# Evaluating the Dofetilide Risk Management Program

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# Disclosures

- Research grant funding from Pfizer (2005 - present)

# Background

- Dofetilide - a new antiarrhythmic drug in 2000 for conversion of atrial fibrillation and maintenance of sinus rhythm
- Dofetilide was known to have a dose/concentration-dependent risk of torsades de pointes - a potentially fatal adverse event
- Atrial fibrillation is typically a non-life threatening arrhythmia
- Market withdrawals had occurred or were being contemplated for several other drugs that cause QT-prolongation and torsades de pointes (eg. Cisapride)

# Dofetilide Risk Management Program:Key Elements

- Patient must be hospitalized for initiation
- Mandatory education program
  - Database of prescribers
- Restricted Drug distribution
  - Both for hospital and patient acquisition
    - Added “trained” pharmacies in 2002
- Specific dosing and monitoring recommendations

# Evaluating the Program

- Some of the Challenges
  - Torsades de pointes (TdP) is “relatively” uncommon and is difficult to find from claims data
  - QT prolongation may not always result in TdP
  - How should success or failure of the program be defined?
    - What level of risk is acceptable?
    - Role of potential surrogate endpoints
      - Adherence to labeled instructions
      - Practitioner acceptance of the program/drug

# Our Assessment

- Practitioner perceptions
  - Single hospital
- Prescriber acceptance - use
  - Single hospital and national
- Adherence to labeled dosing and monitoring guidelines
  - Comparison of adherence to labeled dosing and monitoring guidelines for sotalol:
    - FDA approved for similar indication in same time period
    - Has a dose-dependent risk of torsades de pointes
    - Similar dosing and monitoring recommendations in labeling
    - No risk management program

# Practitioner Survey

- Surveyed all practitioners who completed the educational program at DUMC
  - Opinions of the overall program
  - Opinions of the dosing and monitoring guidelines
  - Time required for program implementation and education
  - “Mini-quiz”

# Survey Results - Educational Program

| | Total (91) | Nurse (22) | Pharm (34) | MD (35) |
|---|---|---|---|---|
| Program was necessary prerequisite | 4.2 ± 0.82 | 4.27 ± 0.55 | 4.18 ± 0.90 | 4.17 ± 0.89 |
| Similar program for only QT-prolonging antiarrhythmic agents | 3.1 ± 1.07 | 3.36 ± 1.09 | 3.00 ± 0.98 | 3.14 ± 1.14 |
| Potential risks from dofetilide justify time and resources for program | 3.9 ± 0.85 | 3.82 ± 1.05 | 3.82 ± 0.76 | 3.97 ± 0.82 |
| Dofetilide is potentially more dangerous than other antiarrhythmic agents | 2.8 ± 1.01 | 2.91 ± 1.15 | 3.12 ± 0.81[a] | 2.38 ± 0.99[a] |

1=Strongly Disagree, 2= Disagree, 3= Undecided, 4 = Agree, 5 = Strongly Agree

a=significant difference ($p < 0.05$)

*Pharmacotherapy*;2002;22(8):1041-46

# Survey Results: Guidelines

| | Total (91) | Nurse (22) | Pharm (34) | MD (35) |
|---|---|---|---|---|
| Guidelines are easy to understand | 3.7 ± 0.74 | 3.59 ± 0.96 | 3.76 ± 0.50 | 3.76 ± 0.79 |
| Guidelines are easy to implement | 3.1 ± 0.98 | 3.36 ± 1.00 | 2.85 ± 0.89 | 3.27 ± 1.01 |
| As likely to use dofetilide "off-label" as other antiarrhythmic agents | 2.4 ± 0.90 | 2.89 ± 0.88[a] | 2.29 ± 0.84[a] | 2.30 ± 0.92 |
| Necessary to check QT before starting and after each of first five doses | 4.1 ± 0.93 | 4.32 ± 0.72 | 3.94 ± 0.74 | 4.03 ± 1.19 |
| Patient should be hospitalized for ≥72 hours when starting dofetilide | 4.4 ± 0.71 | 4.23 ± 0.87[a] | 4.18 ± 0.68[b] | 4.79 ± 0.42[ab] |

