Amiodarone Prophylaxis

TO THE EDITOR: Our institution has become increasingly interested in new research on the topic of prophylaxis for prevention of atrial fibrillation in patients undergoing cardiac surgery. However, the 10 studies included in the meta-analysis by Aasbo and colleagues (1) do not appear to be unique. This paper included a study by White and associates (2) that seems to be derived from the same data represented in the study by Giri and colleagues (3). Apparently, the same study was published twice in 2 separate journals. Both studies involve the same 220 patients from Hartford Hospital from 1998 to 1999. I believe further investigation is warranted.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We agree with Mr. Craycraft’s observation that similar cohort data were presented in the studies by Giri and associates (1) and by White and associates (2), both of which were included in our meta-analysis. The number of stroke end points (16 in Giri, 9 in White), the percentage of patients who received β-blockers (72.4% in Giri vs. 89.1% in White), and the percentage of patients who had valvular surgery (26.9% in Giri vs. 18.2% in White) are different in the 2 papers. Although the Annals of Thoracic Surgery identified the publication by White and colleagues as an “Original Article,” in retrospect, it appeared likely (to us) that the authors reported a sub-study (rather than a duplicate) of AFIST (Atrial Fibrillation Suppression Trial). We spoke directly to Dr. White on 14 December 2005. He confirmed that the Annals of Thoracic Surgery article was a sub-study of AFIST and that the same patient population was used.

We regret the inadvertent inclusion of duplicate cohort data in our meta-analysis. To assess the effect of including the patient data twice, we performed a meta-analysis that excluded the latter of these 2 publications (2). From the 9 remaining trials, we evaluated the effect of amiodarone on incidence of atrial fibrillation or flutter (relative risk, 0.65 [95% CI, 0.55 to 0.77]; P < 0.00001; I² = 0%); incidence of atrial fibrillation or flutter in patients receiving the drug preoperatively (relative risk, 0.63 [CI, 0.48 to 0.84]; P = 0.0001; I² = 0%); incidence of atrial fibrillation or flutter in patients receiving the drug perioperatively (relative risk, 0.65 [CI, 0.53 to 0.81]; P < 0.00001; I² = 5.6%); incidence of atrial fibrillation or flutter in patients receiving the drug orally (relative risk, 0.63 [CI, 0.48 to 0.84]; P = 0.001; I² = 0%); incidence of ventricular tachycardia and fibrillation (relative risk, 0.44 [CI, 0.29 to 0.67]; P = 0.0001; I² = 0%); incidence of stroke (relative risk, 0.44 [CI, 0.21 to 0.91]; P = 0.03; I² = 0%); and length of stay (weighted mean difference, −0.7 day [CI, −1.18 to −0.22 days]; P = 0.005; I² = 22%).

Excluding the data from White and associates does not substantially alter the results of our meta-analysis. Our conclusion that amiodarone prophylaxis significantly reduces atrial fibrillation, major cardiovascular morbidity, and length of hospital stay after cardiac surgery remains firm.

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Genetic Risk Assessment and BRCA Mutation Testing

TO THE EDITOR: The National Society of Genetic Counselors (NSGC) Familial Cancer Risk Counseling Special Interest Group has reviewed the U.S. Preventive Services Task Force (USPSTF) recommendations (1) regarding BRCA genetic risk assessment and commends Annals for creating a patient summary on this topic (2). The NSGC would like to emphasize that the Task Force’s recommendations highlight the importance of genetic counseling to the risk assessment process and that genetic counseling facilitates informed decision making about genetic testing and management. In and of itself, counseling has not been associated with increased anxiety or other adverse outcomes. Professionals who are trained in the field of cancer genetics include genetic counselors, medical geneticists, and advanced practice oncology nurses. Directories of these specialists can be found on the Web sites for the National Cancer Institute (www.cancer.gov/search/geneticservices/) and the National Society of Genetics Counselors (www.nsgc.org).

We feel that 4 key points were either omitted from the summary or were misleading as written when compared with the pub-
lished USPSTF guidelines. First, although the Task Force has not addressed genetic counseling and testing for men, they do discuss the importance of recognizing cases of male breast cancer; therefore, the inclusion of male relatives (that is, brothers, fathers, grandfathers, and nephews) in any family history is necessary. Second, the patient summary implies that the identification of a mutation makes a woman more likely to experience anxiety, insurance problems, or unnecessary procedures—none of which have been found in actual practice. Third, the definition of high-risk women of Ashkenazi (Eastern European) Jewish heritage should be amended. Unlike women from other ethnic backgrounds, these women are considered to be at high risk if they have any first-degree relative with breast or ovarian cancer at any age or (not “and”) at least 2 second-degree relatives on the same side of the family with breast or ovarian cancer at any age. Fourth, although the USPTF recommendations were directed to a population without breast or ovarian cancer, it is very important to provide access to genetic risk assessment and counseling to women who are affected with these diseases. Such individuals, especially those with a known family member who has a BRCA mutation, stand to potentially benefit to an even greater extent from genetic risk assessment and BRCA testing.

