Editorial

Problems Related to the Application of Guidelines in Clinical Practice: A Critical Analysis

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"Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house". Henri Poincaré, Science and Hypothesis (1905) ch. 9.

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Even though the use of guidelines in the treatment of patients has led to a reduction of cardiovascular events in comparison with patients where guidelines were not applied, as a rule guidelines are not widely used in clinical practice.[1,2] But why does this happen? Is it the result of physicians' non-compliance because of a lack of knowledge, or are the guidelines themselves difficult to apply?[3]

Guidelines have certain advantages, but also serious disadvantages, of which the physician should be well aware.[4,5] Here, we summarise the pros and cons of guidelines and suggest ways in which they could be improved.

The pros of guidelines

Some randomised prospective trials are able to provide data concerning the survival of groups of patients that have small differences among them, which clinical physicians are unable to distinguish, no matter how careful they may be or how systematically they follow up their patients. This is because a very large number of patients is required for such small differences to appear. A typical example is the CAST trial (cardiac arrhythmia suppression trial),[6] which showed that, while treatment with antiarrhythmic drugs reduced the incidence of arrhythmias in patients who had recovered from a myocardial infarction, the rate of sudden cardiac death was increased. These data are naturally included in the guidelines and are of great help to the clinical physician.

Guidelines are also very useful in the case of homogeneous populations, such as the recommendation for preventive vaccination—mainly in children but also other age groups—preventive colonoscopy, preventive monitoring of cholesterol, serum glucose, etc.

The cons of guidelines

Problems related to prospective trials

One of the problems of guidelines is related to randomised or non-randomised trials, which usually study homogeneous populations, whereas in daily clinical practice the patients are as a general rule inhomogeneous.

In the SOLVD trial (Studies of Left Ventricular Dysfunction),[7] patients with a left ventricular ejection fraction >35%, aged >79 years, or with serum creatinine >2 mg/dl, were excluded from the study. In clinical practice, however, patients with heart failure often have those characteristics. Moreover, in the COURAGE trial (Clinical Outcomes Utilizing Revascular-

ization and Aggressive Drug Evaluation),[8] of an initial population of 35,539 patients who were evaluated for enrolment in the study 32,468 were excluded for various reasons, while of the 3071 patients who fulfilled the study criteria only 2287 were finally included: i.e. only 6.3% of the original number took part in this trial.

Thus, randomised trials aim to answer only a very specific question that concerns a clearly predefined cohort.[9] In consequence, they must be directed at a specific population. In daily clinical practice, however, patients rarely have only the characteristics of those who were enrolled in trials. How should we treat the patient who has 3 or 4 diseases at the same time, e.g. coronary artery disease, kidney failure, diabetes mellitus and respiratory failure?[10]

Barry Greenberg, Associate Editor of the Journal of the American College of Cardiology, likens the population that participates in randomised trials and the guidelines to muzak, namely monotonous background music that is usually played in elevators or through telephones on "hold". Clinical practice, in contrast, is more like the music of Mozart, which has a large variety and a wide scale of musical notes, since the patients seen in everyday clinical practice represent a wide spectrum of cases from the very mild to the very severe, and from the very simple to the very complex with multiple problems.[4] Since one cannot compose Mozart's music starting from muzak, it is also difficult to apply the results of trials, which come from the study of a homogenous group of patients, to patients with various and complex conditions.

Another disadvantage is the fact that in randomised trials it is not usually taken into account that clinical practice often includes the coadministration of drugs, one of which could alter the effect of the other. The coadministration of clopidogrel, for example, with proton pump inhibitors in patients with an acute ischaemic syndrome or after stenting, could reduce the effect of clopidogrel, resulting in an increase in cardiovascular events in these patients.[11]

In many cases the guidelines are based on trials where the initial analysis was followed by subgroup analyses of different sub-populations, or a meta-analysis.[12] These multiple analyses, however, have the potential to change the findings of a study and lead to conclusions that, while being statistically significant, are without clinical value. In the ISIS study (International Study of Infarct Survival),[13] subgroup analysis showed that the effect of aspirin differed according to the patients' zodiac sign.

In addition, a study with negative results has much less chance of being published than one with positive results – especially if the studies are funded by the biomedical industry, which is often the case (around 60% of studies).[14] For this reason, many studies with negative results are not included in the meta-analyses, so that the findings of the latter do not represent reality. Also, meta-analyses may include inhomogeneous studies, so that the final conclusion again may not be representative of reality. The problem is even bigger when the initial studies were performed at different times and the alternative treatment, apart from that being subjected to the meta-analysis, is different.

