Outpatient Prescribing of Antiarrhythmic Drugs from 1995 to 2000

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There is growing evidence that some class III antiarrhythmic drugs, unlike class I agents, are not associated with an increased risk of death in patients with prior myocardial infarction and left ventricular dysfunction.[1–14] For this reason, we evaluated the extent to which the current prescribing of antiarrhythmic medications complies with the evidence that supports the use of class III rather than class I agents. Using pharmaceutical marketing research data, we reviewed outpatient antiarrhythmic drug prescriptions in the United States from 1995 through the third quarter of 2000, to characterize the prescribing of these drugs and to examine drug use trends over this period.

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Data on antiarrhythmic drug prescribing were derived from 2 audits owned by IMS Health (Plymouth Meeting, Pennsylvania): the National Prescription Audit (NPA) Plus and the National Disease and Therapeutic Index (NDTI).

The NPA Plus audit measures the retail outflow of prescriptions in the United States. This includes prescriptions dispensed by retail pharmacies and mail-order pharmacies. The NDTI audit contains data on drug mentions associated with a diagnosis during a specific clinic visit. These data are collected by a continuing survey of 343,655 physicians in office-based practices in the United States. An NDTI panel of physicians, a subset of 343,655, is selected every 2 weeks to provide demographic information, diagnoses, and recommended drugs for each diagnosis on all patients encountered. This is then projected to the national level.

The NPA Plus audit was queried for all class I and class III antiarrhythmic drugs for which an oral dosage form was marketed and sold in the United States between January 1995 and September 2000. The numbers presented for the year 2000 represent a 9-month period. Class I agents included the class IA agents quinidine, procainamide, and disopyramide, the class IB agents mexiletine and tocainide, and the class IC agents flecainide, propafenone, and moricizine. Class III agents included amiodarone and sotalol. We limited this analysis to class I and III antiarrhythmic drugs because it would be difficult to determine whether β blockers (class II antiarrhythmic agents) and calcium channel blockers (class IV antiarrhythmic agents) were prescribed solely for an arrhythmic indication.

The NDTI audit was queried for all oral class I and class III antiarrhythmic agents stratified by physician specialty and diagnoses for which the agent(s) was used. Trends in antiarrhythmic drug prescriptions were evaluated based on physician specialty and the diagnosis for which each agent or class of agents was reported to be prescribed.

From the NPA Plus audit, the projected total number of prescriptions dispensed in 1995 for antiarrhythmic agents was 6.7 million. This number did not substantially change during the study period (5.1 million prescriptions dispensed from January to September 2000). Figure 1 shows prescribing trends of each antiarrhythmic agent from 1995 to September 2000. There was a notable decrease in the number of class I antiarrhythmic prescriptions (5.5 million in 1995 vs 2.4 million in 2000); however, until 2000, class I antiarrhythmic drugs remained the most commonly prescribed antiarrhythmic agents (3.6 million class I prescriptions vs 3.2 million class III prescriptions in 1999). The reduction in the number of class I antiarrhythmic prescriptions mostly reflected a decrease in class IA prescriptions (4.1 million in 1995 vs 1.2 million in 2000). During this period, the number of prescriptions for class IC antiarrhythmic agents slightly increased (0.9 million in 1995 vs 1.3 million in 1999 and 1 million from January 2000 to September 2000).

There was a doubling in the number of class III antiarrhythmic prescriptions (1.2 million in 1995 vs 2.7 million in 2000). This rise was largely due to the increase in amiodarone prescriptions, which outnumbered prescriptions for any other antiarrhythmic agent from January 2000 to September 2000 (1.8 million amiodarone prescriptions vs 1.2 million class IA prescriptions, 1.0 million class IC prescriptions, and 0.97 million sotalol prescriptions).

The NDTI audit indicated that over the 6-year period, antiarrhythmic drug mentions were most often associated with a diagnosis of atrial fibrillation or flutter. Figure 2 shows trends of antiarrhythmic medications for atrial fibrillation or flutter. This diagnosis was the only diagnosis for which mentions of antiarrhythmic drug use increased (Figure 3). Notably, antiarrhythmic drug use for hypertensive disease was among the 3 most frequent diagnoses for the study