Finally, we strongly encourage Annals to consider collaborating with recognized leaders in the field of cancer genetics to develop a revised version of the patient summary that incorporates these concerns.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate the opinions expressed by the NSGC Familial Cancer Risk Counseling Special Interest Group, but we respectfully disagree that a major revision of the patient summary accompanying the USPSTF recommendation is warranted. The intent of the summary is to reflect the content of the recommendation statement. The NSGC’s first and fourth comments pertain to genetic counseling of men and counseling of women with a personal history of breast or ovarian cancer. These issues are beyond the scope of the USPSTF recommendation. Although the NSGC believes that the summary is misleading with respect to the potential harms of screening, the editors believe that the summary is accurate when it states, “. . . since not all women who have a BRCA mutation develop cancer, identification of mutations may also needlessly expose women to anxiety, insurance problems, or unnecessary procedures.” With respect to the third comment, the version of the summary on Annals.org has been corrected to use the word “or,” not “and,” to describe the characteristics of high-risk women of Ashkenazi Jewish heritage. A correction also appears in this issue.

The Editors

Potential Financial Conflicts of Interest: None disclosed.

The Ethics of Personal Stockpiles

TO THE EDITOR: Bartlett and Hayden (1) provide an excellent overview of the potential catastrophic results from the next pandemic with the influenza A (H5N1) virus. The reported overall mortality rate of 50% of infected persons and estimates of 50 million potential deaths certainly give us cause for concern. It is very reasonable to warn and plan for such an eventuality. However, when this fear is coupled with a recommendation for expanding “personal stockpiles of antiviral agents” (1), I am afraid that we may be crossing the line.

According to 2000 data, there are more than 779,723 physicians in the United States (2). With such a devastating virus potentially facing us, wouldn’t we include enough drugs for our own family and some friends if we were to obtain our own personal stockpile? If each physician wrote only a few prescriptions for personal use, we could easily deplete the supply of oseltamivir before any outbreak occurred.

As physicians, we have been granted the privilege to prescribe drugs for the good of our patients. When there is a known limited supply of an agent and a predicted catastrophic demand, acquiring a personal stockpile by writing our own prescription or by having a colleague do so is unethical. It is tantamount to insider trading, which has brought so much disdain to corporate America recently. Let’s not do the same to medicine.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: In our editorial, we stated that personal stockpiles of antiviral agents may make “good sense.” Dr. Rolfsen makes a now more obvious point about the problem of drug shortage in the event of widespread procurement of personal stockpiles. This is an issue that has become the subject of some substantial analysis and concern since our editorial was submitted. We agree with Dr. Rolfsen and with the position statement of the Infectious Diseases Society of America (www.idsociety.org), which advises against personal stockpiling of these drugs. The possible need for personal stockpiles was
mitigated when the U.S. Department of Health and Human Services recently announced that 1 goal of its new pandemic plan is to obtain sufficient drugs to treat 25% of the population (1), although an even higher target should be considered.

In the near term, health care institution stockpiling remains appropriate because it targets drug availability to the 2 groups that are highest in the National Vaccine Advisory Committee/Advisory Committee on Immunization Practices prioritization scheme: hospitalized patients and health care workers.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

Relevance of Patient Diagnosis to Analysis of the Terri Schiavo Case

TO THE EDITOR: The recent review and ethical analysis of the Terri Schiavo case by Perry, Churchill, and Kirshner is generally excellent (1). The authors do, however, make 1 important claim that is incorrect: that the Schiavo case “rests critically on the concept of the persistent vegetative state.” This mistake is made by most observers of the case and tends to detract from, rather than contribute to, the discourse regarding Terri Schiavo’s case.