The results of randomised trials, in an attempt to create the maximum impression, are usually presented as a percentage (%) reduction in mortality or other events. In these cases, however, a small absolute difference may appear to be a large percentage.[15] In a prospective study of aspirin, for example, which involved apparently healthy doctors, the incidence of myocardial infarction in those taking aspirin was less than in those taking placebo. The absolute difference was less than 1%, but this was presented as a 47% reduction in events. This can give the erroneous impression that the beneficial effect of a therapeutic intervention is much larger than it is in reality. If, for example, the mortality with a treatment is 0.5% and with placebo 1%, the absolute difference of 0.5% is presented as $1 - 0.5 \times 100 = 50\%$ reduction in mortality.

Problems related to committees and the writing of guidelines

Guidelines, naturally, are drawn up by various committees. In many cases, where there is no evidence from randomised trials, recommendations are based to a large extent on the opinions of those who make up the committee. Thus, for example, of a total of 2711 recommendations, in only 50% were there data from trials, while 48% were based mainly on the opinions of the individuals who participated in the committees.[16] It is, then, apparent that the opinion of committee members is of material importance.

There are, however, some problems with regard to the process followed for recruiting the members of these committees, for which there are no clear instructions.[17] Individuals who participate in guideline committees are usually people with seats on the boards of scientific societies, who have many demands on their time, who travel a lot, and who there-

fore do not have the time to deal with patients on a continuous, everyday basis and to acquire or maintain the necessary clinical experience that many of them, unfortunately, nevertheless believe that they possess. Thus, individuals who do not sit on committees in many cases have greater experience than those who do.

Committee members, as determined today, because of the administrative posts they occupy in scientific societies, have – and should have – close relationships with the biomedical industry. This, however, is a serious disadvantage, because such a relationship might potentially influence the recommendations and guidelines, even if subconsciously.

Guidelines are usually presented very analytically, in great detail, with the result that someone who studies them may not be in a position to discern their ultimate or principal message; this makes it very hard for the clinical physician to use them. The summary guidelines, or "pocket guidelines", help to some extent but do not solve the problem. Also, the guidelines in their current form are designed solely for memorisation, rather than for stimulating the critical capability and the curiosity of the thoughtful physician. In the final analysis, guidelines are difficult to read and assimilate.

Because of the procedures required to produce guidelines, they tend to be published years after the end of a clinical trial, this is also a serious disadvantage.[17,18]

Guidelines do not take clinical experience into account and may inhibit the physician's critical capability

There are hundreds of guidelines; however, there is no mention of how they should be applied in clinical practice, in combination with a physician's clinical experience, in the case of a specific patient. Guidelines are presented in a way reminiscent of a duty sergeant's order to a private and tend to quash the physician's autonomy. Physicians who are concerned for their patients, having experience and knowledge of pathophysiology and taking account of the guidelines, may arrive at a different therapeutic regimen in each individual case. The guidelines take no account of the experience of the clinical physician. Clinical experience is only acquired by carefully following countless patients continuously over many years.[19-21] On certain occasions, the physician, on the basis of long experience, may act instinctively. It is analogous to the "Eureka!" phenomenon described by Archimedes. Unfortunately, experience can neither be taught nor studied, but is acquired with the passage of years; since it cannot be written down, the guidelines almost ignore it.

There are, however, examples where the physician's clinical experience plays a crucial role. It has been observed, for example, that in some randomised trials, after randomisation to one or another group, some patients decided not to take part in the trial and left the final decision as to which therapy they would receive to their treating physician. After the end of the trial it was found that the patients who followed their physician's recommendation had a better outcome than those who ultimately took part in the trial.[22,23]

In the MASS II trial (Medicine, Angioplasty or Surgery Study)[24] two cardiologists determined their preference regarding the treatment patients should receive, prior to their randomisation to percutaneous or surgical myocardial reperfusion. Patients who were randomised to the treatment favoured by the cardiologists had fewer cardiovascular events than those whose received treatment different to the cardiologists' preference.

The wide implementation of guidelines, as defined today, will result in the inhibition of the physician's critical capability, which is developed and maintained over time by solving clinical problems on a daily basis. That will have sad consequences in the future.

