-7

Table 33b - Total mortality by age and gender-Hazards ratio CHF/MI - ITT*

| Group | CHF | | | MI | | |
|-----------------|---------------------|--------------------|-------------------------------------|--------------------|--------------------|-------------------------------------|
| | Dofetilide | Placebo | Hazards Ratio Dofetilide/Placebo | Dofetilide | Placebo | Hazards Ratio Dofetilide/Placebo |
| Median Age(yrs) | | | | | | |
| <70 | 128/401 (31.9%) | 138/388 (35.6%) | 0.88 (0.69-1.12) | 89/406 (21.9%) | 93/379 (24.5%) | 0.86 (0.65-1.15) |
| >70 | 183/361 (50.71%) | 179/368 (48.6%) | 1.03 (0.83-1.26) | 141/343 (41.1%) | 150/382 (39.3%) | 1.05 (0.84-1.33) |
| Gender | | | | | | |
| Male | 228/546 (41.8%) | 237/568 (41.7%) | 1.00 (0.83-1.20) | 157/542 (29%) | 172/569 (30.2%) | 0.94 (0.76-1.17) |
| Female | 82/216 (38.4%) | 80/188 (42.6%) | 0.85 (0.62-1.15) | 73/207 (35.3) | 71/192 (37%) | 0.92 (0.66-1.28) |

*See Appendix Tables 4-7

10.2 Reinfarctions CHF/MI - ITT

A total of 179 out of 1510 (11.9%) randomized MI patients had at least one infarction / reinfarction during the study. For Dofetilide and placebo groups, 75/749 (10.1%) and 104/761(13.7%) patients experienced 1, 2, or 3 infarctions , respectively (Table 34). The total number of reinfarctions in the MI study were 96 and 126 for Dofetilide and placebo, respectively. There is no significant difference in the frequency of reinfarctions between the treatment groups.

In the CHF study, a total of 89 out of 1518 (5.9%) randomized patients had at least one infarction/reinfarction during the study. For Dofetilide and placebo groups, 47/762 (6.2%) and 42/756 (5.5%) patients experienced 1,2, or 3 infarctions, respectively (Table 35). There is no significant difference in reinfarctions between treatment groups.

Table 34: Reinfarctions - MI - ITT

| REINFARCTIONS-MI | | |
|--|---------------------|------------------|
| No of events | Dofetilide N=749 | Placebo n=761 |
| 0 | 673(89.9%) | 657(86.3%) |
| 1 | 59(7.9%) | 89(11.7%) |
| 2 | 15(2.0%) | 12(1.6%) |
| 3 | 1(0.1%) | 1(0.1%) |
| >3 | 1(0.1%) | 2(0.3%) |
| Total no of subjects with at least one reinfarction | *76(10.1%) | 104(13.7%) |

*1 patient was excluded (n=75)

Table 35: Reinfarctions - CHF - ITT

| No of Infarctions/ Reinfarctions | Dofetilide n (%) | Placebo n (%) |
|-------------------------------------|---------------------|------------------|
| 0 | 715(93.8) | 714(94.4) |
| 1 | 43(5.6) | 35(4.6) |
| 2 | 3(0.4) | 6(0.8) |
| 3 | 1(0.1) | 1(0.1) |
| Total | 47/762(6.2) | 42/756(5.6) |

10.3 Worsening of Heart Failure-CHF-ITT(Summary Table 37c page 43)

A total of 521/1518 (34.3%) randomized patients to the CHF study had at least one episode of worsening of heart failure. For Dofetilide and placebo groups, 231/762 (30.3%) and 290/756 (38.4%) patients experienced 1, 2, 3 or >3 episodes of worsening heart failure (Table 36a). The total number of episodes of worsening of heart failure requiring hospitalization were 352 and 422 for Dofetilide and placebo, respectively. There is a significant difference in worsening of heart failure and death over the entire period of study between treatment groups ($p < 0.001$), and this benefit was maintained for the duration of the study period. This suggests that the time-to-first event of worsening heart failure was longer in Dofetilide-treated patients compared to placebo, and the probability of remaining event-free is also significant between the treatment groups ($p = 0.0004$) (Table 37). The probability of remaining event-free for 12 months in the dofetilide treatment group was 70.5% (95% CI: 66.9, 74.2) compared to 59.9 (95% CI: 56.0, 63.8) in the placebo group.

For the CHF patients in DIAMOND studies, analysis of time-to-first event of worsening of heart failure and death is graphically presented in Figure 24 and Table 36a. The frequency of hospitalization in the CHF group, over 1100 days, is graphically depicted by the reviewer in Figures 25 and 26 using the data from the electronic submission. The reviewer finds very little difference between the treatment groups in the frequency of hospitalization when time to first event, death or withdrawal for any reason were analysed ($p = 0.076$). However, analysis of time to first event of hospitalization for worsening of heart failure for the 506 patients in the combined DIAMOND-AF population showed a significant difference in favor of Dofetilide. In this population, 73/249 and 102/257 CHF-AF patients were hospitalized with worsening CHF on dofetilide and placebo respectively. The RR was 0.69 (95% CI: 0.51-0.93; $p = 0.014$ and the log rank test had a p value of $p = 0.012$). Using NYHA classification of all the patients at the end of study, there was no statistically significant difference in the downward shift of NYHA class in favor of the Dofetilide group compared to placebo (Table 36b) which suggests that there was no significant difference subsequent to the time-to-first event of hospitalization (Tables 36b and 37). However, the lack of clinical benefit among patients without documented AF/AFL in respect of time-to-first event of hospitalization would suggest that Dofetilide may play a role in the observed clinical benefit among patients with AF/AFL. This indirect evidence provides some support for Dofetilide effect on cardiac rhythm and forms the basis for the reviewers recommendation (See page 66).

It is noteworthy that this study did not specifically look for nor did it evaluate the magnitude of symptomatic benefit between treatment groups. Therefore the data only provides information on frequencies of all-cause hospitalization between treatment groups (Table 37c). It is conceivable that the favorable event-free worsening of heart failure observed in the CHF Dofetilide group may be due to other factors and not Dofetilide-related. For example, the possible effects of concomitant medication cannot be validated because there was an amendment (Amendment VIII/115 -400 subsection j) removing the requirement to collect data on dose and frequencies of concomitant medication.

Figure 24 (Table 42) CHF

FIGURE 4.2
DOFETILIDE PROTOCOL 400 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
KAPLAN MEIER PLOT OF TIME TO FIRST EVENT OF WORSENING HEART FAILURE OR DEATH (95% CI): CHF STUDY - INTENT-TO-TREAT POPULATION

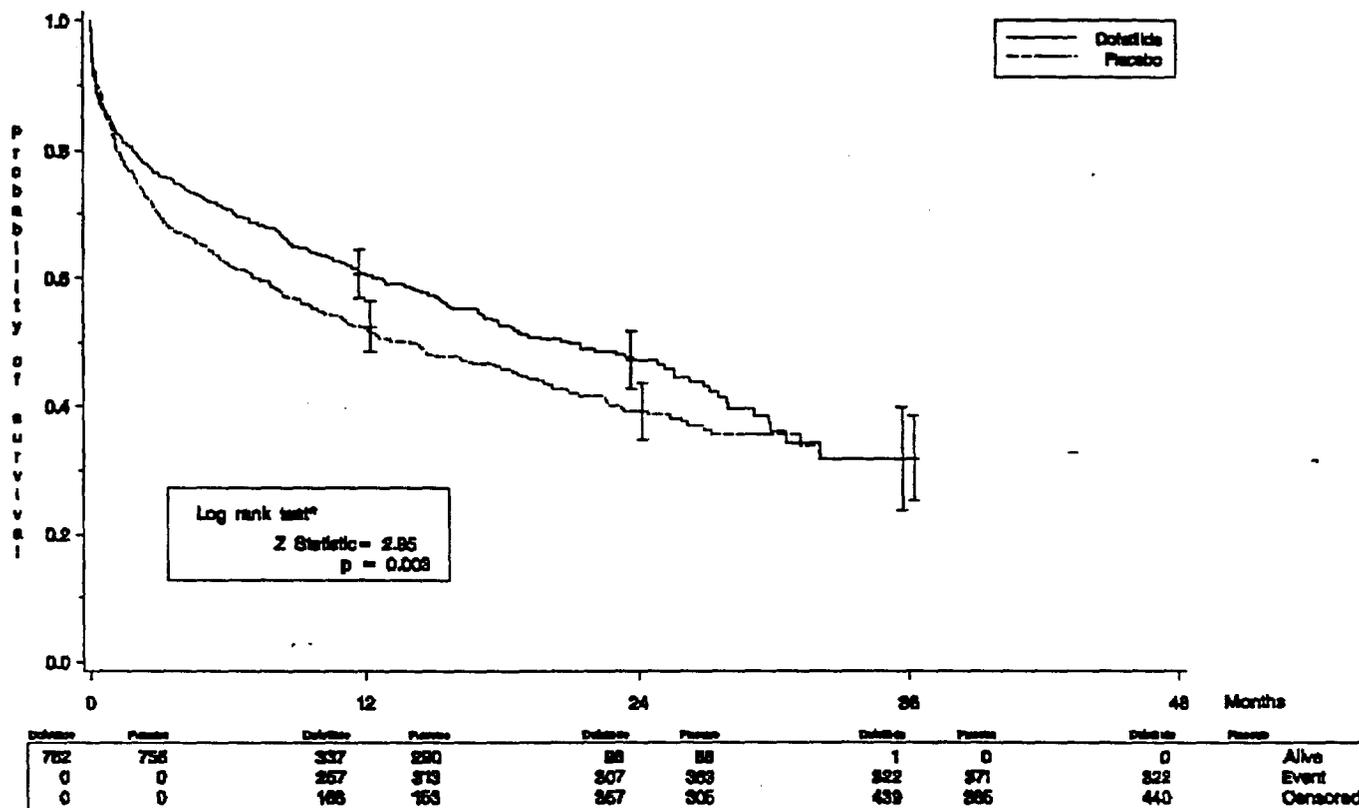
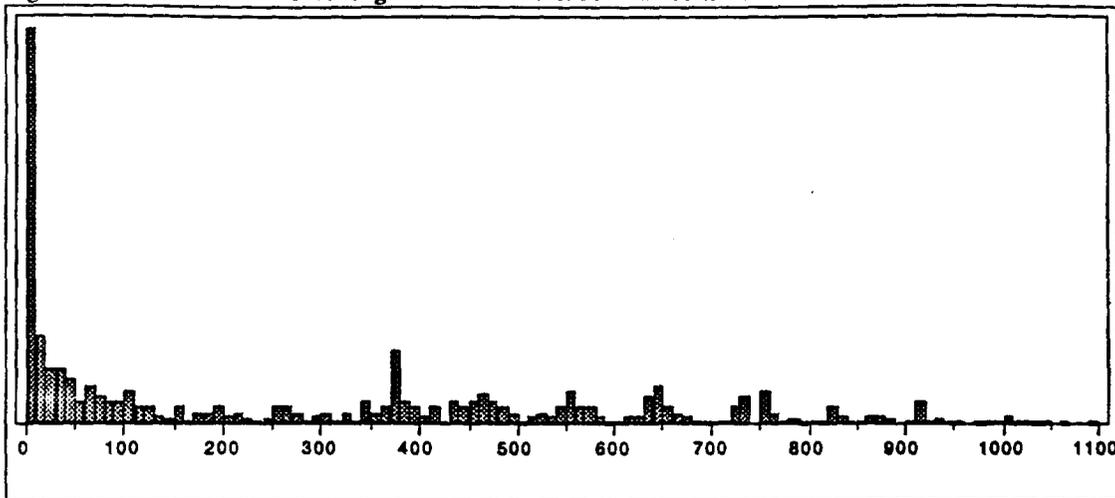