Robert and Mary Schindler went to great lengths, including distributing videos of their daughter, to convince the court and the public that their daughter was not in a persistent vegetative state. Much of the courts’ efforts were spent determining whether she was in a persistent vegetative state. Senator Bill Frist thought it was important to point out that he did not believe Mrs. Schiavo was in a persistent vegetative state on the basis of his review of the video footage (2). The Schindlers apparently continue to believe that the diagnosis was incorrect and that a different diagnosis—presumably minimally conscious state—would have led to a different ethical and legal analysis. The media and the public mistakenly believed that the autopsy would provide more certainty than was already available about Mrs. Schiavo’s diagnosis, and that this in turn would determine “who was right” in the case.

This was all wasted effort. The distinction between persistent vegetative state and minimally conscious state was irrelevant. Even if the Schindlers had agreed that the proper diagnosis was the former, it seems clear that they would not have chosen termination of hydration and nutrition. Conversely, even if his wife had been in a minimally conscious state, Michael Schiavo probably would still have concluded that her condition was unacceptably poor from her perspective. He even could have plausibly believed that her interest in terminating hydration and nutrition would be stronger if she were in a minimally conscious state.

What should have been important to everyone was the prognosis, not the diagnosis, and prognosis for further recovery from either persistent vegetative state or minimally conscious state after 10 years is probably equally poor.

The particular diagnosis in this case is irrelevant to any analysis that does not take the position that one has a right to refuse hydration and nutrition if one is vegetative but does not have that right if one is minimally conscious. The proper ethical analysis in this case, elegantly delineated by the authors, rests a right to refuse treatments on individual liberty and a right to self-determination and does not limit such a right to particular diagnoses.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Dr. Cochrane suggested that the distinction between persistent vegetative state and minimally conscious state in the Schiavo case was “irrelevant.” At least as a matter of legal importance, we do feel that the diagnosis of persistent vegetative state is critically important to the case.

The operative Florida statute (1) specifically classifies persistent vegetative state as 1 of only 3 conditions in which artificial life-prolonging procedures can be withdrawn. Florida law defines persistent vegetative state as “a permanent and irreversible condition of unconsciousness in which there is: (a) The absence of voluntary action or cognitive behavior of any kind. (b) An inability to communicate or interact purposefully with the environment” (2).

A diagnosis of minimally conscious state would not be explicitly covered under the Florida law that governed Mrs. Schiavo’s fate. Consequently, the fact that the court concluded on 2 separate occasions (the 2000 trial and the 2002 hearing) that Mrs. Schiavo was in a persistent vegetative state is, from the perspective of the law, a fact of critical importance to all relevant decision makers.

In addition, the medical certainty of the diagnosis of persistent vegetative state is much greater than that of minimally conscious state, which has not been as well defined or as well documented in terms of poor prognosis. Families can much more easily accept a diagnosis with a wealth of medical documentation than one with less certain implications.

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Setting the Agenda for the Clinical Interview

TO THE EDITOR: Drs. Baker, O’Connell, and Platt (1) presented an articulate, valuable, and enjoyable analysis of a major problem we physicians face in meeting the needs of our patients. Early in my 40 years of cardiology and internal medicine practice, I learned how to avoid another “doorknob” question that would add significant time to the visit. Before I start any important discussion with patients about their diagnoses and their testing and treatment recommendations, I ask: “Is there anyone with you today who you want to hear our discussion?”

This question evolved after many instances of having to repeat my detailed discussion after patients asked, “Doctor, can my wife/husband/parent/daughter/son come in now, and would you tell them what you just told me?”

This paper should be required reading for all medical students and graduate physicians in training.

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Potential Financial Conflicts of Interest: None disclosed.

References

CLINICAL OBSERVATIONS

Reporting of Drug Tolerance in Randomized Clinical Trials: When Data Conflict with Authors’ Conclusions

TO THE EDITOR: Background: Double-blind randomized trials that compare the efficacy of a new drug with an older drug or with placebo also often provide information regarding safety. When these findings are published, some authors conclude that the new drug has a “good safety profile” just because they failed to find any statistical difference in frequencies of adverse effects.

Objective: The goal of this study is to illustrate this misreporting of data and to propose parameters that would promote more objective reports of safety results.

Methods: We selected 2 published clinical trials (1, 2) that compared pharmacologic treatments for which the authors clearly stated that there was no difference in the occurrence of adverse effects. We chose these 2 randomized, controlled trials because the lower safety of the new treatment was confirmed by additional analysis (3) or was already known. For each adverse effect, we estimated the relative increase in adverse effect incidence (4), defined as 100 × (RR - 1) in which RR is the relative risk for adverse effects, and the difference in adverse effect incidence with 95% CIs (5, 6).