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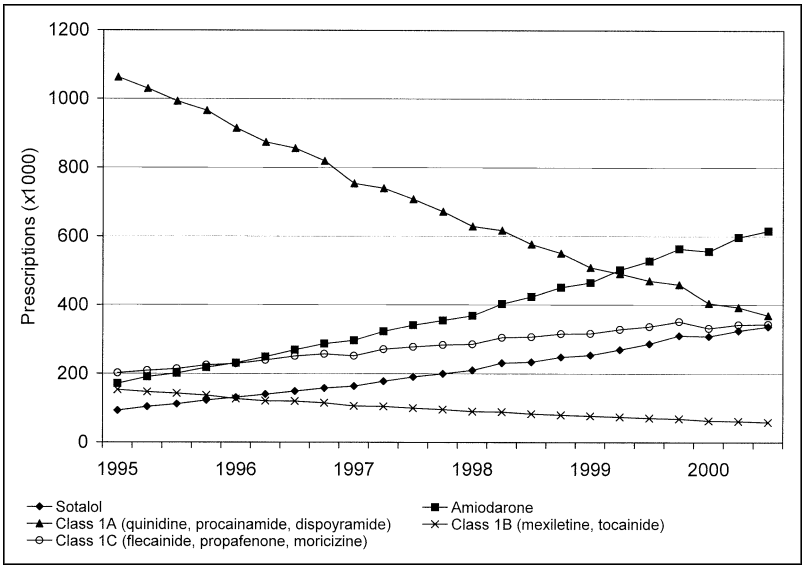

FIGURE 1. Prescribing trends for antiarrhythmic agents (1995 to 2000): total number of prescriptions.

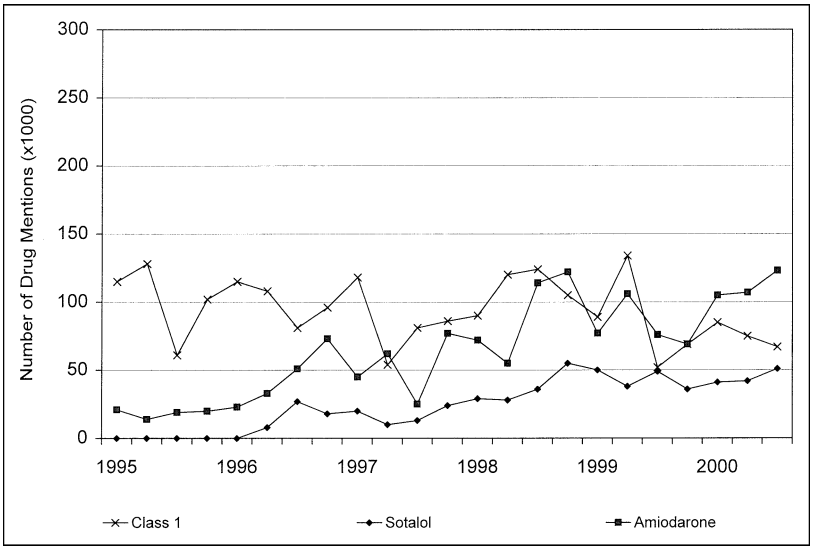

FIGURE 2. Prescribing trends for antiarrhythmic agents associated with atrial fibrillation (1995 to 2000).

period, and in 1999 and 2000, was second only to antiarrhythmic drug use for atrial fibrillation or flutter. Although mentions of antiarrhythmic drug prescriptions for ischemic heart disease decreased from 1995, antiarrhythmic drug use was reported for this diagnosis about 0.3 million times from January 2000 to September 2000. There was a trend toward a decrease in antiarrhythmic drug prescriptions for paroxysmal supraventricular tachycardia and arrhythmias other than atrial fibrillation and ventricular arrhythmias. Antiarrhythmic drug prescriptions associated with a diagnosis of ventricular arrhythmias was relatively low and did not change appreciably during the study period.

In the first 3 quarters of 2000, 65% of antiarrhythmic drug prescriptions was associated with cardiologists (Figure 4). In each year after 1997, cardiologists prescribed more amiodarone than any other antiarrhythmic drug. Cardiologists' prescribing of sotalol began to increase in 1998, since then, sotalol has been second only to prescribing of amiodarone. In 1995, cardiologists most commonly prescribed class IA agents, but in later years, they prescribed these drugs considerably less.

In the first 3 quarters of 2000, 24% of antiarrhythmic drug prescriptions was associated with internists. Since 1998, internists have prescribed more amiodarone than any other antiarrhythmic agent. In 1995, internists most commonly prescribed class IA agents, and, although their prescribing of these agents decreased in later years, these drugs still were the third most commonly prescribed antiarrhythmic agents by internists from January to September 2000.