Table 36a: Worsening of Heart failure - CHF-ITT

| No of Events of worsening Heart failure | Dofetilide n = 762 (%) | Placebo n = 756 (%) |
|---|---------------------------|------------------------|
| 0 | 531 (69.7) | 466 (61.6) |
| 1 | 160 (21.0) | 206 (27.2) |
| 2 | 43 (5.6) | 51 (6.7) |
| 3 | 17 (2.2) | 24 (3.2) |
| >3 | 11 (1.4) | 9 (1.2) |
| Total number of events | 231 (30.3%) | 290 (38.4%) |

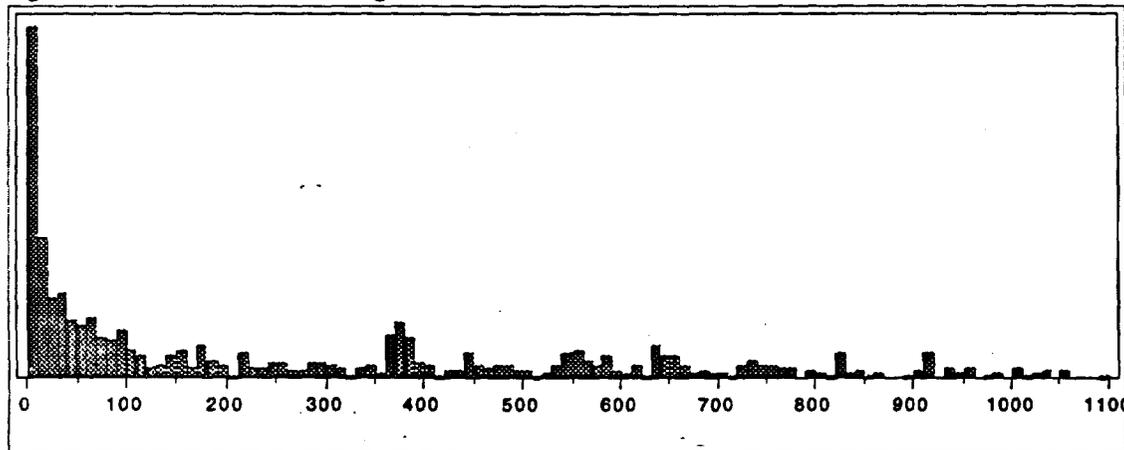
Source: Sponsor

Figure 25: Time to worsening of Heart Failure - Dofetilide - CHF-ITT



Source: Reviewer

Figure 26: Time to worsening of Heart Failure - Placebo - CHF-ITT



Source: Reviewer

Changes in NYHA classification and hospitalization

Using downshifting of the NYHA as a measure of improvement of heart failure requiring hospitalization, and upshifting as a measure of worsening of heart failure, we have found no statistical significance in analysis of NYHA and hospitalization between treatment groups for both DIAMOND MI and CHF groups (Table 36b)(Statistician Dr L Cui). The probability of event free worsening of heart failure based on the investigator ticking a box for worsening heart failure, however, shows a significant difference for DIAMOND CHF patients ($p=0.0004$) but not for MI DIAMOND patients ($p=0.5127$) (Table 37).

Table 36b: Shifts (Improvement) in NYHA classification - CHF/MI

| | No. of patients with NYHA classification | | p-value |
|------------|--|-----------------|---------|
| | No shift /Yes shift (%) | | |
| | Dofetilide | Placebo | |
| CHF | 530/232(30.5%) | 530/225(29.8%) | 0.784 |
| MI | 523/220(29.6%) | 522/232(30.8%) | 0.625 |
| CHF and MI | 1053/452(30.0%) | 1052/457(30.3%) | 0.880 |

Source: Dr L.Cui (Statistician) and Reviewer. Data on NYHA from sponsor

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A.O.Williams, M.D.

Table 37: Probability of event-free worsening of heart failure-CHF/MI

| | CHF | | | | MI | | | |
|--------|-------------|-------------------|-------------|----------------|-------------|-------------------|-------------|----------------|
| | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% |
| Year 1 | 0.705 | 0.669-0.742 | 0.599 | 0.560-0.638 | 0.721 | 0.686-0.757 | 0.726 | 0.692-0.761 |
| Year 2 | 0.603 | 0.557-0.649 | 0.497 | 0.449-0.544 | 0.672 | 0.632-0.712 | 0.681 | 0.643-0.720 |
| Year 3 | 0.444 | 0.342-0.547 | 0.416 | 0.336-0.496 | 0.651 | 0.607-0.695 | 0.664 | 0.618-0.709 |
| EOS | 0.444 | 0.342-0.547 | 0.416 | 0.336-0.496 | 0.651 | 0.607-0.695 | 0.664 | 0.618-0.709 |

LogRank Test** Z=0.6546, p=0.5127 for MI; and for CHF Z = 3.5336; p=0.0004 ** Tests for a difference in remaining event-free between the two treatment groups, after allowing for center and wall motion index category. Significance at the 5% level.

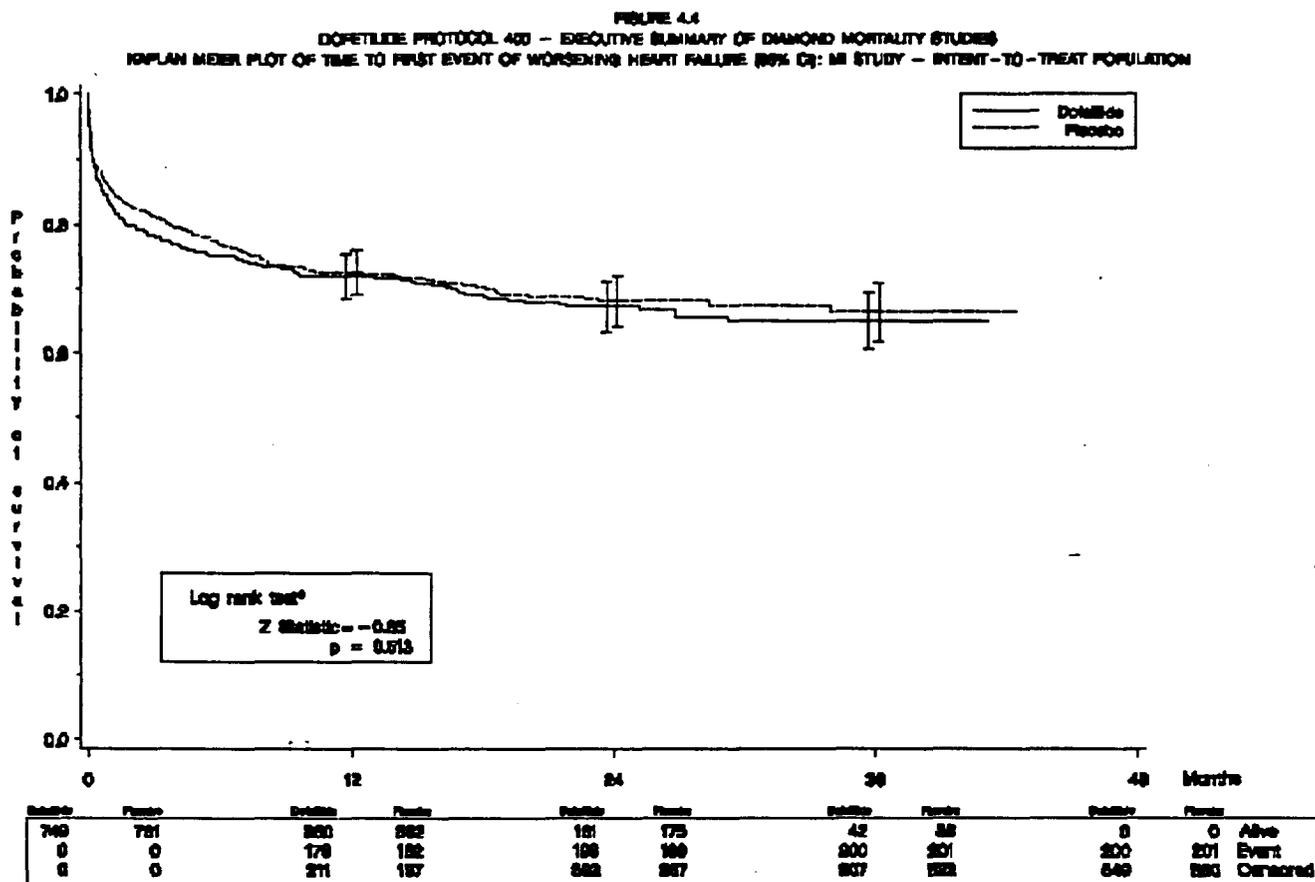
Worsening of Heart Failure - MI - ITT

A total of 405 out of 1510 (26.6%) randomized patients to the MI study had at least one episode of worsening heart failure during the study. For Dofetilide and placebo groups, 200/749 (26.7%) and 205/761(26.9%) patients experienced 1, 2, 3 or >3 episodes of worsening heart failure (Table 37a). The total numbers of episodes of worsening heart failure were 257 and 274 for Dofetilide and placebo, respectively (Table 37a). There is no significant difference in worsening of heart failure between treatment groups (p=0.513) and the probability of remaining event free is also not significant (p=0.5127) (Table 37 and 37a; Figure 27).

Table 37a: Worsening of Heart failure - MI

| No of events | Dofetilide N=749 | Placebo n=761 |
|--|---------------------|------------------|
| 0 | 549(73.3%) | 556(73.1%) |
| 1 | 159(21.2%) | 160(21.0%) |
| 2 | 28(3.7%) | 32(4.2%) |
| 3 | 10(1.3%) | 5(0.7%) |
| >3 | 3(0.4%) | 8(1.1%) |
| Total no of subjects with at least one event | 200(26.7%) | 205(26.9%) |

Figure 27 (Table 37) Time-to-first-event of worsening heart failure MI-ITT



Worsening of Heart Failure - MI with AF/AFI

There is also no significant difference in time to first event of worsening heart failure between treatment groups of DIAMOND MI - patients with supraventricular tachycardia alone, and or death, and or withdrawal, or death (Table 37b). Similarly, there is no significant difference in time to first event of all cause hospitalization between treatment groups in this population, including death and withdrawals (Table 37b).

Table 37b: Worsening of Heart Failure, death, withdrawal, and hospitalization - MI/AF

| Population: Event | No. Subj. in Population/ No Subj. with event (%) | | |
|---|---|-----------|---------|
| | Dofetilide | Placebo | P-value |
| DIAMOND -MI- AF population | | | |
| First event of worsening heart failure | 59 (28.8) | 56 (35.7) | 0.506 |
| First event of worsening heart failure, or death | 59 (40.4) | 56 (50.0) | 0.502 |
| First event of worsening heart failure, withdrawal or death | 59 (73.0) | 56 (71.5) | 0.777 |
| DIAMOND - MI- AF population | | | |
| First event all cause hospitalization | 59 (35.6) | 56 (60.7) | 0.092 |
| First event of all cause hospitalization, or death | 59 (49.0) | 56 (73.0) | 0.115 |
| First event of all cause hospitalization, withdrawal or death | 59 (79.6) | 56 (65.7) | 0.853 |

No significant difference between treatment groups

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Worsening of Heart Failure, withdrawal and death - CHF - ITT and CHF+AF
 For Dofetilide and placebo groups, 322/762 (42.3%) and 371/756 (49.1%) patients experienced at least one episode of worsening of heart failure or death. The significant difference in the combined worsening of heart failure and death over the entire period of study between treatment groups ($p < 0.003$) is most likely due to the difference in the worsening of heart failure in the CHF group (Table 37) because there is no difference in the MI group (Tables 37 and 37b). Table 37c summarizes the significant differences between treatment groups in patients with CHF for worsening of heart failure and also for all cause hospitalization. This is in contrast to the ischemic group (MI and AF) which shows no significant difference for first event of worsening heart failure and first event of all cause hospitalization (Table 37b).