Findings: For each adverse effect, the authors stated there was no difference between drugs in safety profile; however, the findings were statistically compatible with a relative increase or substantial difference in incidence (Table). For example, findings in the study by Lassen and colleagues (1) were compatible with a 6.1% relative decrease in major bleeding as well as a 127% relative increase in major bleeding (suggesting a lower tolerance for fondaparinux).

Discussion: When researchers plan a randomized clinical trial comparing 2 drugs, sample size is most often calculated with regard to efficacy. Adverse effects are rare and differences in incidence are generally small, albeit clinically relevant. Planned sample sizes are therefore generally not large enough to demonstrate a difference in the incidence of adverse effects. Consequently, small but clinically important differences may be overlooked (type II errors), and detection of adverse effects requires a larger sample size or a pooled estimate of several studies (3). Ignorance of the concept of type II error (β) is therefore responsible for such statements as “the 2 groups did not differ in frequency of adverse events,” which is an incorrect conclusion. As specified by Altman and Bland (7), a negative result (defined as a result associated with a P value < 0.05) only means that there is “an absence of evidence of a difference.” By no means does this finding demonstrate equivalence. The absence of significant differences in incidence of adverse effects must therefore be interpreted more cautiously.

We must remember to acknowledge that a negative result is potentially associated with a type 2 error. Substantial differences between incidences of adverse effects may be detected in a small trial, but more subtle differences require larger sample sizes to achieve statistical significance.

Conclusion: The CONSORT (Consolidated Standards of Reporting Trials) statement recommends that authors report estimates of the frequency of the main severe adverse events separately for each intervention group. We suggest that authors go beyond this descriptive reporting and report 95% CIs for the differences in incidence of adverse effects, the relative increase in adverse effects, or both. This strategy, which is similar to the CONSORT statement’s recommendation to report CIs for the difference in primary outcomes, would encourage more objective reports of drug safety data.

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Potential Financial Conflicts of Interest: None disclosed.

References
5. Newcombe RG. Interval estimation for the difference between independent propor-
### Table. Examples of Adverse Event Reporting in Randomized Clinical Trials with Estimates of the Associated Relative Increases and Differences in Incidence

<table>
<thead>
<tr>
<th>Study, Year (Reference) and Adverse Event</th>
<th>Sample Size, n</th>
<th>Adverse Events, n (%)</th>
<th>P Value</th>
<th>Authors’ Comment</th>
<th>Relative Increase in Incidence (95% CI), %*</th>
<th>Difference in Incidence Observed (95% CI), %†</th>
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</thead>
<tbody>
<tr>
<td>Lassen et al., 2002 (1)</td>
<td></td>
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<tr>
<td>Major bleeding</td>
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<tr>
<td>Drug (fondaparinux)</td>
<td>1140</td>
<td>47 (4.1)</td>
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<tr>
<td>Control (enoxaparin)</td>
<td>1133</td>
<td>32 (2.8)</td>
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<td>de Gans et al., 2002 (2)</td>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Drug (dexamethasone)</td>
<td>157</td>
<td>50 (31.8)</td>
<td>0.24</td>
<td>“Treatment with dexamethasone did not result in an increased risk of adverse events.”</td>
<td>23.9 (−13.5 to 77.6)</td>
<td>6.1 (−4.6 to 16.6)</td>
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<tr>
<td>Control (placebo)</td>
<td>144</td>
<td>37 (25.7)</td>
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<tr>
<td>Herpes zoster</td>
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<tr>
<td>Drug (dexamethasone)</td>
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<td>37.6 (−60.4 to 377.7)</td>
<td>1.0 (−4.1 to 6.1)</td>
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<tr>
<td>Fungal infection</td>
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<tr>
<td>Drug (dexamethasone)</td>
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<td>83.4 (−43.6 to 496.2)</td>
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<td>4 (2.8)</td>
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</tbody>
</table>

* The relative increase in risk equals $100 \times (RR - 1)$ where RR is the relative risk defined as the ratio of the 2 incidences. A point estimate and the 95% CI are provided.

† Differences in incidences are crude differences. The observed difference is derived from reported incidences of adverse events, and 95% CIs are estimated.

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**Correction**

**Correction: Summary for Patients: Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility**

In the Summary for Patients (1) that accompanied the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility (2), the third sentence under the heading “What does the USPSTF suggest that patients and doctors do?” should have read as follows: “For women of Ashkenazi (Eastern European) Jewish heritage, these include any first-degree relative with breast or ovarian cancer at any age or at least 2 second-degree relatives on the same side of the family with breast or ovarian cancer at any age.”

**References**