1=Strongly Disagree, 2= Disagree, 3= Undecided, 4 = Agree, 5 = Strongly Agree

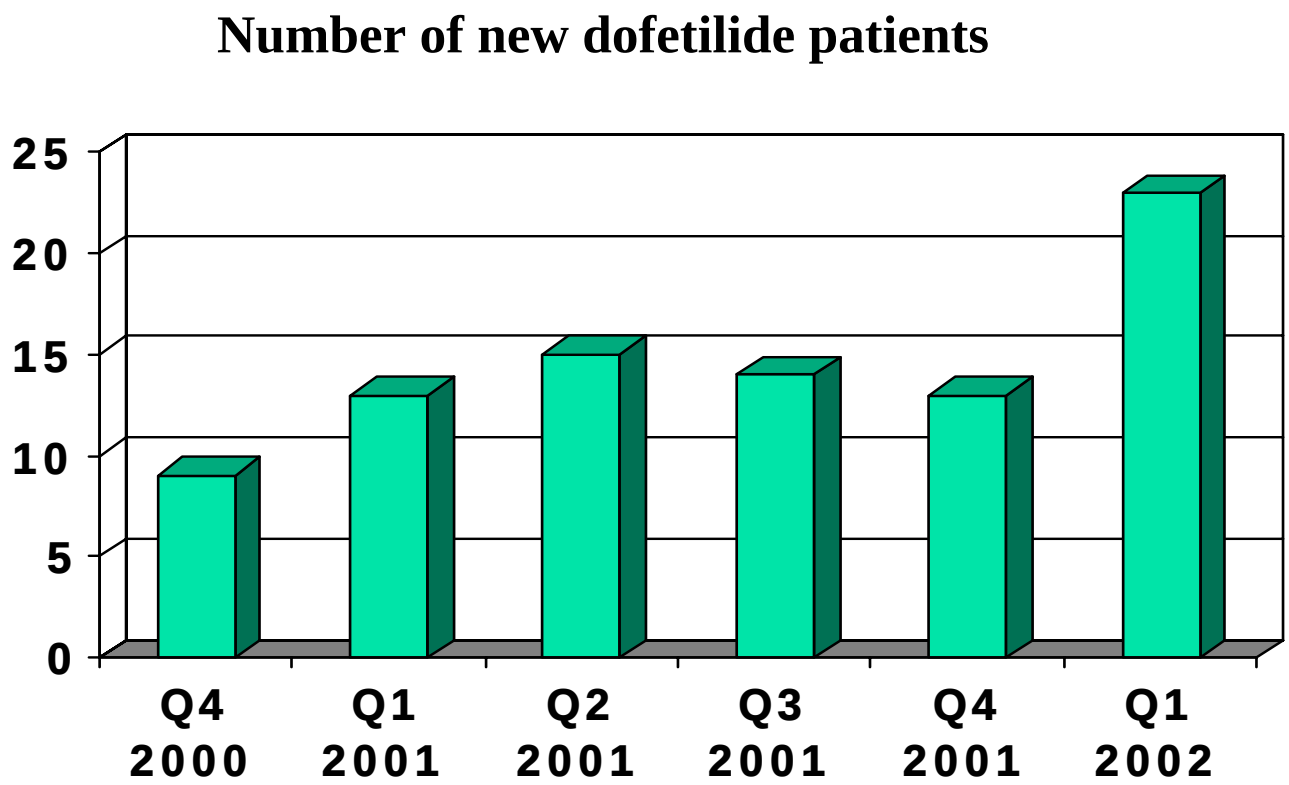
# Survey Results: “Mini Quiz”

- Recollection of facts from the educational program
  - Dofetilide is contraindicated in patients with a CrCl below 20 ml/min
    - 94% of physicians, 82% of pharmacists, and 32% of nurses
  - An ECG should be checked 2-3 hours after the first dofetilide dose
    - 87% of physicians, 74% of pharmacists, and 59% of nurses
  - Identify the 6 medications contraindicated with dofetilide (there are now 7)
    - 25% of respondents were able to correctly identify all 6 medications