Guidelines limit personalised medicine

In biology variety is the rule and not the exception (Figure 1). This variety is difficult or even impossible to record in guidelines. Only the treating physician is in a position to determine the peculiarities of a patient and to apply the appropriate treatment. The view that all patients with the same disease are the same is not only wrong, but against nature. Guidelines are directed at the disease and not at the specific patient.[25]

The guidelines reflect the view that one size fits all; this is obviously not correct. The response to a drug, as mentioned above, also depends upon the genetic substrate. Nor do the guidelines take account of drug interactions, the patient's compliance with therapy, and many other factors. There is a trend nowadays towards personalised medicine, which in the near future will be widely used in clinical practice.[26] Here the guidelines take us at least one step backwards, and not forwards.

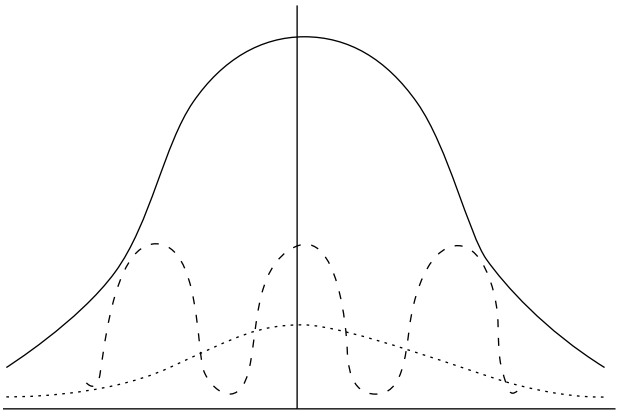

Figure 1. In biology, variety is the rule and not the exception. The large bell curve represents the total number of patients with a particular disease. The small bell curves it contains represent different subgroups of patients with the same disease. It is apparent that each subgroup differs significantly from the others (from reference 19).

Proposals

Guidelines should be aimed at the thoughtful physician, rather than someone who just obeys orders, leaving scope for sufficient autonomy and flexibility.

Today more than ever, there is a need for physicians to be trained, not in guidelines, but in basic pathophysiological and molecular mechanisms. Starting from undergraduate level, the Student of Medicine should be coached in judgement and not memorisation.[20,27] Memorisation is passive, while judgement is active. The physician must know how a drug acts on the pathophysiological and molecular mechanisms that have been disturbed. With this knowledge of mechanisms and a complete understanding of them, the physician can arrive at conclusions and ideas that nobody before has ever reached or conceived of. From an understanding of only 30-40 basic mechanisms one can generate millions of combinations. The memorisation of, say, 100 guidelines is nothing more than 100 instructions, even if someone can remember them all. The time required for the memorisation of instructions, if used instead for the understanding of basic physiological mechanisms, which usually develops over time, will be much more useful and productive for the physician.

Guidelines should be simple and brief and should not be an alphabet soup—A, B, C, AI, AII, BI, BII, etc.[1,2] Instead of giving detailed instructions, it would be preferable to summarise interventions that increase survival or decrease the incidence of myocardial infarction or stroke in one or at most two pages. That would then leave room for them to be updated regularly, enhancing their practical value. In the case of chronic coronary artery disease, for example, it could be stated briefly that giving up smoking, administration of aspirin, beta-blockers, statins, and angiotensin-converting enzyme inhibitors, all increase survival after a myocardial infarction, while nitrates and calcium channel blockers control angina but do not increase survival. Since guidelines are based on randomised studies, it should be stressed that the results come from a homogeneous population and that the findings apply to such a population. The implementation of guidelines in individual cases depends on the judgement of the physician.

Meta-analyses, mainly of studies with inhomogeneous populations, such as the analysis of subgroups, should be avoided and as a rule should not be taken into consideration for guidelines. The results should be given in absolute values and not as percentage reductions in mortality, so as to avoid giving an erroneous impression.[15]

The committees that draw up the guidelines should be composed of physicians who have spent their professional career in one or at most two related fields and in consequence have extensive personal clinical experience therein. Physicians who conduct research in the field, and perhaps pharmacologists who fully understand the pharmacokinetics, pharmacodynamics and pharmacogenetics of specific drugs, should also participate in the committees.

It should not be possible for a physician to sit on more than two guideline committees, nor to be on more than two successive committees for the same guidelines. Individuals who participate in many guideline committees will not, as a general rule, have the time needed to examine and follow patients regularly and to gain the clinical experience required for the writing of guidelines.

