Learning From Mistakes: The Case of Clinical Electrophysiology
A Perspective on Evidence-Based Rhythmology

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Since the time of Claude Bernard, progress has been based on medical evidence. Today, however, statistical findings increasingly prevail over the spirit customarily required for evaluating medical evidence. We may have to change our mode of reasoning to prevent the discovery of error from becoming our primary source of progress. A statistics-based conclusion is relevant only if the contribution and importance of the criteria studied are taken into account. Statistical science recognizes this, but statistics users, particularly physicians, often ignore it. Consequently, the inappropriate use of statistics leads to mistakes, even misinformation, at times when clinical judgment would be a more reliable way of avoiding error.

Assessment of Arrhythmias and Drugs
Therapeutic trials are regulated by strict rules: They must be prospective, placebo-controlled, randomized, and analyzed according to predefined end points on an intention-to-treat basis. Moreover, the analysis of non-prestratified subgroups is discouraged. Nevertheless, instances in which an observational study leads to significantly different conclusions are quite exceptional; to quote Benson and Hartz,1 “... [there is] little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials.”

When investigating a drug combination that is considered clinically valid, it is almost impossible to carry out the trial in full compliance with all regulations. This is exemplified by the study on the combination of amiodarone and β-blockers in sudden-death prevention.2 It is difficult to reconcile so-called pragmatic trials (ie, those with large, nonrelevant targets) and so-called tedious trials (ie, those with exaggeratedly narrow targets).

Certain methods for investigating arrhythmias and assessing antiarrhythmic drugs were considered essential until the day they were challenged. Clinical electrophysiology began in the late 1960s with programmed stimulation to investigate sustained arrhythmias; this was followed by the Holter method for quantification of spontaneous events. The use of only type IA antiarrhythmic drugs suggested that the prevention of arrhythmia inducibility and the removal of extrasystoles were two relevant, clinically efficient methods. Amiodarone was developed in Europe solely on the basis of clinical efficacy. Because of assessment standards, however, amiodarone remained unauthorized for a long period of time in the United States. This example shows that when a drug does not satisfy the established criteria, the criteria must be challenged, not the drug.

The same applies to arrhythmias themselves when they are not easy to evaluate. A good example was the approval of type IC drugs for atrial arrhythmias in France as early as the mid-1980s because of their efficacy and thanks to more flexible legal requirements. The pernicious effect of rigid rules and erroneous targets finally culminated in the design of the Cardiac Arrhythmia Suppression Trial (CAST)3 in the late 1980s. This experience demonstrates how mistakes can be ultimately beneficial, provided they are recognized, but it also demonstrates how high the price may be for having ignored the premonitory signs. Two years before CAST, the International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT)4 had shown an exaggerated mortality, but because the number of patients was twice as small, their identical mortality rate did not reach significance and the results were disregarded. Also, as early as 1986 the deleterious effect of type I antiarrhythmics was suspected.5

French groups challenged6 the purely quantitative use of the Holter technique. Their Dutch colleagues7 questioned the validity of serial programmed stimulation. Preventing arrhythmia inducibility and cleaning Holter recordings from spontaneous events using sodium-channel blockers was considered predictive of a therapeutic effect in the long term. We now know that this applies to individual patients whose prognosis is naturally more favorable, but an additional requirement is that the outcome must not be worsened by the actual use of these drugs. Thus, the good news for a patient is that his or her arrhythmia is sensitive to an antiarrhythmic drug, and the bad news is that the drug has been prescribed for the long term. Only after such mistakes were the notions of prognosis marker and factor clearly differentiated. Also, clinical observations of patients led to the combination of amiodarone and β-blockers,8 a strategy now encouraged by...
post-hoc analysis of major trials. How long will it take until this therapy is based on evidence?