Table 37c : Worsening of Heart Failure, death, withdrawal, and hospitalization CHF +AF

| Population: Event | No. Subj.in Population (%) or No Subj. with event (%) | | P-value |
|---|--|------------|---------|
| | Dofetilide | Placebo | |
| DIAMOND -CHF-AF population | 190 (100%) | 201(100%) | |
| First event of worsening heart failure | 56(29.5%) | 82(40.8%) | 0.011 |
| First event of worsening heart failure, or death | 79(41.6%) | 100(49.8%) | 0.044 |
| First event of worsening heart failure, withdrawal or death | 126 (66.3%) | 153(76.1%) | 0.028 |
| DIAMOND --AF population | 249(100%) | 257(100%) | |
| First event of worsening heart failure | 73(29.3%) | 102(39.7%) | 0.012 |
| First event of worsening heart failure, or death | 103(41.4%) | 128(49.8%) | 0.040 |
| First event of worsening heart failure, withdrawal or death | 169 (67.9%) | 193(75.1%) | 0.070 |
| DIAMOND - CHF-AF population | 190(100%) | 201(100%) | |
| First event all cause hospitalization | 107(56.3%) | 125(62.2%) | 0.026 |
| First event of all cause hospitalization, or death | 122(64.2%) | 140(69.7%) | 0.030 |
| First event of all cause hospitalization, withdrawal or death | 153(60.5%) | 176(87.6%) | 0.024 |
| DIAMOND - AF population | 249(100%) | 257(100%) | |
| First event of all cause hospitalization | 128(51.4%) | 158(61.5%) | 0.006 |
| First event of all cause hospitalization, or death | 151(60.6%) | 181(70.4%) | 0.007 |
| First event of all cause hospitalization, withdrawal or death | 200(80.3%) | 224(87.2%) | 0.030 |
| DIAMOND -CHF-all subjects 115-400 CHF | 762(100%) | 756(100%) | |
| First event of worsening heart failure | 229(30.1%) | 290(38.4%) | <0.001 |
| First event of worsening heart failure, or death | 322(42.3%) | 371(49.1%) | 0.003 |
| There is significant difference between treatment groups in patients with CHF +AF but not in patients with MI + AF (Table 37b). | | | |

Total Mortality - CHF with AF/AFl - ITT

A total of 391 out of 1518 (25.8%) with AF/AFl in the CHF study were randomized at baseline - 109/762 (24.9%) to Dofetilide and 201/756 (26.6%) to placebo. Of the randomized patients, a total of 106/391 (27.1%) either died, had a stroke or developed systemic embolism during the study. For Dofetilide and placebo groups with AF/AFl at baseline, 52/190 (27.4%) and 54/201 (26.86%) patients, respectively, had combined events of deaths, stroke or systemic embolism. There is no significant difference between the treatment groups ($p=0.850$).

Excluding stroke and systemic embolism, there is also no significant difference in mortality between treatment groups [(84/190 [(44.2%)] for Dofetilide and 88/201 [(43.78%)] for placebo) $p = 0.733$]. The direction of increased deaths is in the Dofetilide group which was expected to show a mortality benefit among patients with AF/AFl. The lack of a significant difference in patients with CHF and AF/AFl indicates that Dofetilide does not appear to confer survival benefit on CHF patients with AF/AFl. When combined with 115 patients in the MI group, no mortality benefit was also observed.

10.4 Total arrhythmic deaths (TAD) - CHF

A total of 307 out of 1518 (20.2%) with TAD in the CHF study were reported up to the end of study. Of these, 156/762 (20.5%) in the Dofetilide group and 151/756 (20%) in the placebo group had arrhythmic deaths. There is no significant difference between the treatment groups. There is also no significant difference between the number of patients requiring treatment and withdrawal of study drug for their arrhythmias between treatment groups [(89/762 (11.7%) for Dofetilide, and 81/756 (10.7%) for placebo)]. There is also no significant difference in the probability of arrhythmic events between the treatment groups ($p = 0.14$ for MI, and $p = 0.97$ for CHF (Table 38a) using the log rank test. The number of TAD as reclassified by the Events committee is presented in Table 38b.

Table 38a: Total arrhythmic deaths (TAD) CHF - ITT

| | CHF | | | | MI | | | |
|--------|-------------|-------------------|-------------|----------------|-------------|-------------------|-------------|----------------|
| | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% | Probability | Dofetilide CI@95% | Probability | Placebo CI@95% |
| Year 1 | 0.855 | 0.829-0.881 | 0.860 | 0.835-0.886 | 0.871 | 0.847-0.896 | 0.857 | 0.832-0.883 |
| Year 2 | 0.763 | 0.727-0.799 | 0.765 | 0.729-0.801 | 0.821 | 0.791-0.851 | 0.805 | 0.774-0.836 |
| Year 3 | 0.664 | 0.594-0.733 | 0.691 | 0.638-0.744 | 0.786 | 0.749-0.822 | 0.752 | 0.707-0.796 |
| EOS | 0.664 | 0.594-0.733 | 0.691 | 0.638-0.744 | 0.755 | 0.700-0.809 | 0.752 | 0.707-0.796 |

LogRank Test $Z = 1.4785$ $p = 0.1393$ for MI ; for CHF $Z = -0.0377$; $p = 0.9699$ ** Tests for a difference in events between the two treatment groups, after allowing for center and wall motion index category. Significance at the 5% level.

Table 38b: Total arrhythmic events reclassified-Events committee* ITT

| Number of subjects with an event | CHF | | MI | |
|----------------------------------|--------------------|-----------------|--------------------|-----------------|
| | Dofetilide (N=762) | Placebo (N=756) | Dofetilide (N=749) | Placebo (N=761) |
| VF | 14 | 12 | 12 | 10 |
| Sustained VT | 11 | 13 | 15 | 19 |
| Torsades de Pointes* | 25 | 0 | 7 | 0 |
| Sustained polymorphic VT | 3 | 4 | 3 | 3 |
| Total | 53 | 29 | 37 | 32 |

*Note differences from investigators listing.

10.5 Causes of Death - CHF/MI

The causes of death in the CHF and MI studies are classified under 3 headings, namely, 1) Cardiac, 2) Non-Cardiac and 3) Unclassified (Tables 39a-d). There was no significant difference between the treatment groups. Investigators were required to report any event which they considered to be proarrhythmic.

The boundaries between an arrhythmic event classified as proarrhythmic, thus related to treatment, and an arrhythmic event resulting from the progression of the underlying disease were very subjective. The sponsor issued guidelines for criteria of events to be considered as proarrhythmic.

Table 39a: - Causes of Death CHF-ITT-Dofetilide

| Dofetilide | | Investigators classification | | | | | | | | | | | | |
|------------------|--------------|------------------------------|----|----------------------------|----|----------------------|-----|-------------|----|--------------|----|-------|-----|------|
| | | Cardiac | | | | | | Non-cardiac | | Unclassified | | Total | | |
| | | Presumed arrhythmia (PA) | | Documented arrhythmia (DA) | | Non-arrhythmias (NA) | | N | % | N | % | N | % | |
| N | % | N | % | N | % | N | % | | | | | | | |
| Events committee | Cardiac | PA | 66 | 21.2 | 9 | 2.9 | 16 | 3.1 | 7 | 2.3 | 13 | | 111 | 33.7 |
| | | DA | 2 | 0.6 | 14 | 4.3 | 6 | 1.9 | 1 | 0.3 | 3 | | 28 | 9.0 |
| | | NA | 8 | 2.6 | 4 | 1.3 | 71 | 22.8 | 9 | 2.9 | 7 | | 99 | 31.8 |
| | Non-cardiac | | 4 | 1.3 | 1 | 0.3 | 8 | 2.6 | 41 | 13.2 | 2 | | 36 | 18 |
| | Unclassified | | 4 | | 0 | | 2 | | 2 | | 9 | | 17 | |
| | Total | | 84 | 27 | 28 | 9 | 103 | 33.1 | 60 | 19.3 | 36 | | 311 | |

Table 39b: - Causes of Death CHF-ITT-Placebo

| Placebo | | Investigators classification | | | | | | | | | | | | |
|------------------|--------------|------------------------------|----|----------------------------|----|----------------------|----|-------------|----|--------------|----|-------|-----|------|
| | | Cardiac | | | | | | Non-cardiac | | Unclassified | | Total | | |
| | | Presumed arrhythmia (PA) | | Documented arrhythmia (DA) | | Non-arrhythmias (NA) | | N | % | N | % | N | % | |
| N | % | N | % | N | % | N | % | | | | | | | |
| Events committee | Cardiac | PA | 67 | 21.1 | 11 | 3.3 | 7 | 2.2 | 5 | 2.3 | 11 | | 101 | 31.9 |
| | | DA | 6 | 1.9 | 12 | 3.8 | 5 | 1.6 | 0 | 1.6 | 3 | | 28 | 8.8 |
| | | NA | 14 | 4.4 | 7 | 2.2 | 63 | 20.3 | 10 | 20.5 | 4 | | 100 | 31.5 |
| | Non-cardiac | | 1 | 0.3 | 0 | | 15 | 4.7 | 42 | 13.2 | 8 | | 66 | 20.8 |
| | Unclassified | | 9 | | 1 | | 4 | | 1 | | 7 | | 22 | |
| | Total | | 97 | 30.6 | 31 | 9.8 | 96 | 30.3 | 58 | 18.3 | 35 | | 317 | |

Table 39c: - Causes of Death MI-ITT-Dofetilide

| Dofetilide | | Investigators classification | | | | | | | | | | | | |
|------------------|--------------|------------------------------|----|----------------------------|----|----------------------|----|-------------|----|--------------|----|-------|-----|------|
| | | Cardiac | | | | | | Non-cardiac | | Unclassified | | Total | | |
| | | Presumed arrhythmia (PA) | | Documented arrhythmia (DA) | | Non-arrhythmias (NA) | | N | % | N | % | N | % | |
| N | % | N | % | N | % | N | % | | | | | | | |
| Events committee | Cardiac | PA | 57 | 24.8 | 7 | 3.0 | 11 | 4.8 | 0 | | 12 | | 87 | 37.8 |
| | | DA | 0 | - | 17 | 7.4 | 6 | 2.6 | 0 | | 8 | | 31 | 13.5 |
| | | NA | 2 | 0.9 | 7 | 3.0 | 45 | 19.6 | 3 | 1.3 | 5 | | 62 | 27.0 |
| | Non-cardiac | | 0 | | 0 | 0 | 8 | 3.5 | 22 | 9.6 | 9 | | 39 | 17 |
| | Unclassified | | 2 | | 0 | 0 | 0 | | 0 | | 9 | | 11 | |
| | Total | | 61 | 26.5 | 31 | 13.5 | 70 | 30.4 | 25 | 10.9 | 43 | | 230 | |

Table 39d: - Causes of Death MI-ITT-Placebo

| Dofetilide | Investigators classification | | | | | | | | | | | | | |
|------------------|------------------------------|----|--------------------------|------|----------------------------|-----|----------------------|------|-------------|-----|--------------|-----|-------|------|
| | Cardiac | | | | | | | | Non-cardiac | | Unclassified | | Total | |
| | | | Presumed arrhythmia (PA) | | Documented arrhythmia (DA) | | Non-arrhythmias (NA) | | | | | | | |
| | | N | % | N | % | N | % | N | % | N | % | N | % | |
| Events committee | Cardiac | PA | 63 | 25.9 | 17 | 7 | 9 | 3.7 | 2 | 0.8 | 10 | | 101 | 41.6 |
| | | DA | 3 | 1.2 | 21 | 8.6 | 4 | 1.6 | 0 | 0 | 8 | | 36 | 14.8 |
| | | NA | 4 | 1.6 | 8 | 3.3 | 47 | 19.3 | 7 | 2.9 | 6 | | 72 | 29.6 |
| | Non-cardiac | 2 | 0.8 | 0 | | 5 | 2.1 | 22 | 9.1 | 2 | | 31 | 12.8 | |
| | Unclassified | 0 | | 0 | | 0 | | 0 | | 3 | | 3 | | |
| | Total | 72 | 29.6 | 46 | 18.9 | 65 | 26.7 | 31 | 12.8 | 29 | | 243 | | |

Safety

10.6 Proarrhythmic events

The defined features by an independent expert panel resulted in differences in the classification of proarrhythmic events between the investigator defined events compared to those of the Events committee (Tables 38b and 40). The investigator defined listing of events showed a 4-fold increase in frequency of proarrhythmic events in the CHF Dofetilide group compared to placebo (47:11), and in the MI Dofetilide group, there was about a 2-fold increase in frequency of events compared to placebo (28:15) (Table 40). Excluding Torsades in the combined CHF and MI data, there is still a 2-fold increase in frequency of arrhythmic events in the Dofetilide group compared to placebo (48:21). Investigators reported Torsades in both treatment groups but the Events Committee reclassification indicated a lack of Torsades in the placebo groups. By so doing, the Events committee's showed no difference in the frequency of arrhythmic events between treatment groups except in TdP.