Physicians who have some financial interest or other benefit associated with the products that will be included in guidelines should not sit on committees. Furthermore, those who do participate in the preparation of guidelines should not be allowed to give lectures on the relevant topic in return for honoraria, or to reap any other reward. The relationship of committees with the biomedical industry should be constructive and transparent. Committee members should be entirely free of influence during the guideline publication process, should not have any financial relationship with industry, and once they have

participated in a committee there should be a commitment not to develop such relationships in the immediate future.[28]

The various registries, in which all patients are recorded and followed on a daily basis, together with their treatment, provide data that are much more representative than those from randomised trials, where only a small proportion of patients are studied. If registries were to be more generalised, it would be possible for physicians to monitor on a daily basis which treatment was favoured by the majority of their colleagues for a given disease. In addition, it would be possible for each to compare him or herself with colleagues in the same region or internationally regarding how they manage a specific condition, thus having a stimulus for continual improvement.[29,30]

Since in biology variety is the rule and not the exception, guidelines should always include a *caveat* that, before their implementation in the clinic, an individualised analysis should be performed for each patient so that any individual peculiarities can be taken into account.[19,20,31,32]

The physician should not lose contact with patients and their special features for the sake of following guidelines (Figure 2); in other words, the physician must treat the patient and not the guidelines.[20] Guidelines provide another element to help the physician make a decision, but should not be given any more weight than the evidence arising from a basic paraclinical examination.

Good physicians base their clinical practice on their experience, as well as on scientific knowledge and specific technologies (Figure 3). Both clinical experience and science undergo constant development (*Τά Πάντα ῥεῖ* – everything flows). Physicians who have concern for their patients are always adapting

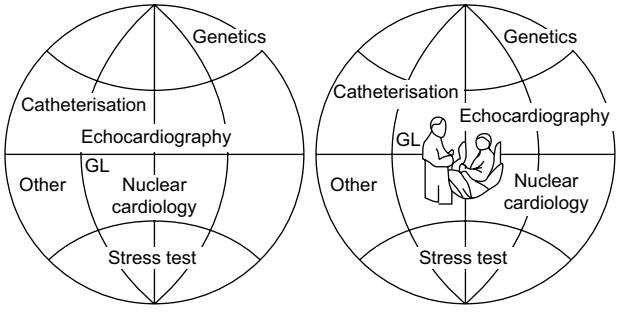

Figure 2. The physician must not lose contact with the patient and his or her individual peculiarities for the sake of paraclinical examinations and guidelines (GL). The patient should always be the focus of the physician's attention.

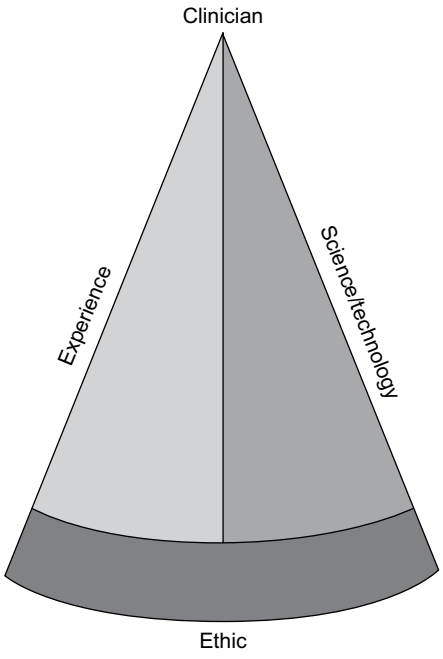

Figure 3. Good physicians base their clinical practice on experience, combined with scientific knowledge and technology, which must all be based on a solid ethical foundation (from reference 19).

these developments to the particular patient. Guidelines are nothing more than one small element on the side of the triangle that represents science and technology.[19] In medical practice, both science and technology – to which guidelines also belong, as do the selection and actions of the committees that draw them up – as well as the physician's clinical decision making, in order to serve the purpose they were intended to serve, must be based on a stable ethical foundation.[19,20,31]

Concluding remarks

There are multiple problems involved in the writing of guidelines and their implementation in clinical practice. For guidelines to be useful, they should be recommendations and not rules, leaving the treating physician with sufficient autonomy. Guidelines should be brief, and written in such as way as to be easily assimilated. It should be stressed that they apply to the disease and not to the patient, and should therefore not supersede individualised medicine. Physicians who participate in guidelines committees should have spent their professional career in one or at most two related fields, should not participate

in more than two such committees at one time, and should not serve on more than two successive committees. Their relationship with the biomedical industry should be absolutely transparent.

The problems associated with guidelines need to be stressed. The perfect balance between clinical experience, science and technology – in which guidelines are included – is an essential element in good medical practice and must have a solid ethical base.

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