Past mistakes led to understandable caution in the use of antiarrhythmics. Conversely, it must be emphasized that β-blocker efficacy for sudden-death prevention in patients with some degree of heart failure was demonstrated not by electrophysiologists, but by heart failure studies courageously initiated in conditions far removed from evidence-based medicine. The reason for the use of β-blockers at a very early stage was their obvious antiarrhythmic efficacy despite heart failure rather than because of its presence. The more serious heart failure is, the more efficient β-blockers are; the adrenergic paradox derives from the fact that the adrenergic dependence of arrhythmias is all the less detectable that it is more operative. Evidence-based medicine does not handle paradox skillfully and struggles with such situations.

In considering the rate at which β-blockers are prescribed for heart failure (5% in the Multicenter Automatic Defibrillator Implantation Trial [MADIT] and 15% in the Antiarrhythmics Versus Implantable Defibrillators [AVID] trial), it is clear that the taboo of their contraindication has not yet been overcome. Possible causes are reluctance to break a taboo and a lack of information. If the information is inadequate, however, what is required is to disseminate it, not to replace these drugs by defibrillators.

**Sudden Death and the Implantable Cardioverter-Defibrillator**

The implantable cardioverter-defibrillator (ICD) has challenged the purely preventive nature of sudden-death treatment. It is legitimate to compare the respective merits of a preventive or curative, pharmacological or technological, approach to the problem of rhythmic death, but there is no ground for carrying out that research in a black-and-white manner. Comparing one technology with several so-called conventional drug treatments to suggest their apparent unity is incorrect, and it is quite misleading to suggest the advantages of technology over pharmacology.

Patients undergoing medical therapy experienced sharp mortality variances between MADIT (32% mortality at 2-year follow-up) and the Coronary Artery Bypass Graft (CABG) Patch trial (18% mortality), both of which were primary prevention trials, whereas secondary prevention trials show mid-range mortality rates: 25% in AVID, 22% in the Canadian Implantable Defibrillator Study (CIDS), and 20% in the Cardiac Arrest Study Hamburg (CASH). The fact that a single technology was tested makes the various trials consistent, and there is low variance in mortality in ICD-implanted groups (15% to 18%). For nonimplanted patients, we can consider that the variances derive mainly from the quality of the medical treatment, but it is incorrect to test two methods when one of them is not used optimally.

In this respect, MADIT is a classic case because this trial reflects many biases. Nonimplanted patients whose arrhythmias were inducible but not suppressible by procainamide (10% of nonimplanted patients) were given drugs that had been demonstrated to be ineffective, whereas <50% of nonimplanted patients finally received amiodarone and 5% received β-blockers (versus 27% for implanted patients). Furthermore, the ICD was supposed to address only the problem of rhythmic sudden death. Why then did the ICD’s better results derive not so much from the device itself (3 sudden deaths in the implanted group versus 13 in the nonimplanted group) than from the number of nonsudden cardiac deaths (7 versus 13) and even extracardiac deaths (4 versus 12)? All in all, in two thirds of the cases, the ICD benefit in MADIT did not derive from rhythmic death. The CABG Patch trial did not confirm the ICD benefit, although the proportion of rhythmic deaths is the same in both trials (29% in CABG Patch and 33% in MADIT), which, incidentally, shows that the explanation put forward, ie, a poorer selection, is invalid. As a matter of fact, patients in the CABG Patch trial received higher-quality medical treatment: coronary bypasses, β-blockers, and no antiarrhythmics.

MADIT was the first trial on the primary prevention of sudden death, of the pragmatic type in the most questionable sense of the word. In the United States, MADIT led to a change in recommendations on defibrillators. Its biases reflected US, not European habits; indeed, only one of the 32 centers involved was European. In the light of better-conducted trials now published, the validity of MADIT quite surprisingly remains unchallenged although its results amount to dual misinformation concerning both high- and low-risk subgroups. CIDS clearly demonstrated that the ICD benefit only applies to patients with major risk factors (age, ejection fraction, and functional class). Patients in CIDS received real treatment combining β-blockers, aspirin, amiodarone, ACE inhibitors, and statins. The post-hoc analysis of MADIT and AVID confirmed that defibrillator benefit only applies to patients with the most reduced myocardial function.