Table 40: Proarrhythmic events - CHF/MI-Investigators listing

| Number of events | CHF | | MI | |
|----------------------------|---------------------|------------------|---------------------|------------------|
| | Dofetilide n=762 | Placebo n=756 | Dofetilide n=749 | Placebo n=761 |
| New VF | 12 | 1 | 7 | 4 |
| New Sustained VT | 8 | 1 | 8 | 5 |
| New Sustained Incessant VT | 2 | 0 | 0 | 2 |
| TdP | 20 | 4 | 7 | 3 |
| Other | 11 | 5 | 10 | 4 |
| Total* | 47 | 11 | 28 | 15 |

*Total number of subjects with at least 1 event. Source Table 7.5.1 in (115-400) DIAMOND CHF/MI

See Figure below which shows no significant difference in ventricular arrhythmias between treatment groups

10.7 Torsades de Pointes

Analysis of TdP showed significant differences between the frequencies between treatment groups regardless of dose adjustment of Dofetilide in both studies (Table 41 and Figures 28 and 29, page 48). In contrast, there was no difference in the frequencies of ventricular tachyarrhythmic events in both treatment groups suggesting a lack of efficacy on ventricular tachyarrhythmias.

Table 41: Summary of Torsades - CHF/MI

| | DIAMOND - CHF | | DIAMOND - MI | |
|--|---------------|---------|--------------|---------|
| | Dofetilide | Placebo | Dofetilide | Placebo |
| Dose: 500mcg bid | | | | |
| Number of subjects | 762 | 756 | 749 | 761 |
| Subject years of drug exposure | 812.8 | 798.6 | 944.4 | 996.2 |
| Torsades de Pointes (%) | 25 (3.3%) | 0 | 7 (0.9%) | 0 |
| Dose: 500mcg bid adjusted for creatinine clearance | | | | |
| Number of subjects | 614 | 613 | 648 | 670 |
| Subject years of drug exposure | 619.6 | 596.1 | 771.9 | 819.4 |
| Torsades de Pointes (%) | 18 (2.9%) | 0 | 4 (0.6%) | 0 |

Torsades de Pointes (TdP), mortality and sex

Analysis of TdP showed that there was statistical evidence ($p < 0.01$) of a difference in the risk of TdP for male subjects as compared to female subjects. The estimated risk (95% CI) for female subjects was 3.77 (1.74, 8.17) times that of males. In all, 1088 male and 423 female subjects received 1327.8 and 429.4 subject years of Dofetilide treatment, respectively, in the DIAMOND studies. Of these subjects, 17 (1.56%) and 15 (3.55%), respectively, experienced TdP. Analysis of TdP showed that there was statistical evidence ($p = 0.0220$) of a difference in the risk of TdP for male subjects as compared to female subjects. The estimated risk (95% CI) for female subjects was 2.32 (1.15 - 4.68) times that of males (Table 42). The effect of creatinine clearance dependent dosing in females is noteworthy.

Table 42: TdP by sex - CHF/MI Dofetilide - ITT

| Risk Factor: Gender | Torsades: N for Y/N | Total (%) | RR | 95%CI | p-value |
|--|---------------------|-------------------------------|------|------------|---------|
| Pooled data without dose adjustment CHF-MI | | | | | |
| Male | Yes 17 No 1071 | 1088 (1.56%) 1088 (98.44%) | | | |
| Female | Yes 15 No 408 | 423 (3.55%) 423 (96.45%) | 2.32 | 1.15-4.68 | 0.0220 |
| Pooled data - creatinine clearance dependent dosing - CHF-MI | | | | | |
| Male | Yes 14 No 898 | 912 (1.54%) 912 (98.46%) | | | |
| Females | Yes 8 No 342 | 350 (2.29%) 350 (97.71%) | 1.50 | 0.62-3.61 | 0.3746 |
| Preactinine clearance dependent dosing | | | | | |
| Male | Yes 3 No 173 | 176 (1.70%) 176 (98.30%) | | | |
| Female | Yes 7 No 66 | 73 (9.59%) 73 (90.41%) | 6.12 | 1.54-24.36 | <0.01 |

Table 43: TdP by age - pooled data from CHF/MI Dofetilide - ITT

| | Age(yrs) | | | | | | Total |
|---------------------------|----------|-----|-------|-----|--------|------|----------|
| | <45 | | 45-64 | | >=65 | | |
| | N | % | N | % | N | % | |
| Number of patients | 25 | 100 | 420 | 100 | 1066 | 100% | 1511 |
| Patient-yrs drug exposure | 30.4 | | 575.7 | | 1151.1 | | 1757.2 |
| Torsades | 0 | 0 | 6 | 1.4 | 26 | 2.4 | 32(2.1%) |

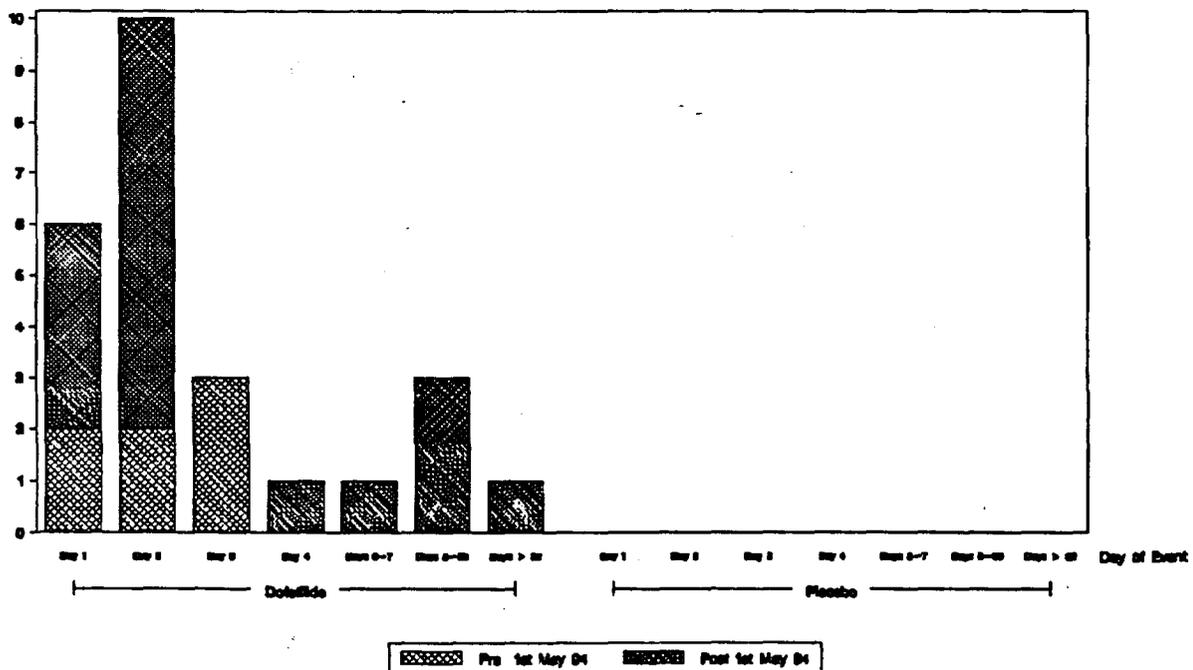
Torsades de Pointes (TdP) and QT/QTc prolongation

A total of 25/762 patients (3.3%) experienced Torsade de Pointes on Dofetilide treatment in the CHF population with a post amendment adjustment for creatinine making it 2.9% (18/616). The incidence of TdP did not drop as claimed by the sponsor but adjusting for renal impaired patients, there was a 0.4% difference. In the MI Dofetilide treatment group, the incidence of TdP was 0.9% (n=7/749), which adjusted to 0.6% (4/649) for renal impaired patients with reduced creatinine clearance (Table 41).

A total 39 patients had prolongation of QT/QTc interval, out of which 11 (28.2%) died. Of the 39 patients with prolonged QT/QTc interval, 14 and 19 were in the CHF and MI Dofetilide treatment groups, respectively, and 3 patients each were in corresponding placebo treatment groups. Of the 11 patients who died, 10 were on Dofetilide, 2 CHF and 8 MI and 1 CHF patient was on placebo (Table 15). There was no significant difference in the incidence of QT prolongation between the CHF and MI groups on Dofetilide, but there was a 2.5-fold increase in the number of MI patients who died compared to CHF patients. There was no significant difference in gender among patients with prolongation of QT/QTc interval. The significant increase in the number of TdP in the early days of the trial among Dofetilide-treated patients is striking compared to placebo (Figures 28-29). The majority of patients on Dofetilide developed Torsades (23 /32 (72%) during the first four study days of hospitalization in both studies (Figures 28-29). An initial peak of QT and QTc interval prolongation coincided with the same period of maximum mortality during the first four days of therapy (Figures 31-33). This significant prolongation of QT / QTc persisted throughout the study among Dofetilide-treated patients compared to placebo (Figures 34-35). This trend was observed in both studies but was more striking in the CHF group compared to MI group (Figures 35-36).