The remaining 11% of antiarrhythmic drug use was associated with family practitioners. Until 1998, family practitioners still prescribed class IA agents more often than any other antiarrhythmic class. Although family practitioners prescribed class IA drugs less often over time, since 1999, these agents have been the second most commonly prescribed antiarrhythmic drugs by family practitioners.

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Our study is the first to describe the changes in prescribing antiarrhythmic drugs in the United States in the 1990s, and to examine how these changes comply with the overall evidence that supports the use of class III rather than class I agents.

Compared with the 11.4 million antiarrhythmic prescriptions written in 1986, the 5.1 million prescriptions written through the third quarter of 2000 were an appreciable decrease.[15] This likely reflects physicians' reaction to the evidence from major clinical trials, indicating either no benefit or an adverse effect of antiarrhythmic drugs on survival.[1–14]

Our study showed a considerable decrease since 1995 in the prescribing of class I antiarrhythmic agents in favor of class III drugs. This observation shows compliance with evidence advocating lesser prescribing of class I antiarrhythmic agents. This change, however, occurred at a disappointingly slow pace. Class IA agents still were the most commonly prescribed antiarrhythmic drugs until 1998, although evidence of potential harm with these agents in certain populations had been disseminated in the early 1990s.[4–6]

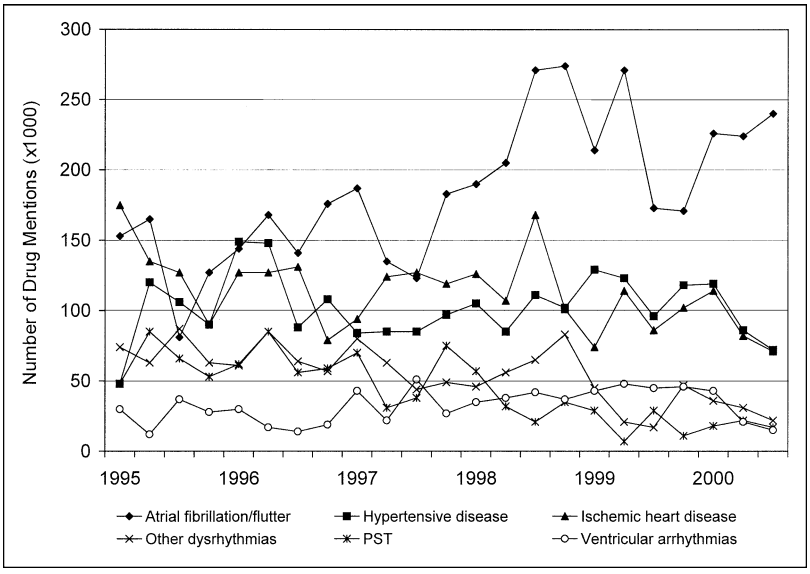

FIGURE 3. Prescribing trends for antiarrhythmic agents by diagnosis (1995 to 2000).

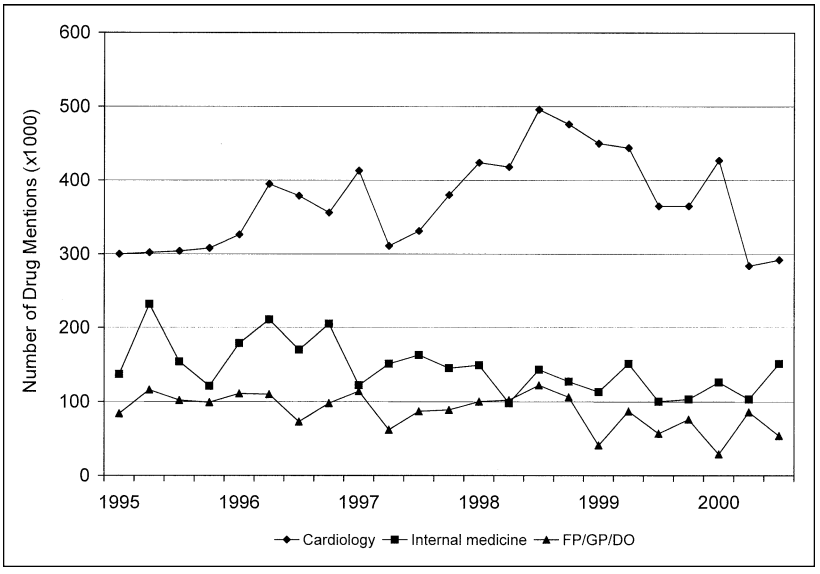

FIGURE 4. Prescribing trends for antiarrhythmic agents by provider type (1995 to 2000). DO = doctor of osteopathy; FP = family practitioner; GP = general practitioner.

