



Current opinion

Medical Practice Guidelines

Separating science from economics

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Introduction

Over the past twenty years, practice guidelines have become an increasingly popular tool for synthesis of clinical information.

The objectives of guidelines are to enhance the appropriateness of practice, improve quality of cardiovascular care, lead to better patient outcomes, improve cost-effectiveness, help authorities to decide on the approval of drugs and devices and identify areas of research needed. Guidelines may also be used as quality measurement for the health insurance.

Evidence-based medicine is a relatively recent concept: indeed, it is only within the past two decades that prospective, randomized clinical trials have become widely accepted, creating the foundation for modern clinical research. Thanks to the *evidence* coming from these trials, physicians have been forced to abandon some concepts that were previously considered 'logical' or 'good common sense' and which had provided the rationale for what was in fact empirical treatment. The scientific community has been adopting the new concepts introduced by 'evidence based medicine' so rapidly that we can hardly remember our recent past. For example, not so many years ago, cardiologists were taught, based on theoretical assumptions and some small acute studies, to avoid beta-blockers in patients with heart failure. Now, after several randomized trials have disputed that concept using a gradual step dosage, we learn that these are precisely the patients who may benefit most from that therapy.^{1,2} Another example of the risk of linking the practice of medicine to what

'seems logical', comes from the assumption made in the seventies and in the eighties that reducing premature ventricular contractions would lower arrhythmic deaths. To our surprise, we learnt from the Cardiac Arrhythmias Suppression Trial (CAST), that drugs highly 'effective' in reducing premature ventricular beats actually *increased* patient mortality due to *proarrhythmia*.³ There are of course many more examples of how carefully collected data may open unforeseen scenarios that will help us to practice better medicine.

Based on a solid commitment to help European cardiologists practise medicine according to the best available evidence, the European Society of Cardiology (ESC) has undertaken a major effort in promulgating and updating *Guidelines* for clinical practice. Less than ten years have elapsed since the first ESC guidelines were published, and the number of documents produced since has grown dramatically. Within the past two years alone, the ESC has issued guidelines for management of patients with acute coronary syndromes, syncope, chronic heart failure, atrial fibrillation, sudden cardiac death and chest pain. Many other guidelines were published in the past, and more are forthcoming.

The ESC's foremost responsibility is to ensure that their Guidelines are based on *sound and compelling* clinical/scientific evidence. The specific criteria with which ESC Task Forces must comply in reaching consensus on these guidelines are discussed below.

Credibility of the evidence

The first prerequisite for new data to be considered for integration into Guidelines is the credibility of the data. The evidence – usually derived from clinical trials – needs to pass strict criteria for *credibility*. The study hypothesis, design and statistical aspects must be

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credible. This task is facilitated by the fact that major medical journals, which publish these studies, require them to fulfil high standards as regards study design and statistical methodology. Furthermore, it is important to be vigilant about potential sources of *bias* in the study: patient selection, their allocation to the randomized arms, equivalent treatment except for the therapy being tested, drop-outs/crossovers, definition of endpoints and their evaluation when the study ends. Studies least susceptible to such biases are those that are conducted in many centres, not just one or a few; use proper randomization schemes; apply methods to assure that patient profiles and their therapies are similar for patients assigned to the randomized arms; verify that the drop-outs/crossovers (between study arms) are within the limits defined in the study design; and ensure that *independent* Endpoint Review Committee and Data Safety and Monitoring Board (DSMB) have evaluated study compliance and endpoints. The DSMB also serves to verify that there have been no unacceptable patient safety issues, e.g., complications beyond those anticipated by the study.

A further means of evaluating the credibility of the outcome is to examine whether the study results are consistent with those of other trials of the same therapy in similar populations. For instance, there are by now a multitude of studies in post myocardial infarction patients. By selecting studies on patients with similar characteristics, such as time from onset of symptoms, and extent of myocardial damage as expressed by left ventricular ejection fraction, it is possible to obtain a good estimate of the prognosis of such patients, both from a standpoint of 'natural history', and under various medical therapies. A therapy that gives results consistent with those from other studies in similar situations obviously reinforces the credibility of the data and strengthens the recommendation provided by the guidelines.

Of course, large-scale controlled and randomized study designs such as those that have provided important answers regarding the management of coronary artery disease or congestive heart failure cannot be applied to all cardiac diseases, especially if they are rare, for instance, hypertrophic cardiomyopathy or long QT syndrome. The level of evidence governing management decisions can often be derived only from non-randomized, retrospective and observational data and sometimes only from expert opinions.

It is most important that the European Society of Cardiology takes responsibility for selecting the best available experts to develop a consensus.