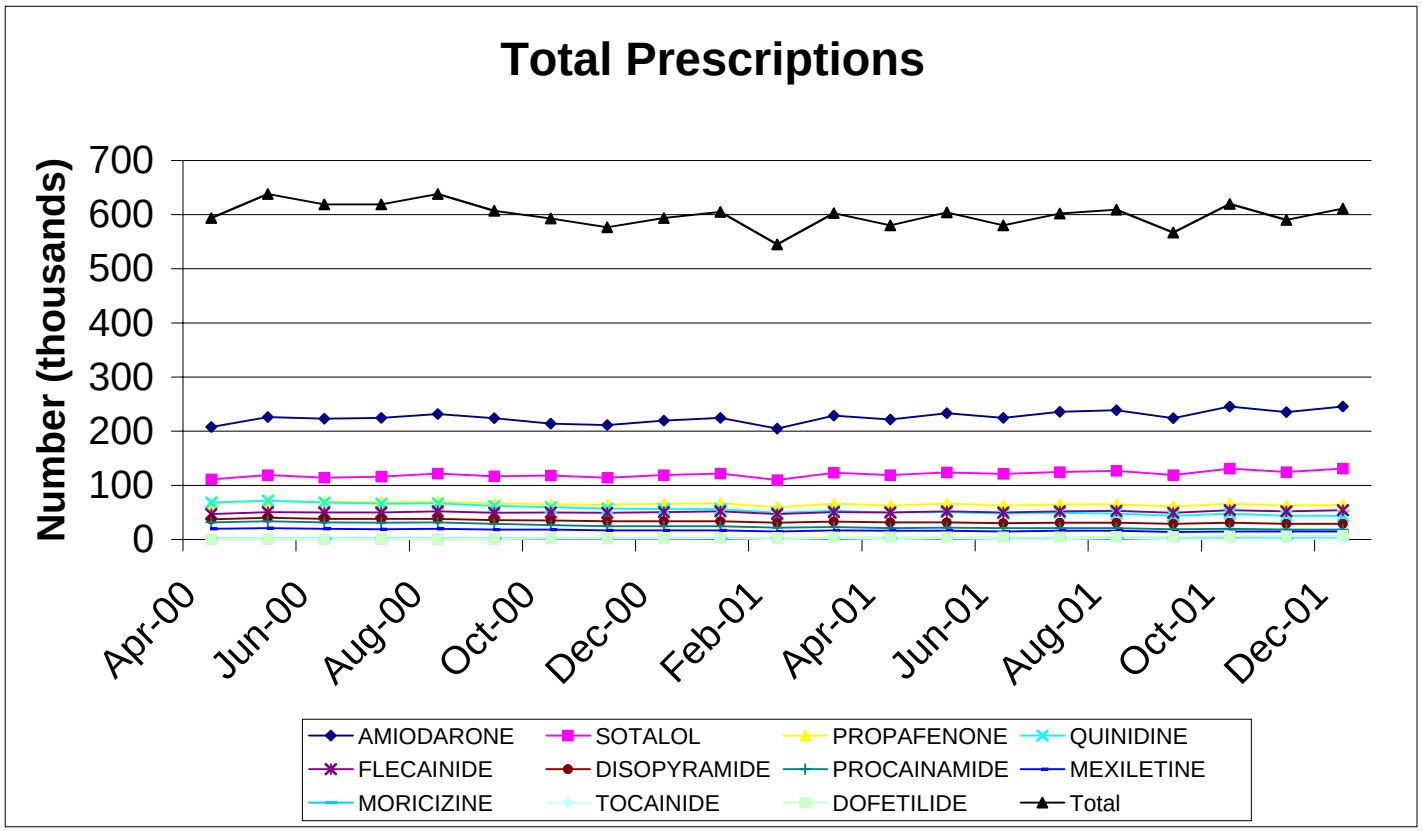
# Practitioner Survey:Summary

- General agreement that the program was necessary
  - Did not think that dofetilide was more “dangerous” than other antiarrhythmic agents
  - Undecided as to whether potential risks from dofetilide justified the time required for the program
- General agreement with the dosing and monitoring recommendations
  - Less agreement that the recommendations were easy to understand or implement
- 145 hours invested in preparing the hospital for dofetilide
  - Does not include the ~ 0.9 hours/practitioner to complete the educational program