Any compliance with rules implying a methodologically incorrect subgroup analysis necessarily has a highly pernicious effect. The most frequent error is that a treatment that is in actual fact beneficial or detrimental to one subgroup is extended to the whole group. At this end, this amounts to dual misinformation concerning, in opposite directions, various subgroups. The less the negative influence of drug treatment in trials, the less likely it is that the technological and the pharmacological approaches will lead to diverging results. In CASH, the ICD gives a significantly better performance only compared with propafenone. The ICD performance improves nonsignificantly when compared with metoprolol or amiodarone. Moreover, CASH is a clean trial, in which the patients treated with an ICD did not receive amiodarone or β-blockers, so they could not benefit medically from these treatments; this is in contrast to patients in MADIT and AVID, who actually suffered from a medical treatment that was far less than optimal. In fact, everything suggests that drugs and the ICD must be combined to obtain optimal efficacy.

Likewise, an amalgamation process that causes a subgroup to be inadequately included in the indications can also be found in the analysis of β-blocker effects in congenital long-QT syndrome (LQTS) by Moss and colleagues. This study is questionable because it utilizes a posteriori a register that was not designed for testing the β-blocker efficacy hypothesis. An attentive recount of the cases reveals the
biases that form the basis of the so-called imperfect security offered by β-blockers. The most obvious bias is that there is absolutely no certainty that the treatment was actually given to the patients, as regards what we may call a retrospective intention-to-treat. As a matter of fact, 8 of the 33 patients who died did not receive β-blockers and for 3 the situation was unknown. Altogether, at most 15 patients (if we include the latter 3) received treatment according to the questionnaire, with reservations about actual compliance on the last day before death. All in all, a maximum of 15 of 869 patients were really at risk in this registry, ie, 1.72% over 5.3 years. Although it may be statistically correct to use at-risk patients who died did not receive β-blockers, but are counted in the results assessing the effects of that treatment. Of the 33 who died, 11 patients comprised an unusual subgroup of babies who had almost a caricature of symptomatic LQTS. Of the 22 other patients who died, 7 did not receive β-blockers, and for 3 the situation was unknown. Altogether, at most 15 patients (if we include the latter 3) received treatment according to the questionnaire, with reservations about actual compliance on the last day before death. All in all, a maximum of 15 of 869 patients were really at risk in this registry, ie, 1.72% over 5.3 years. Although it may be statistically correct to use at-risk babies to conclude that ICDs should be implanted in adults whose sensitivity to β-blockers has not even been tested, the data gathered from the babies are clinically irrelevant. The combined experience of the two authors of the present article in their respective countries covers an LQTS population equivalent in number to that studied by Moss et al15 and clearly belies such a pessimistic attitude toward β-blocker treatment performance. It is a shame that all the progress achieved in the field in recent years leads to a pragmatic but unrealistic decision to recommend the use of ICDs outside the difficult case of LQTS. Indeed, in the latter case, β-blocker therapy proved to have no efficacy in reducing symptoms and, of note, 3 of the above-mentioned 15 patients were LQTS patients. Alternative treatment options (ie, sodium-channel blockers) have been suggested, but those might have potential lethal side effects. At present, an ICD might indeed be the best option for LQTS patients. We realize that in the near future other genetic subtypes may be at particular risk, even when on β-blockers.

Conclusions
The preceding examples of so many apparently evidence-based but ultimately questionable beliefs about the clinical management of arrhythmias and the therapeutic strategy should make us cautious. The physician’s priority is to ensure in the best possible way the patient’s survival. In our modern world, however, the financial implications of public health are necessarily present, and doctors must admit that even if health is priceless, it does have a cost. We must be credible and produce convincing evaluations that do not ignore the socioeconomic impact. We must be the first to point out our mistakes and correct them when they have not only health but also cost implications. In the real world it may be easier and less risky for the physician to prefer technology to drug treatment, but physicians cannot ignore their economic responsibility. The validity of studies must be continuously reassessed, and it is in that sense that evidence-based medicine makes as much progress through mistakes as it does through true findings.

References

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