Compelling magnitude of treatment effect

The second prerequisite for data to be introduced into Guidelines is that the magnitude of the benefit should have true clinical (not just statistical) significance. Here, it is important to take into account the significance of the outcome of the study, i.e. *vis-à-vis* other established data or studies in the population tested. For instance, in an all-cause mortality trial, it is important to examine

both the reduction in *relative risk*, as well as the *absolute risk* reduction in the total population who would be candidates for the therapy being studied.⁴ Thus, two studies may show a 33% reduction in relative risk of mortality, but in one, the mortality could be reduced from 6% to 4% while in the other, from 30% to 20%. Both studies might well show the same level of statistical significance, but clearly, the latter has a significantly more compelling treatment benefit.

Guidelines and conflict of interest

Expert guidelines are expected to be objective, impartial and independently derived. Sponsorship from organizations that stand to gain from recommendations favourable to their products threatens to undermine such objectivity. Given the profitability of industry, such neutrality is needed. In this respect it is important that Task Forces are not developed by a selected group of experts of a specific field but rather they provide a balanced representation of clinical cardiologists, allied professionals, epidemiologists, pharmacologists and patients' associations. It is expected that through the involvement of such a composite panel of stakeholders, guidelines will provide a more objective evaluation of treatment options.

Professional societies like the European Society of Cardiology and particularly those with influences on medical practice, should adopt rigorous standards with regard to industry sponsorship.

From evidence based guidelines to clinical practice

After the exercise of comparing clinical trials and ranking the benefit of the various treatments is concluded, guidelines are ready to be implemented in clinical practice. The 'implementation phase' is a most important step in the educational effort of scientific societies. There may be obstacles to successful implementation related to the complexity of dissemination and adoption^{5,6} of the guidelines. Recently, new factors are further complicating the applicability of guidelines in medical practice.

New therapies, which improve patient prognosis and quality of life, come at a price – often quite high – and are directly contrary to the limitations in health expenditures stipulated by our governments. As per the *Hippocratic Oath*, physicians have a clear obligation to do what is in the best interest of our patients. If a new therapy is found to provide substantial benefit for the patient, they feel compelled to make every effort to provide him/her with that benefit. However, physicians are increasingly obliged to operate under strong economic pressure and therefore, despite being aware of the recommendations for optimal patient management, may not receive the financial support to offer these treatments to the majority of patients. This situation is not only frustrating, but it also raises the issue of the legal implications for the physicians when 'not adhering' to recommendations.⁷ As a result, the question of whether

the development of guidelines should include the concept of 'affordability' of a medical therapy has recently been raised. As previously anticipated, the official position of the ESC is in disagreement with this approach, and it will therefore not be adopted in ESC guidelines, for the reasons indicated below.

First of all, the guidelines produced by the ESC are endorsed and implemented in a variety of different countries. It is therefore impossible to provide an accurate economic assessment that would be simultaneously applicable in a set of healthcare systems as profoundly different as those present in the 47 ESC member countries.

Furthermore, we believe that as discussed in the ESC document on the legal implications of guidelines,⁷ guidelines should be regarded as educational tools that help physicians formulate their clinical judgements and make their independent therapeutic choices.

As discussed in a previous ESC statement⁸ 'the guidelines of the ESC have no formal legal power': before they become enforceable by national health authorities, they need to be endorsed and translated by national societies. In this process, 'annotations' may be needed to adapt guidelines to each individual country.

In this regard, most of the member societies of the ESC have announced that they would consider the possibility of discontinuing all further individual guidelines development, and instead, adapt and endorse the guidelines of the ESC, translating them into the local language where necessary.

Although the economic considerations certainly need to be addressed, this is not the role of the physicians called upon to prepare a document that is essentially aimed at translating the results of clinical trials into recommendations for clinical practice, based on their scientific merit. Within the individual countries there are people in responsible positions in their respective governments and health administrations whose first order of business is to address these issues and resolve them. What they require from us as physicians is clarity and consensus on the validity and strength of the data supporting a new medical indication or therapy. If members of guidelines committees were to allow economic aspects to influence their judgments on the validity and strength of such data, they would be diverging from their real responsibility. The risk would be that the end result –

the guidelines created under such circumstances – might be interpreted by the health administration as a sign of our lack of confidence in the validity and strength of the data itself. That in turn will diminish the impact of the work of researchers and of the investigators involved in clinical trials. Conversely, maintaining the focus on the medical/scientific evaluation of new data will direct the health authorities in their deliberations on a proper allocation of funds for medical care. In particular, the inclusion of the magnitude of benefit of a tested therapy as a key criterion for its recommendation in Guidelines will aid these authorities in setting out priorities for allocating funds to new therapies or indications.

In conclusion, ESC Guidelines will continue to be produced with the primary aim of assessing the quality of science and the strength of evidence of clinical studies. They are an important tool of communication between European cardiologists and healthcare providers that will eventually decide on the 'affordability' of novel therapies in the individual countries. It is in fact the responsibility of health care authorities in the member states to put guidelines in the economic context of a specific healthcare system and to decide which therapies and which investigations will be reimbursed in each individual country.

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