# Uptake at Duke Medical Center (DUMC)

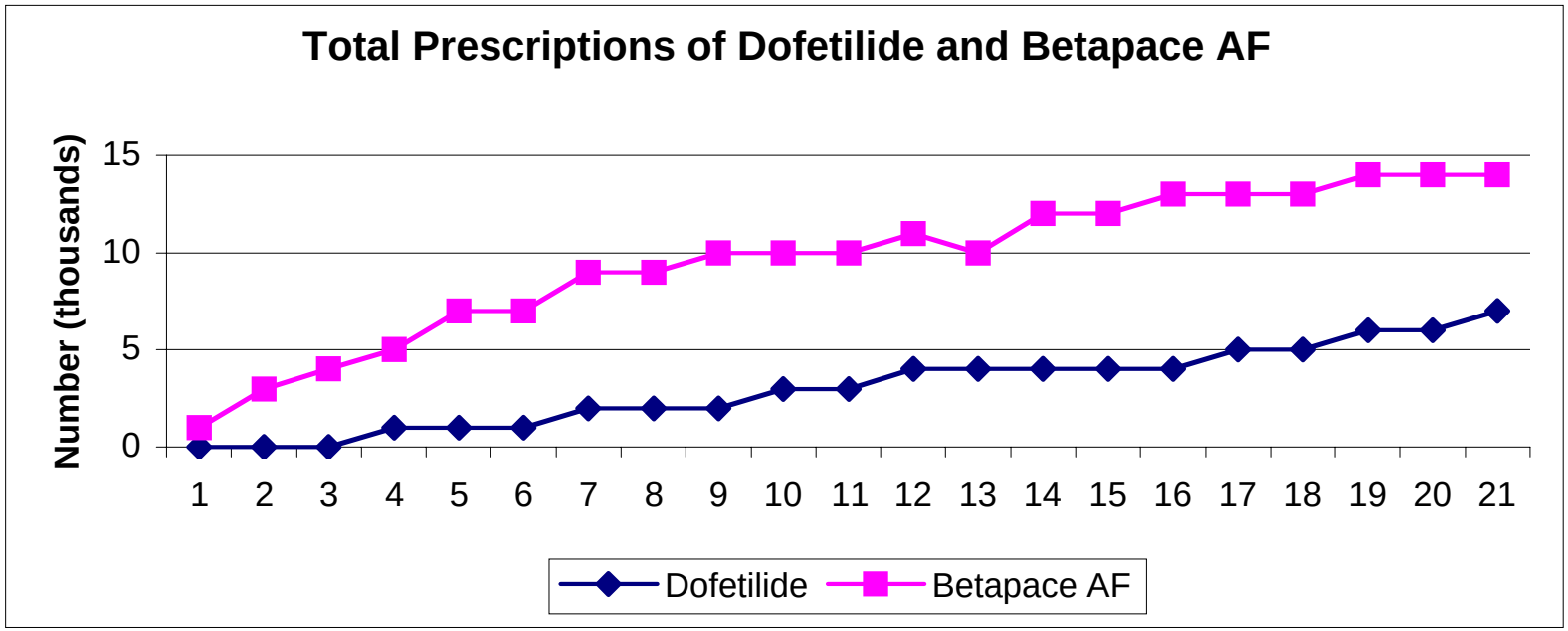


# Acceptance: Market Uptake



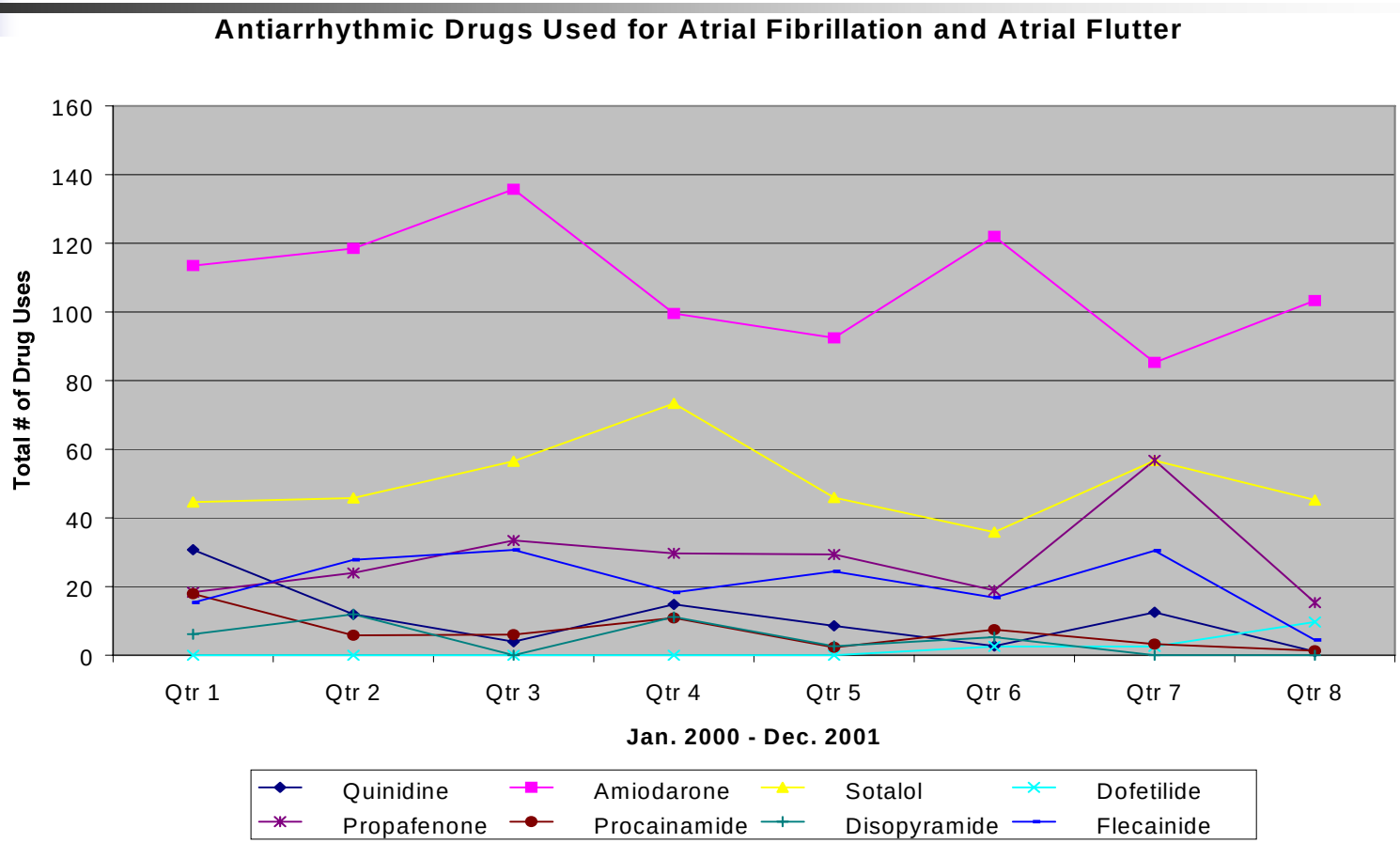

*Pharmacotherapy* 2003;23(10):1316-1321

# Acceptance: Market Uptake




*Pharmacotherapy* 2003;23(10):1316-1321

# Acceptance: Use for Atrial Fibrillation/Flutter

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# Adherence to Dosing and Monitoring Recommendations

- All patients with a pharmacy order for dofetilide or sotalol over a 1 year period
- Chart abstractions
  - All dofetilide patients – new starts
  - 50% of the sotalol patients who had no diagnosis for a ventricular arrhythmia and were new starts
- Note: Duke implemented standardized order set for dofetilide

# Results

| | Dofetilide (N=47) | Sotalol (N=117) | P value |
|---|---|---|---|
| Correct starting dose | 37 (79%) | 41 (35%) | p < 0.001 |
| Contraindicated based on baseline ECG | 11 (27%) N=44 | 33 (42%) N=78 | NS |
| Baseline ECG done | 44 (94%) | 78 (67%) | p < 0.001 |
| ECG done after 1st dose | 44 (94%) | 50 (43%) | p < 0.001 |
| ECG done after subsequent doses | 35 (80%) N=44 | 4 (4%) N=113 | p < 0.001 |

# Results (continued)

| | Dofetilide (N=47) | Sotalol (N=117) | *P* value |
|---|---|---|---|
| Baseline potassium obtained | 47 (100%) | 96 (82%) | p < 0.001 |
| Baseline magnesium obtained | 42 (89%) | 45 (38%) | p < 0.001 |
| Medication stopped for adverse event | 5 (11%) | 10 (9%) | p = 0.7 |
| Medication held for adverse event | 4 (9%) | 16 (14%) | p = 0.4 |

# Results (continued)

- 94% of dofetilide prescriptions written by “approved” physician
- No interacting medications at initiation or hospital discharge

# Summary

- Program was viewed favorably
  - At start-up
- Very little dofetilide used locally or nationally
  - ? Too burdensome
    - May limit use (1 of 3 hospitals in DUHS added dofetilide to formulary)
    - Unintended consequence - use of other drugs with similar risks that do not have RM program
- Better adherence to dosing/monitoring guidelines for dofetilide compared to sotalol
  - Indicates “success”
    - Standard order set