Figure 28 (CHF)

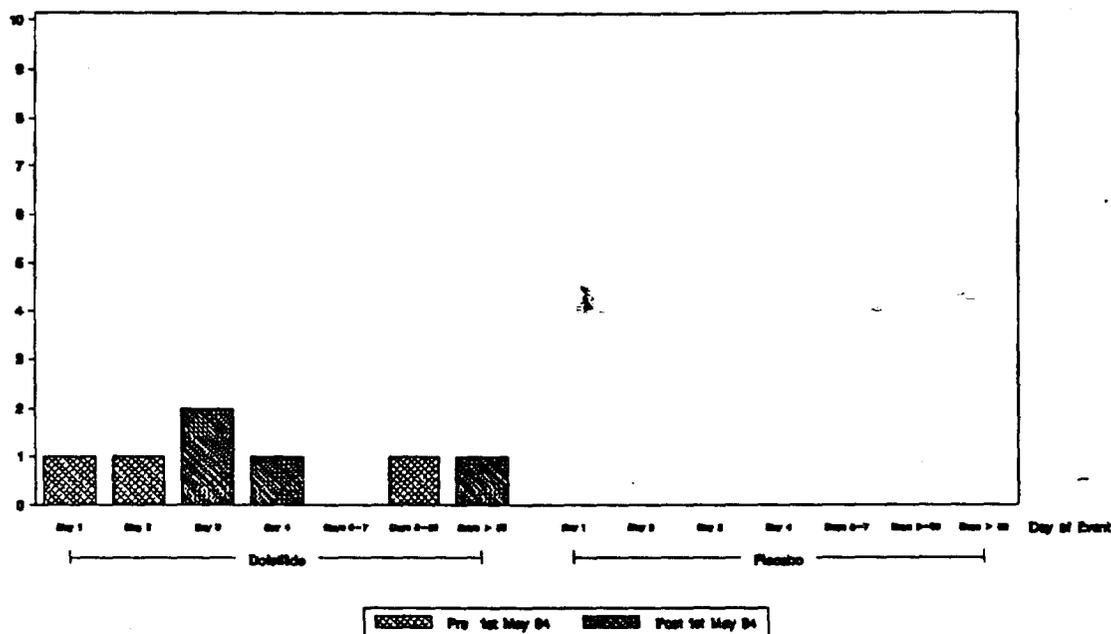
FIGURE 8.1
DOFETILIDE PROTOCOL 400 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
NUMBER OF TdP BY DAY OF EVENT AND PRE AND POST CREATININE CLEARANCE AMMENDMENT: CHF STUDY - INTENT-TO-TREAT POPULATION



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Figure 29 (MI)

FIGURE 42
DOFETILIDE PROTOCOL 402 - EXECUTIVE SUMMARY OF DIAMOND MORTALITY STUDIES
NUMBER OF TdP BY DAY OF EVENT AND PRE AND POST CREATININE CLEARANCE AMMENDMENT MI STUDY - INTENT-TO-TREAT POPULATION



Torsades (TdP) by Age and gender

Age and sex are significant risk factors for Torsades in CHF group (Tables 42 and 43). There is increased frequency of TdP in females compared to males with a two-fold increase females (3.5% versus 1.6% in males). In the CHF population, 14 females from a population of 216 (6.5%) developed TdP compared to 11/546 males (2.0%). This was not observed in the MI population where only 1/207 (0.5%) female developed TdP compared to 6/542 (1.1%) males. Although the incidence of TdP among females compared to males suggests gender susceptibility (RR 2.32, 95% CI 1.15-4.68; $p=0.0220$), the relative risk (RR) for females compared to males showed no gender difference after dose was adjusted for creatinine clearance (RR=1.50; 95%CI 0.62 - 3.61; $p=0.375$). Prior to dose adjustment for creatinine clearance, however, the RR of TdP for females compared to males was 6.12 (95%CI 1.54-24.36; $p<0.01$) (Table 43). The lack of gender significance after creatinine clearance dependent dosing is consistent with the overall finding in the DIAMOND studies. This illustrates that dose adjustments for creatinine is critical for reduction of Torsades.

10.8 ECG

Some pathophysiological factors that may affect outcomes of any anti-arrhythmic drug therapy include myocardial ischemia, conduction defects due to structural heart disease, heart rates, and electrolyte disturbances due to heart failure. Because Dofetilide is pro-arrhythmic, and the serious adverse events are dose dependent, dose adjustments were effected throughout the studies to reduce the frequencies of SAEs in patients deemed to be at risk. Relevant ECG parameters in the DIAMOND studies were evaluated by the reviewer with emphasis on temporal relationships to arrhythmogenic events, Torsades and mortality (Figures 30- 43). Analysis of QT dispersion has been analysed in other studies in this NDA (115-250).

Prolongation of QT/QTc in randomized patients

The reviewer analyzed the QT, QTc intervals, heart rates in addition to other ECG changes in the study population. All the graphs in Figures 30-43 are by the reviewer and the statistical analyses (Appendix Tables 8-11) were carried out by Dr Kooros Majoob (Statistician).

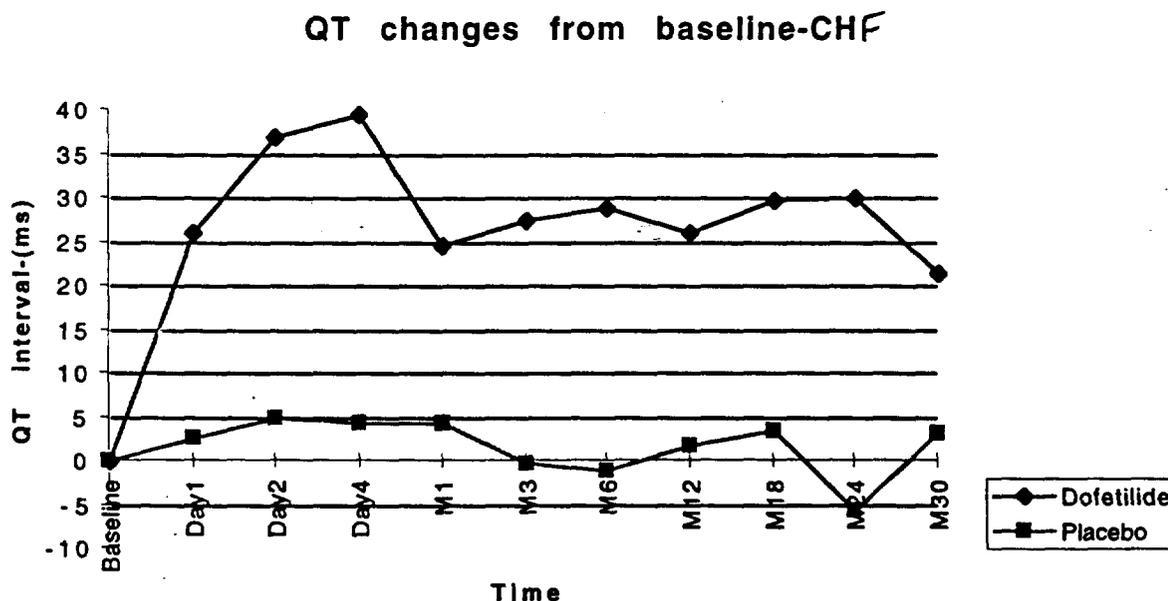
Dofetilide was proarrhythmic in 33/39 (85%) discontinued patients with prolonged QTc intervals compared to 6/39 (15%) discontinued patients on placebo (Tables 15 and 17). Analysis of mortality among the 39 discontinued patients with prolonged QTc intervals showed 11 (28%) deaths, out of which 10 (91%) were on Dofetilide compared to 1 (9%) patient on placebo (Table 15). The abnormal ECG changes and the heart rate changes are most likely due to Dofetilide effect (Figures 40-43).

Prolongation of QT and QTc changes in the CHF group is evident in Figures 30 and 31. The biggest changes in QT and QTc prolongation occurred in the first 4 days, post dose, in the Dofetilide group. In contrast, only minimal changes were observed in the placebo group (Figure 30). In the placebo group, there is a time-dependent decrease in the QTc interval during the 2 year follow-up period (Figure 33), and the placebo-subtracted difference is consistent with drug effect on the QTc interval (Figure 34).

QT/QTc intervals: Relationship to mortality-CHF/MI

Among the patients who died, QT/QTc intervals showed a statistically significant difference between treatment groups from Days 1-4, and throughout the study ($p=0.000$) (Figures 30-32; 35-36; Appendix Tables 8-9).