This lag between onset of a change in practice and attainment of a new steady-state could be attributed to several factors, including physicians' lack of knowledge, their skepticism about the applicability of the results of trials to their patients, and their doubts about the cost effectiveness of a new therapy. This lag also could be attributed to the lack of standard guidelines about the proper use of antiarrhythmic drugs. Prescribing behavior may have changed more rapidly by establishing national, standard guidelines for the prescribing of antiarrhythmic drugs. In contrast, guidelines should reflect evidence of safety and efficacy from clinical trials for broad applicability. The recent guidelines for the management of atrial fibrillation raise some concern in this regard because many of the recommendations are based on expert analysis of available data and evidence of efficacy but not safety from clinical trials.[16]

Atrial fibrillation or flutter was the most common diagnosis for the prescribing of antiarrhythmic drugs; however, as suggested by our data, physicians also may be using antiarrhythmic drugs for ischemic and hypertensive heart diseases, a practice not based on evidence derived from clinical trials. Before drawing definitive conclusions from these data, however, it is important to verify that physicians truly are prescribing antiarrhythmic drugs for these diagnoses.

Internists and family practitioners prescribed more class I antiarrhythmic drugs than did cardiologists. This observation may have resulted from the cardiologists being more aware of evidence from clinical trials,[17,18] but it also may reflect that internists and family practitioners are more likely than cardiologists to see patients who have no cardiac disease. Because class I antiarrhythmic drugs have not been shown to have an adverse effect on the survival of patients without cardiac disease, using these drugs to treat such patients may be acceptable. However, this will need to be confirmed by future randomized clinical trials.

In conclusion, physicians now prescribe antiarrhythmic drugs less often than they did in the 1980s. Although the prescribing of class I agents has decreased in favor of class III antiarrhythmic drugs, this change occurred very slowly. The most common associated diagnoses were atrial arrhythmias, ischemic heart disease, and hypertensive heart disease; prescriptions for the latter 2 conditions represent a practice not based on evidence from clinical trials.

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Usefulness of Myocardial Tissue Doppler Echocardiography to Evaluate Left Ventricular Dyssynchrony Before and After Biventricular Pacing in Patients With Idiopathic Dilated Cardiomyopathy

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Recently, simultaneous biventricular pacing has been proposed as an alternative treatment in patients with drug refractory heart failure.[1] The clinical benefit of biventricular pacing has been demonstrated in various studies; improvement in heart failure symptoms, quality-of-life, exercise capacity, and left ventricular (LV) systolic performance have been shown.[2] It has been suggested that the success of biventricular pacing is mainly related to resynchronization of the ventricular septum to the LV lateral free wall.[2] Myocardial tissue Doppler imaging (TDI) is an echocardiographic technique that allows noninvasive quantification of the peak systolic myocardial velocity and the timing of this peak velocity in relation to electrical activity (QRS on electrocardiogram).[3] Theoretically, this technique could be very useful in evaluating the dyssynchrony in patients with dilated cardiomyopathy and the resynchronization after biventricular pacing; initial data are promising.[4,5] Accordingly, consecutive patients with drug refractory heart failure who underwent implantation of a biventricular pacemaker were evaluated with TDI before and after implantation.

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Consecutive patients with end-stage heart failure secondary to idiopathic cardiomyopathy who were scheduled for implantation of a permanent biventricular pacemaker were included in the present study. The following selection criteria for biventricular pacing were used: (1) severe heart failure (New York Heart Association [NYHA] functional class III or IV), (2) severely depressed left ventricular ejection fraction (LVEF $\leq$35%), and (3) QRS exhibiting left bundle branch block configuration with a duration of $>$120 ms. These criteria have been used in small clinical studies[3] and in ongoing multicenter trials.[6]

Before implantation (baseline), both clinical parameters and echocardiographic parameters were derived. The echocardiographic parameters included: (1) LVEF determined by 2-dimensional echocardiography,[7] (2) peak systolic velocities (in basal septal and lateral segments) assessed by TDI, and (3) septal to lateral dyssynchrony derived from TDI. These parameters were reassessed the day after implantation. The pacemaker was turned off on the day after implantation in 10 patients, and the echocardiographic parameters were reassessed.

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system FiVe, General Electric–Vingmed, Milwaukee, Wisconsin). Images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and 2- and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine loop format. The LVEF was cal-

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