ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment) trial (NCT00373451), all of which had patient populations that were similar to the FAME study population, were 3.0%, 6.6%, and 3.7%, respectively. Might the standard-intervention group in the FAME study have been unlucky?

Fourth, the centers that were chosen to participate in this study had a long-standing interest in FFR. Can the study results be generalized to other centers?

Finally, perhaps the research question addressed in the trial was itself something of a "straw man," since FFR does not have to be used on all or none of the stenoses that might be treated but rather can be used selectively.

History has shown us that not all statistically significant results from studies of this size are repeatable. It is likely, however, on the basis of results from other relevant trials noted above, that the investigators are on to something. A validation study addressing the issues raised here would be very helpful for the interventional cardiology community. In the meantime, interventional cardiologists should recognize the limitations of coronary angiography and PCI, while of course not forgetting their benefits.

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Antipsychotic Agents and Sudden Cardiac Death — How Should We Manage the Risk?

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Antipsychotic medications are commonly used across the entire age spectrum, both within and outside their labeled (and evidence-based) indications.[1,2] Three atypical antipsychotic medications, olanzapine (Zyprexa, Eli Lilly), risperidone (Risperdal, Janssen), and quetiapine (Seroquel, AstraZeneca) are among the 10 top-selling drugs worldwide, with a combined sales volume of $14.5 billion in 2007.[3]

A thorough evaluation of risks is particularly important in the case of medications that are used so frequently and in such diverse patients, many of whom (e.g., children and the elderly) are particularly vulnerable. The effect of most antipsychotic medications on the electrophysiology of the heart has long been known, and several studies have shown an association between older, conventional (typical) antipsychotic medications (e.g., haloperidol and thioridazine) and death,[4] including sudden cardiac death.[5] In this issue of the *Journal*, Ray et al.[6] have now extended our knowledge of this problem to atypical antipsy-

chotic drugs with the finding that the risk for sudden cardiac death is at least as high for atypical antipsychotic medications as it is for conventional agents, and that it is dose-dependent for all agents. The reported incidence-rate ratios for sudden cardiac death among users of high-dose antipsychotic drugs as compared with the rates among nonusers varied from 1.72 for haloperidol to 5.05 for thioridazine, and these rates correlate with the relative respective potential of these drugs to cause prolongation of the QT interval.

It is striking that it took so long to establish the elevated risk associated with atypical antipsychotic medications given that the first agent in this class (clozapine) entered the U.S. market in 1989. Ray et al. present a comprehensive study that makes a clear case for the increased risk of sudden cardiac death associated with all antipsychotic drugs. Their research has all the attributes of a well-designed pharmacoepidemiologic study; many of these attributes seem obvious but are too often poorly implemented. The authors confine their analysis to new users of the study drugs; this design accurately represents events that happen shortly after the initiation of therapy, events that could otherwise be underestimated by including the greater person-time contributed by long-term users (or "survivors") of the drug, who may be less susceptible to the outcome that is being studied.[7] They also establish a clear temporal sequence between patient characteristics before the initiation of treatment and the outcomes after initiation.

Sudden cardiac death can be a difficult end point to capture in databases of health care use. Ray et al. developed and tested an algorithm that combined information from death certificates with data on health care use. This algorithm resulted in a positive predictive value of 86%, which would result in only minor underestimation of risk, unless reporting were differential between users and nonusers, an unlikely scenario. Comparing users of a given drug with nonusers is always problematic in observational studies, since the treatment choice is likely to be affected by poorly measured differences in disease severity or prognosis, differences that might introduce confounding. Matching according to propensity score (i.e., the predicted probability that a person would be a user of antipsychotic drugs) helped Ray et al. to achieve cohorts that were largely balanced with regard to measured patient characteristics, even though the use of other psychiatric medications remained slightly imbalanced between users and nonusers. However, in this study, which was performed in a routine-care environment, it is unlikely that psychiatrists took into account the risk of sudden cardiac death before prescribing an antipsychotic agent.

Should the use of antipsychotic medications be restricted on the basis of these data? Much of their use is in vulnerable populations and outside the labeled indications, including the use in children and in the elderly with dementia,[1,2] and there is much less evidence of efficacy in these populations. In the absence of clearly established benefits for many of these patients, the risk of a fatal side effect is not likely to be acceptable. For these patients, the use of antipsychotic medications should be reduced sharply, perhaps by requiring an age-dependent justification for their use. Educating prescribers on the benefit–risk relationship of such drugs in vulnerable populations has also proved effective.[8] However, physicians should continue to be able to prescribe antipsychotic drugs when there is clear evidence of benefit, for conditions such as schizophrenia and bipolar disorders. In patients for whom the drug is truly indicated, a small risk of rare but fatal side effects may be acceptable until new medications with a safer cardiac risk profile are developed.

How common is sudden cardiac death among adults treated with antipsychotic medications? Some computations can help put this risk in perspective. The incidence rate reported by Ray et al. was 478 events per 166,324 patient-years of use, or 2.9 events per 1000 patient-years. Among patients given higher doses, the rate was 3.3 events per 1000, a level of risk that would be described as between "moderate" and "low," but not "rare."[9] Although this risk might initially appear low, the rate of agranulocytosis among clozapine users has been reported to be 6.8 events per 1000 patient-years,[10] close to twice the rate of sudden cardiac death among users of high-dose antipsychotic medications.

The rate of death from clozapine due to agranulocytosis was about 0.2 per 1000 patient-years,[10] much less than the risk of sudden cardiac death in patients taking antipsychotic medications. An elaborate risk-management program has been in place for almost two decades for clozapine, re-

quiring close monitoring of white cell counts before a prescription can be refilled. Given these observations, although this proposal has not yet been formally tested, in our view if an antipsychotic agent is necessary, it seems reasonable to obtain an electrocardiogram before and shortly after initiation of treatment with an antipsychotic drug. This modest effort could enable each patient starting on a high-dose antipsychotic to be screened for existing or emergent prolongation of the QT interval.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that 3% of patients with schizophrenia (mean age, 40 years) who were treated with risperidone and quetiapine had prolongation of the QT interval.[11] The risk was doubled (6%) among patients with dementia (mean age, 78 years)[12]; these proportions are probably even higher among elderly users of high-dose drugs. We think that once prolongation of the QT interval is detected, a reduction of the dose or discontinuation of the drug should be attempted,[13] concurrent medications should be examined for known interactions,[11] other risk factors for sudden cardiac death should be reduced,[14] and follow-up electrocardiograms should be obtained.

The downside of risk-management programs for mental health drugs is the possibility that effective agents may be underused in a population that is often underserved and frequently not compliant. Clozapine, one of the most effective antipsychotic drugs, may be underused in patients who have schizophrenia that is resistant to treatment because patients and physicians worry about the risk of agranulocytosis or the burden of monitoring the white-cell count.[15] A formal model for decision analysis similar to that used for clozapine[16] would bring clarity about the risks and benefits of such a therapeutic risk-management program, and make it possible to use findings such as those reported in the current study as a springboard to detailed data-driven clinical recommendations. Until then, in patient populations for whom the evidence of the efficacy of antipsychotic medications is limited and the risk of a fatal side effect is clear, prudence would suggest that the use of these drugs should be reduced sharply.

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