Figure 30: QT changes from baseline in DIAMOND CHF



Source: Reviewer

Figure 31: QTc changes in patients who died between days 1-4 in DIAMOND CHF/MI

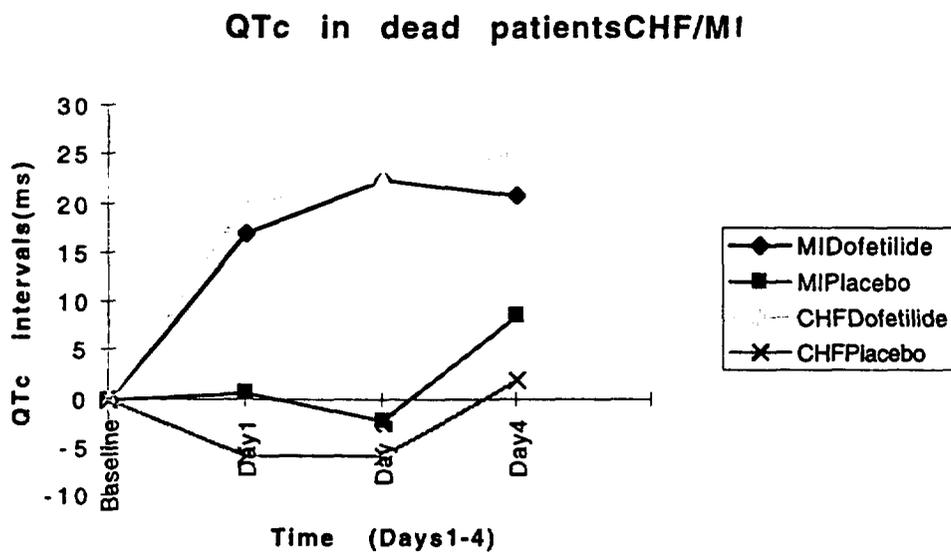


Figure 32: QT changes in patients who died between days 1-4 in DIAMOND CHF/MI

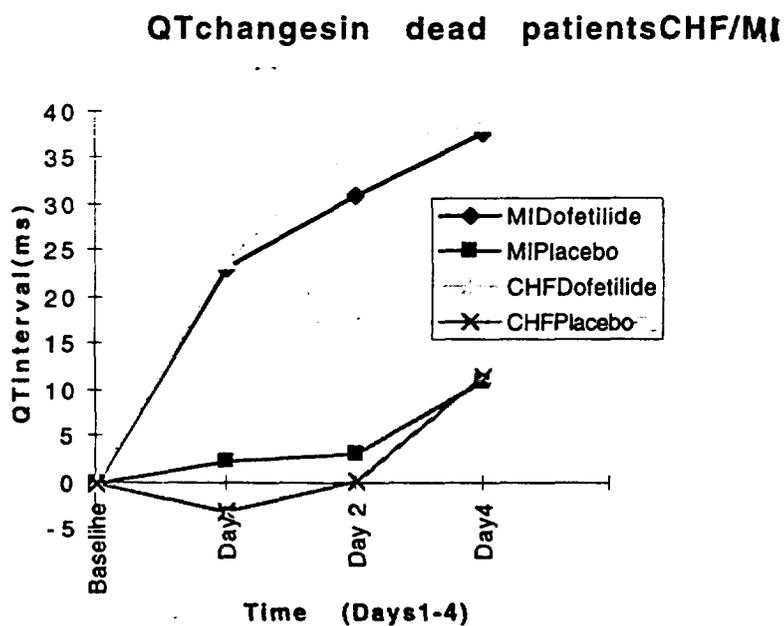


Figure 33: QTc changes from baseline in patients - DIAMOND CHF

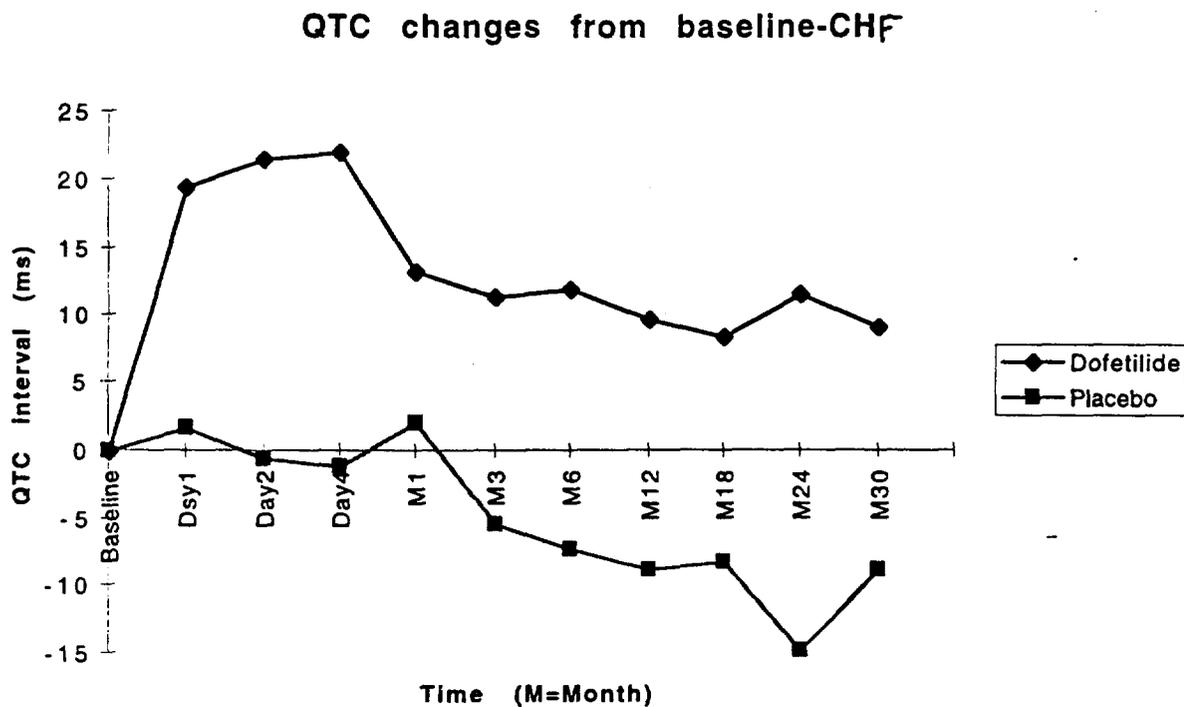
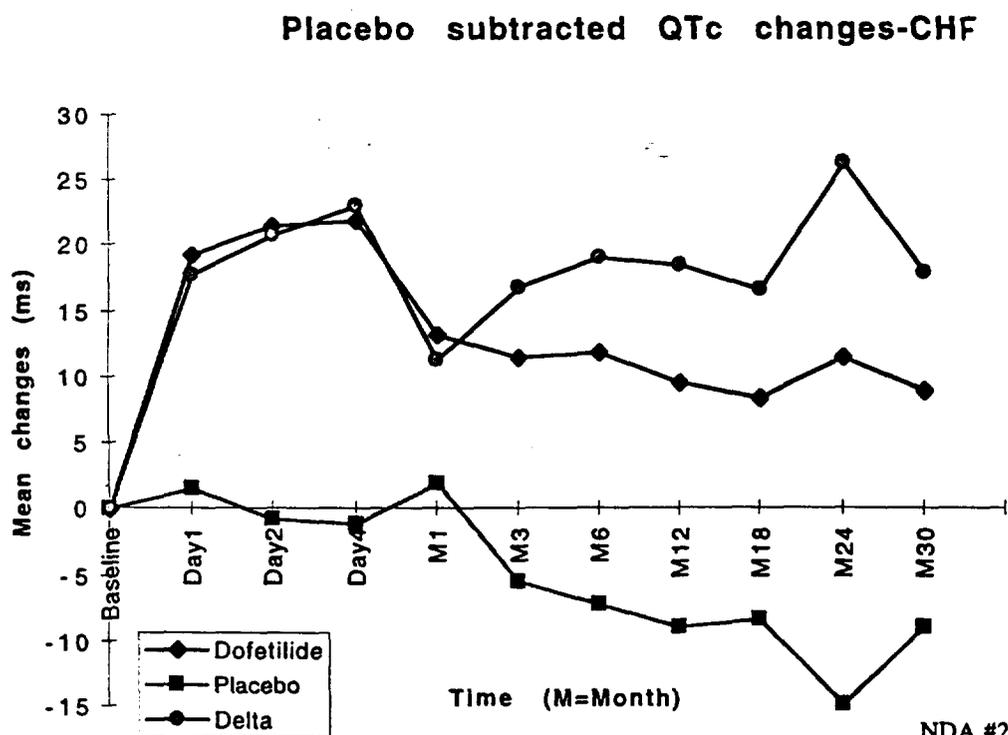
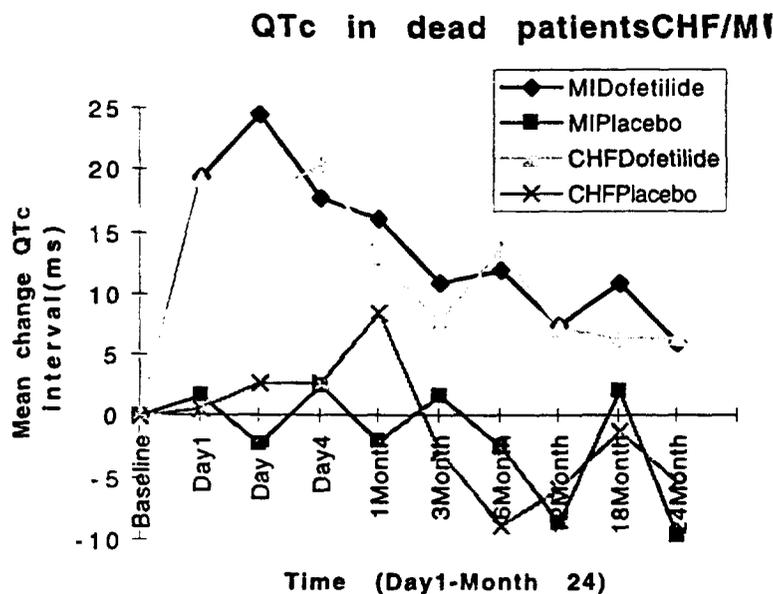


Figure 34: Placebo-subtracted QTc changes in patients - DIAMOND CHF



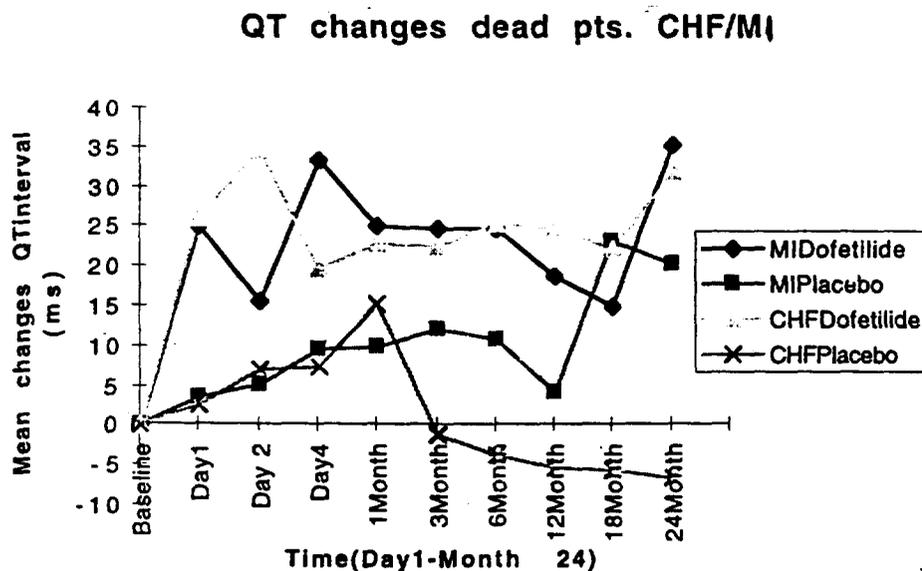
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Figure 35: QTc changes in patients who died - DIAMOND CHF/MI

**QRS Interval**

Anti-arrhythmic drugs that prolong the QT interval may also prolong the QRS interval. Anti-arrhythmic drugs known to prolong the QRS and, or QT intervals include Procaine amide, disopyramide, propranolol, mibefridil, Amiodarone, phenothiazines and tricyclic antidepressants. Dofetilide prolonged the QRS interval in CHF patients during the first four days post dose, compared to placebo (Figure 37), but this was not related to mortality during this period (Figure 39). This suggests that QRS prolongation may not be significant in the arrhythmogenic effect of the drug. This was confirmed by analysis of the QRS interval over the 30 month double-blind study period (Figure 40 and Appendix Table 11). The significance of QRS prolongation in the CHF group during the first 4 days of therapy is not clear (Figure 38). Prolongation of the QRS interval was not observed in MI group.

Figure 36: QT changes in patients who died in DIAMOND CHF/MI



Source: Reviewer

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Figure 37: QRS changes in patients who died between days 1-4 in DIAMOND CHF

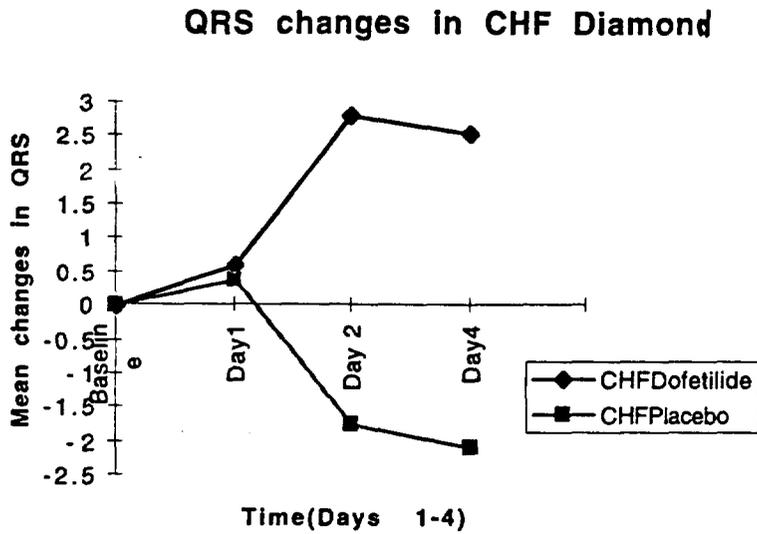
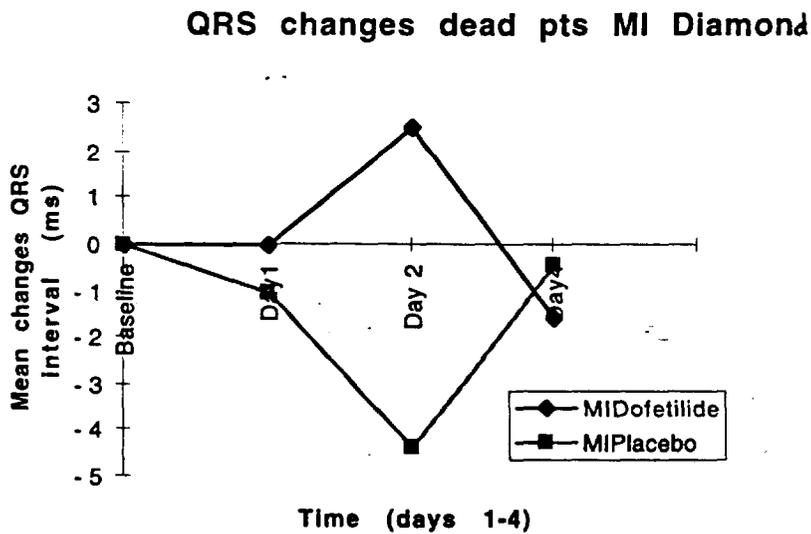
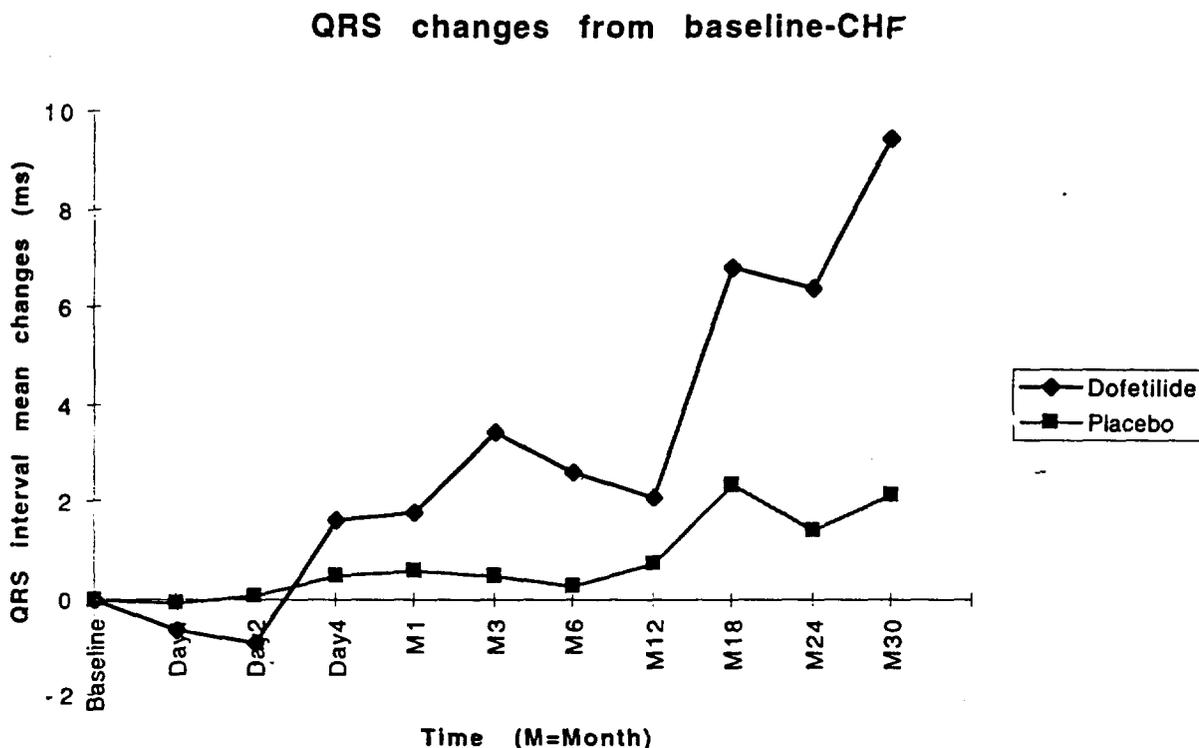


