WHAT SHOULD THE STUDY DESIGN BE TO TEST NEW ANTIARRHYTHMIC DRUGS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION, DIGITALIS TOXICITY AND OTHER ACUTE PROBLEMS

ROGER A. WINKLE, M.D.
CARDIOLOGY DIVISION
STANFORD UNIVERSITY SCHOOL OF MEDICINE
STANFORD, CALIFORNIA 94305

I. ACUTE MYOCARDIAL INFARCTION

In the setting of acute myocardial infarction the largest single use of antiarrhythmic drug therapy is for the prevention of ventricular fibrillation. In this setting drug efficacy cannot be judged in a single patient and can only be inferred from well controlled clinical trials. Traditionally lidocaine has been the most widely utilized drug for this indication. We can learn about the potential flaws to be avoided in antiarrhythmic drug trials by examining the previously performed clinical trials of lidocaine in acute myocardial infarction. Table 1 summarizes some of the larger series evaluating lidocaine efficacy in this setting. None of these studies were able to show a beneficial effect of lidocaine in preventing ventricular fibrillation until the study of Lie et al. The pitfalls of all of these studies (except that of Lie and coworkers) may be listed as follows:

1. Most studies were based on the assumption that warning arrhythmias identified patients at risk of ventricular fibrillation and therefore the endpoint of therapy was suppression of warning arrhythmias. They permitted placebo treated or control patients to crossover to lidocaine therapy once warning arrhythmias occurred.
2. There was inadequate knowledge of the pharmacokinetics of lidocaine. This resulted in several problems:
   a. No initial loading bolus.
   b. Inadequate maintenance infusion rate.
   c. Failure to achieve or document therapeutic lidocaine plasma concentrations.
3. In many instances there was delay in patient arrival at the hospital or in institution of drug therapy so that the period of highest risk of ventricular fibrillation had passed.

J. Morganroth et al. (eds.), *The Evaluation of New Antiarrhythmic Drugs*
In recent years the following facts relating to the design of studies for prophylaxis of ventricular arrhythmias following acute myocardial infarction have become apparent.

1. The role of warning arrhythmias is minimal. A large number of subjects have warning arrhythmias who never develop ventricular fibrillation and a number of patients have ventricular fibrillation without ever having significant warning arrhythmias.

2. The highest risk of ventricular fibrillation is in the very earliest hours following the onset of myocardial infarction and diminishes rapidly over the subsequent 24 hours.

3. Withholding all drugs in the Coronary Care Unit setting and treating ventricular fibrillation with defibrillation when it occurs is probably safe. There is, however, tremendous resistance on the part of non-investigative physicians and nursing personnel to take this approach to therapy.

Based on these observations I would propose the following recommendations for studies of antiarrhythmic drugs for ventricular arrhythmias following acute myocardial infarction.

1. The primary endpoint of the study should be the prevention of sustained ventricular tachycardia and ventricular fibrillation. This will require large numbers of patients to be entered into the study.

2. There should be much less emphasis on the reduction of lesser ventricular arrhythmias.

3. Patients must be entered in within a few hours of the onset of chest pain.

4. The study design should carefully consider the drug's pharmacokinetics and be certain that adequate loading and maintenance doses are utilized to rapidly achieve and maintain therapeutic drug concentrations.

5. The study should be a randomized double-blind comparison with placebo.

6. The study should not exclude patients with relative contraindications to antiarrhythmic therapy such as mild congestive heart failure, minor conduction disturbances, etc.