Figure 38: QRS changes in patients who died between days 1-4 in DIAMOND MI



Source: Reviewer

Figure 39: QRS changes in patients in DIAMOND CHF



Source-Reviewer

10.9 Heart Rate - CHF and MI -ITT

Bradycardia was significantly greater in Dofetilide-treated patients compared to placebo throughout the study ($p=0.0000$) (Figures 40 and 43; Appendix Table 10). Similarly bradycardia was observed in CHF Dofetilide-treated patients who died compared to patients on placebo (Figures 41 and 42).

Dofetilide CHF-treated patients who died during the total period of observation showed a time-dependent bradycardia that was statistically significant compared to placebo groups ($p=0.00$). In contrast, this was not so evident among the MI Dofetilide-treated patients (Figure 43).

The significance of an initial bradycardia during the first 4 days post-dose, as a prognostic risk factor for sudden death or Torsades among CHF patients, requires further evaluation. This initial peak of bradycardia coincides with the highest incidence of Torsades in Dofetilide-treated patients (Figures 41 and 43). The importance of increased bradycardia in Dofetilide-treated CHF patients compared to Dofetilide-treated MI patients may be due to heart rate variability (HRV), which has not been evaluated in the present studies. The possibility of using HRV as a prognostic indicator in patients with CHF, as reported for post-myocardial infarction patients, is derived from accumulated data that has now highlighted the importance of derangement of the autonomic nervous control of the cardiovascular system.

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This mechanism has been invoked in the pathogenesis of sudden cardiac death (*Lombardi F, Mortara A, Heart, 80,213-214, 1998*).

These heart rate abnormalities are not evident on analysis of pooled data submitted by the sponsor, and should be reflected in the label. Covariates such as age, sex, renal function and weight, known to affect the PD of Dofetilide, have not been considered either in the interpretation or in the statistical analyses of the ECG changes (Appendix Tables 8-11).

Figure 40: Heart rate changes from baseline in patients in DIAMOND CHF

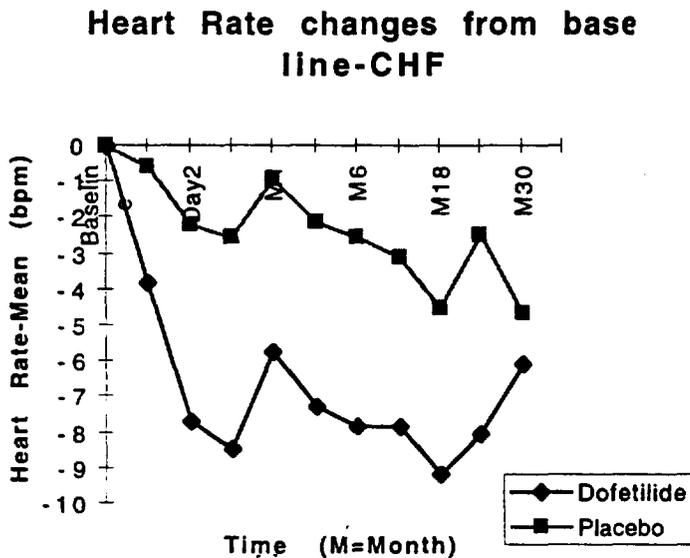
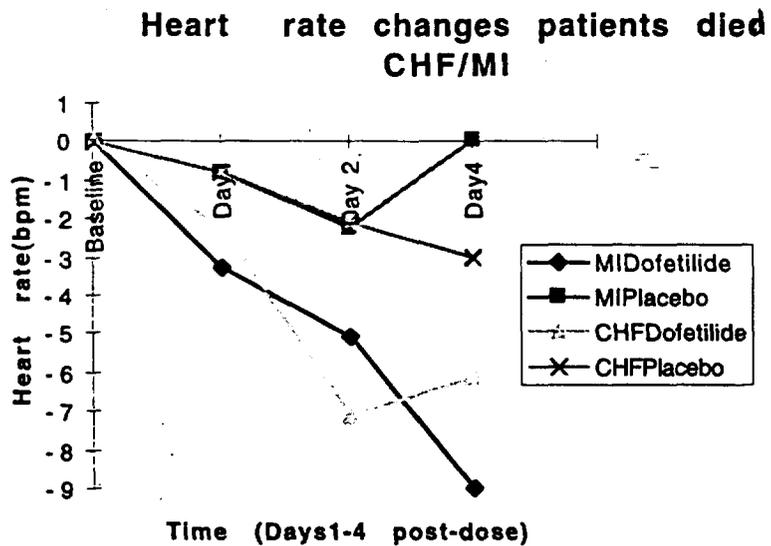


Figure 41: Heart rate changes from baseline in pts who died days 1-4 - CHF/MI

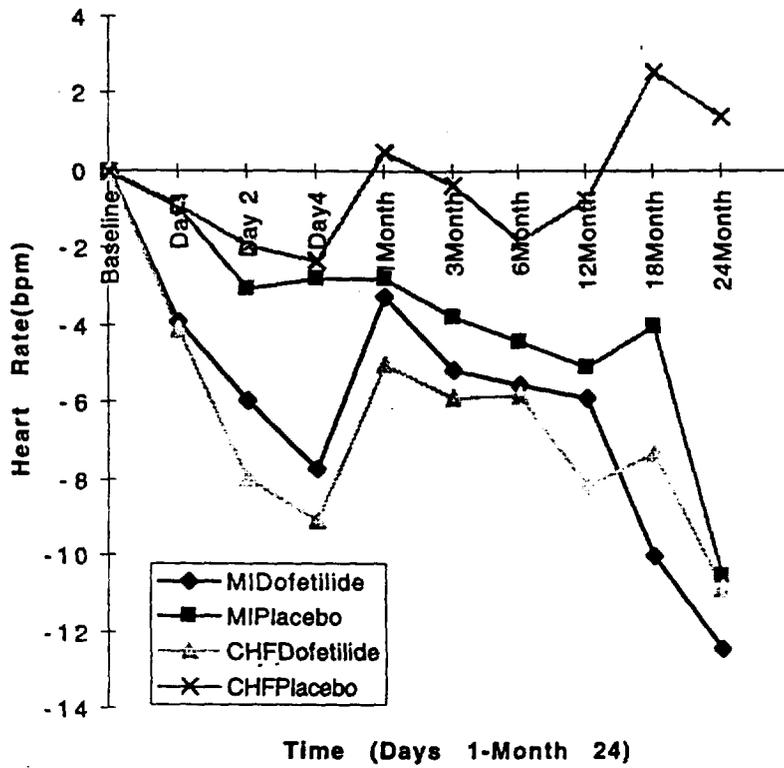


Source: Reviewer

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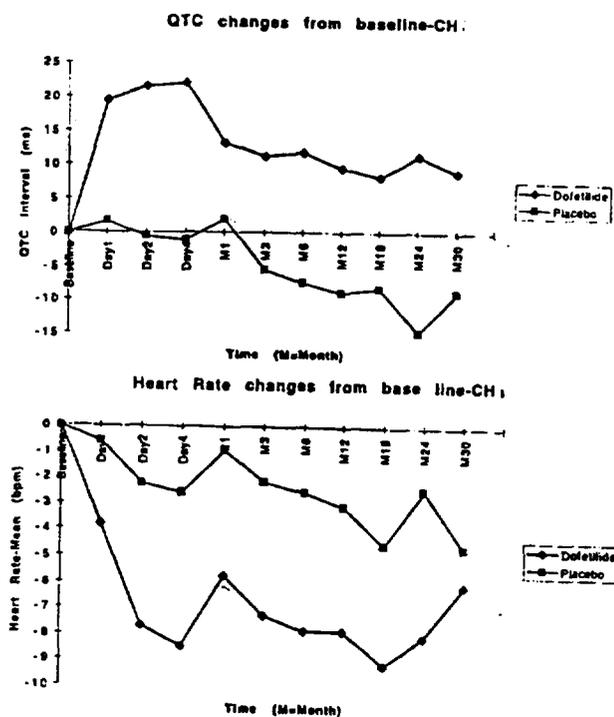
Figure 42

Heart Rate changes patients died CHF/M(



Source: Reviewer

Figure 43: Composite heart rate changes and QTc changes-CHF
 QTc and Heart rate CHF-ITT



Source: Reviewer

10.10 Safety: Adverse Events-CHF/MI-ITT

The treatment groups were well balanced for evaluation of adverse events other than proarrhythmic events (Table 44). There was no difference in incidence of all causality adverse events with time between treatment groups. A relatively high proportion (95%) of randomized patients to CHF and MI experienced at least one adverse event (Tables 45-46) and over 76% experienced serious adverse events. Ninety one percent (91%, n = 1371 patients) of the population receiving Dofetilide, and 92% (n = 1393) receiving placebo experienced one all causality adverse event.

Table 44: Arrhythmias in CHF/MI - ITT

| Study treatment | CHF | | MI | |
|-------------------------------|----------------|-------------|----------------|-------------|
| | Dofetilide (%) | Placebo (%) | Dofetilide (%) | Placebo (%) |
| Number of subjects | 762 | 756 | 749 | 761 |
| Drug exposure (subject years) | 812.8 | 798.6 | 944.4 | 996.2 |
| Subjects with arrhythmic AEs | 212 (27.8) | 257 (34) | 172 (23) | 212 (27.9) |
| Sino-Atrial block | 5 (0.7) | 5 (0.7) | 0 | 0 |
| Atrial arrhythmia | 13 (1.7) | 32 (4.2) | 12 (1.6) | 24 (3.2) |
| Atrial fibrillation | 79 (10.4) | 131 (17.3) | 82 (10.9) | 88 (11.6) |
| Bundle branch block | 0 | 0 | 2 (0.3) | 3 (0.4) |
| Left Bundle branch block | 1 (0.1) | 1 (0.1) | 0 | 0 |
| Heart block | 0 | 0 | 30 (4) | 35 (4.6) |
| AV block complete | 0 | 1 (0.1) | 0 | 0 |
| AV block First degree | 2 (0.3) | 5 (0.7) | 0 | 0 |
| AV block Mixed/unspecified | 12 (1.6) | 9 (1.2) | 0 | 0 |
| AV block Second degree | 7 (0.9) | 11 (1.5) | 0 | 0 |
| Supraventricular Tachycardia | 23 (3.0) | 23 (3.0) | 15 (2.0) | 22 (2.9) |
| Ventricular fibrillation | 43 (5.6) | 26 (3.4) | 39 (5.2) | 48 (6.3) |
| Ventricular Tachycardia | 84 (11.0) | 85 (11.2) | 55 (7.3) | 54 (7.1) |

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Table 45: Summary of Adverse events-CHF-ITT

| Number (%) | Dofetilide | Placebo |
|--|------------|-------------|
| Patients Treated | 762 | 756 |
| Patient-days of Drug exposure | 296881 | 291690 |
| Patients with AEs | 727(95.4%) | 723 (95.6%) |
| AEs | 4039 | 4308 |
| Patients with Serious AEs | 596(78.2%) | 604(79.9%) |
| Patients with severe Adverse events | 373(49.0%) | 376(49.7%) |
| Patients discontinued for AEs | 111(14.6%) | 116(15.3%) |
| Patients with dose reduced or temp discontinuations due to AEs | 109(14.3%) | 93(12.3%) |
| Patients with dose reduced or temp discontinuations on objective testing | 166(21.8%) | 197(26.1%) |

Table 46: Summary of Adverse events-MI-ITT

| Number (%) | Dofetilide | Placebo |
|--|------------|------------|
| Patients treated | 749 | 761 |
| Patient-days of Drug exposure | 344943 | 363848 |
| Patients with AEs | 719(96%) | 734(96.5%) |
| AEs | 3808 | 4156 |
| Patients with Serious AEs | 568(75%) | 583(76.6%) |
| Patients with severe Adverse events | 349(46.6%) | 360(47.3%) |
| Patients discontinued for AEs | 85(11.3%) | 94(12.4%) |
| Patients with dose reduced or temp discontinuations due to AEs | 112(15.0%) | 109(14.2%) |
| Patients discontinued due to objective test | 76(10.1%) | 75(9.9%) |
| Patients with dose reduced or temporary discontinuations | 179(23.0%) | 219(36.1%) |

10.11 Discontinuations for Adverse events

A similar proportion of subjects was discontinued from each study treatment for each indication although the distribution was slightly greater for objective side effects on Dofetilide treatment compared to placebo treatment; 14% of patients on Dofetilide and 12% on placebo in CHF, 10.1% and 9.9%, respectively, in MI. These events were mainly QTc prolongation and proarrhythmias.

The areas of greatest imbalance between the treatments were for the COSTART organ systems in cardiovascular events and body as a whole. Eighteen (18) subjects (1.2%) on Dofetilide treatment experienced cardiovascular events compared to 4 (0.3%) in the placebo group. The key differences were 8 events reported as cardiac arrest in the Dofetilide group compared to 1 in the placebo group, and three cases of bradycardia and one of angina, neither of which occurred in the placebo group. There were 2 patients with heart failure in both groups and two patients with syncope on Dofetilide, one on placebo. Seventeen (17) subjects (1.1%) on Dofetilide treatment had events related to the body as a whole compared to 10 (0.7%) on placebo (Tables 47 and 48). There were discontinuations in 195 (13%) patients receiving Dofetilide and 209 (14%) receiving placebo.

Between the two studies there were 15 subjects receiving Dofetilide whose death was given as a cause of withdrawal and seven subjects with death attributed to placebo, yet only 6 (Dofetilide) and 2 (placebo) of the deaths resulting from serious adverse events gave study treatment as the cause. There were no differences between the treatment groups in either the number of deaths or the mortality rates for either study at any point during the studies. Excluding death as an adverse event, there were no clinically relevant differences in adverse event rates between the treatment groups.

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There were 54 subjects with adverse events in the Dofetilide group (3.6%) who were considered by investigators to have a causal relationship to treatment compared to 36 (2.4%) in the placebo group. There is no proof for causality and this observation should be considered with caution.

Table 47a: Adverse events by body system-CHF

INCIDENCE OF ADVERSE EVENTS (TREATMENT-RELATED, TREATMENT-EMERGENT)
BY BODY SYSTEM (COSTART): INTENT-TO-TREAT POPULATION

| | DOFETILIDE | | PLACEBO | |
|------------------------------------|------------|--------|---------|--------|
| NUMBER(%) OF SUBJECTS: | | | | |
| Evaluable for adverse events | 762 | | 756 | |
| With adverse events | 33 | (4.3%) | 20 | (2.6%) |
| Discontinued due to adverse events | 15 | (2.0%) | 12 | (1.6%) |
| ADVERSE EVENTS BY BODY SYSTEM: | | | | |
| Cardiovascular | 9 | (1.2%) | 3 | (0.4%) |
| Body as a whole | 13 | (1.7%) | 3 | (0.4%) |
| Digestive | 6 | (0.8%) | 6 | (0.8%) |
| Hemic and lymphatic | 0 | | 1 | (0.1%) |
| Musculoskeletal | 0 | | 1 | (0.1%) |
| Nervous | 3 | (0.4%) | 7 | (0.9%) |
| Respiratory | 1 | (0.1%) | 0 | |
| Skin and appendages | 2 | (0.3%) | 3 | (0.4%) |
| Special senses | 2 | (0.3%) | 0 | |

Table 47b: Adverse events by body system-MI

INCIDENCE OF ADVERSE EVENTS (TREATMENT-RELATED, TREATMENT-EMERGENT)
BY BODY SYSTEM (COSTART): INTENT-TO-TREAT POPULATION

| | DOFETILIDE | | PLACEBO | |
|------------------------------------|------------|--------|---------|--------|
| NUMBER(%) OF SUBJECTS: | | | | |
| Evaluable for adverse events | 749 | | 761 | |
| With adverse events | 21 | (2.8%) | 16 | (2.1%) |
| Discontinued due to adverse events | 11 | (1.5%) | 5 | (0.7%) |
| ADVERSE EVENTS BY BODY SYSTEM: | | | | |
| Cardiovascular | 9 | (1.2%) | 1 | (0.1%) |
| Body as a whole | 4 | (0.5%) | 7 | (0.9%) |
| Digestive | 4 | (0.5%) | 5 | (0.7%) |
| Nervous | 5 | (0.7%) | 2 | (0.3%) |
| Respiratory | 1 | (0.1%) | 0 | |
| Special senses | 0 | | 1 | (0.1%) |
| Urogenital | 0 | | 1 | (0.1%) |

Table 48a: Adverse events by body system and gender-CHF

DOFETILIDE PROTOCOL 400 - DIAMOND CHF STUDY
INCIDENCE OF ADVERSE EVENTS (TREATMENT-RELATED, TREATMENT-EMERGENT)
BY BODY SYSTEM (COSTART) AND BY GENDER: INTENT-TO-TREAT POPULATION

| | DOFETILIDE | | | PLACEBO | | |
|---------------------------------------|------------|----------|-----------|-----------|----------|-----------|
| | Male | Female | Total | Male | Female | Total |
| NUMBER(%) OF SUBJECTS: | | | | | | |
| Evaluable for adverse events | 546 | 216 | 762 | 568 | 188 | 756 |
| With adverse events | 26 (4.8%) | 7 (3.2%) | 33 (4.3%) | 15 (2.6%) | 5 (2.7%) | 20 (2.6%) |
| Discontinued due to adverse events | 12 (2.2%) | 3 (1.4%) | 15 (2.0%) | 9 (1.6%) | 3 (1.6%) | 12 (1.6%) |
| ADVERSE EVENTS BY BODY SYSTEM: | | | | | | |
| Cardiovascular | 5 (0.9%) | 4 (1.9%) | 9 (1.2%) | 2 (0.4%) | 1 (0.5%) | 3 (0.4%) |
| Body as a whole | 10 (1.8%) | 3 (1.4%) | 13 (1.7%) | 3 (0.5%) | 0 | 3 (0.4%) |
| Digestive | 6 (1.1%) | 0 | 6 (0.8%) | 4 (0.7%) | 2 (1.1%) | 6 (0.8%) |
| Hemic and lymphatic | 0 | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) |
| Musculoskeletal | 0 | 0 | 0 | 0 | 1 (0.5%) | 1 (0.1%) |
| Nervous | 3 (0.5%) | 0 | 3 (0.4%) | 6 (1.1%) | 1 (0.5%) | 7 (0.9%) |
| Respiratory | 0 | 1 (0.5%) | 1 (0.1%) | 0 | 0 | 0 |
| Skin and appendages | 2 (0.4%) | 0 | 2 (0.3%) | 3 (0.5%) | 0 | 3 (0.4%) |
| Special senses | 2 (0.4%) | 0 | 2 (0.3%) | 0 | 0 | 0 |

Table 48b: Adverse events by body system and gender- MI

| | DOFETILIDE | | | PLACEBO | | |
|---------------------------------------|------------|----------|-----------|-----------|----------|-----------|
| | Male | Female | Total | Male | Female | Total |
| NUMBER(%) OF SUBJECTS: | | | | | | |
| Evaluable for adverse events | 542 | 207 | 749 | 569 | 192 | 761 |
| With adverse events | 12 (2.2%) | 9 (4.3%) | 21 (2.8%) | 12 (2.1%) | 4 (2.1%) | 16 (2.1%) |
| Discontinued due to adverse events | 8 (1.5%) | 3 (1.4%) | 11 (1.5%) | 3 (0.5%) | 2 (1.0%) | 5 (0.7%) |
| ADVERSE EVENTS BY BODY SYSTEM: | | | | | | |
| Cardiovascular | 6 (1.1%) | 3 (1.4%) | 9 (1.2%) | 1 (0.2%) | 0 | 1 (0.1%) |
| Body as a whole | 1 (0.2%) | 3 (1.4%) | 4 (0.5%) | 6 (1.1%) | 1 (0.5%) | 7 (0.9%) |
| Digestive | 3 (0.6%) | 1 (0.5%) | 4 (0.5%) | 1 (0.2%) | 4 (2.1%) | 5 (0.7%) |
| Nervous | 2 (0.4%) | 3 (1.4%) | 5 (0.7%) | 2 (0.4%) | 0 | 2 (0.3%) |
| Respiratory | 1 (0.2%) | 0 | 1 (0.1%) | 0 | 0 | 0 |
| Special senses | 0 | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) |
| Urogenital | 0 | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) |

10.12 Laboratory Safety

The most significant abnormalities affected creatinine clearance, liver function tests and serum glucose levels. The largest number of discontinuations affected patients with changes in creatinine clearance. The abnormal glucose tests reflect the cohorts of diabetics enrolled in the study - 164(26.1%) and 148(23.5%) in the Dofetilide and Placebo groups, respectively. Patients with diabetes in the CHF group are 158(20.7%) and 145(19.2%) in the Dofetilide and Placebo groups respectively, and in the MI group, 98(13.1%) and 97(12.7%), respectively.

The upper limit of normal laboratory values was exceeded for several parameters in a significant number of patients assigned to both treatment groups but there is no significant difference except a slight increase in the number of patients with hypokalemia in the placebo group in the CHF study compared to Dofetilide group. Subjects in the CHF Dofetilide group had fewer abnormal laboratory tests - 74% compared to 77% in the placebo group; and 61% Dofetilide and 64% placebo among MI patients. The summary of adverse events resulting from abnormal laboratory tests is presented in Table 53. There were differences in frequency of hematuria and edema in the Dofetilide group compared to placebo (Table 49).

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