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The Shortcomings of Clinical Practice Guidelines

Konstantinos Dean Boudoulas[a] Carl V. Leier[a] Paraschos Geleris[b]
Harisios Boudoulas[a, c]

[a]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio, USA; [b]Third University Department of Cardiology, Aristotle University of Thessaloniki, and [c]Aristotle University of Thessaloniki, Thessaloniki, Greece

Key Words
Clinical experience · Clinical practice guidelines · Randomized controlled studies · Relative risk reduction · Statistical significance

Abstract
Accumulation of medical knowledge related to diagnosis and management over the last 5–6 decades has altered the course of diseases, improved clinical outcomes and increased survival. Thus, it has become difficult for the practicing physician to evaluate the long-term effects of a particular therapy on survival of an individual patient. Further, the approach by each physician to an individual patient with the same disease is not always uniform. In an attempt to assist physicians in applying newly acquired knowledge to patients, clinical practice guidelines were introduced by various scientific societies. Guidelines assist in facilitating the translation of new research discoveries into clinical practice; however, despite the improvements over the years, there are still several issues related to guidelines that often appear 'lost in translation'. Guidelines are based on the results of randomized clinical trials, other nonrandomized studies, and expert opinion (i.e. the opinion of most members of the guideline committees). The merits and limitations of randomized clinical trials, guideline committees, and presentation of guidelines will be discussed. In addition, proposals to improve guidelines will be presented.

Introduction

> We shall not cease for exploration
> and the end of all of our exploring
> will be to arrive where we started
> and know the place for the first time
> *T.S. Eliot*

To practice medicine in most places of the world one must have appropriate training in a medical school, postgraduate training in an accredited program, take and pass all appropriate medical examinations, and obtain a medical license from the Medical Board. Until the recent past, the practice of medicine was mostly based on knowledge related to basic pathophysiologic mechanisms (i.e. how physiology is altered in a disease process), effects of pharmacologic agents on the human body, how drugs modify the underlying pathophysiology of disease, and the physi-

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E-Mail karger@karger.com
www.karger.com/crd

Harisios Boudoulas, MD
4185 Mumford Court
Columbus, OH 43220 (USA)
E-Mail boudoulas@bioacademy.gr

cian's mentored and clinical experience. The physician had full flexibility and autonomy to apply the knowledge and experience to the individual patient, and to be successful as a practitioner, he/she had to understand the basic mechanisms of disease and the basic principles of clinical pharmacology, and then apply the knowledge and experience to the individual patient [1, 2].

However, the accumulation of knowledge related to diagnostic and therapeutic interventions over the last 5–6 decades has increased dramatically. Thus, it has become apparent that even for the scholar who is dealing with one major illness or disease, it is considerably more difficult to follow all the rapidly evolving information of even this narrow focus. In addition, the development in medicine in many instances itself has altered the natural course of disease, improving clinical outcomes and survival, making it even more difficult for the physician to keep up with the evolving and modified information. It has, therefore, become rather difficult for one individual physician to evaluate the long-term effects of a particular treatment or intervention on 'hard' endpoints such as death, myocardial infarction, stroke, and others. Not surprisingly, the approach by each physician to an individual patient with the same disease is often not uniform, although generally similar. In an attempt to assist physicians in applying more uniform care and render new knowledge to the care of each individual patient and, thus, improve their clinical outcomes, practice guidelines were introduced by scientific societies as a means of 'standardizing' management [3–5].

In 1984, the first set of clinical practice guidelines was published by the American College of Cardiology (ACC)/American Heart Association (AHA) in response to the United States Government's request to review evidence concerning the use of cardiac pacemakers. Over 30 years, the ACC/AHA has developed over 30 clinical practice guidelines for various conditions and procedures with 'updates' and additional modifications at intervals [3]. One can consider the guidelines as a part of a continuous education program introduced to facilitate a more homogeneous approach to all patients with the same disease in order to reduce inappropriate and redundant testing, curb the use of ineffective therapies, decrease costs and eventually improve outcomes.

In 2011, The Institute of Medicine redefined clinical practice guidelines as follows, 'Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options' [3]. The guidelines, however, have gradually shifted the emphasis from the individual patient with a specific disease and the therapy for a sick individual to that of a sick population when, in fact, biological variability and individual differences are the rule rather than the exception. The focus has been shifted from pathophysiology and the understanding of basic disease mechanisms, a foundation on which all subsequent knowledge should be based, to memorizing fast-changing facts and outcomes for populations as well as guidelines for population care. Stated in another way, the memorization of these guidelines 'does not make a physician, but rather a practicing or applied epidemiologist, and population approaches certainly do not provide many of the tools needed by a physician in managing the individual, particularly a complicated patient [6–9].

Guidelines assist in facilitating the translation of new research discoveries into clinical practice; despite the improvements over the years, however, there are still several major issues related to the guidelines, and their clinical applications often appear 'lost in translation' [10].

Guidelines are based on the results of controlled, randomized, clinical trials (RCTs); less involved studies, and 'expert opinion' (i.e. the opinion of most members of the guideline committees; fig. 1) [3, 10]. The merits and limitations of RCTs as performed today, issues related to guideline committees, and the presentation of guidelines will be discussed. Our proposals for guideline improvement will then be presented.

Randomized Clinical Trials

Please! Try an experiment on your servants
for ten days have them give us only vegetables to
eat and water to drink.
Then see how we look,
and compare us with how the boys who eat
the king's food look;
and deal with your servants according to what you see.
Daniels 1:12-1

The clinical trial concept goes back to antiquity. In short, for a RCT, a hypothesis is generated, and based on the hypothesis (typically, a null hypothesis) the study protocol is designed by a committee of experts in the area under study (fig. 1). For the execution of a trial, an overall organization and financial support are needed, and for large clinical trials, the financial requirement can be quite impressive [11–19].

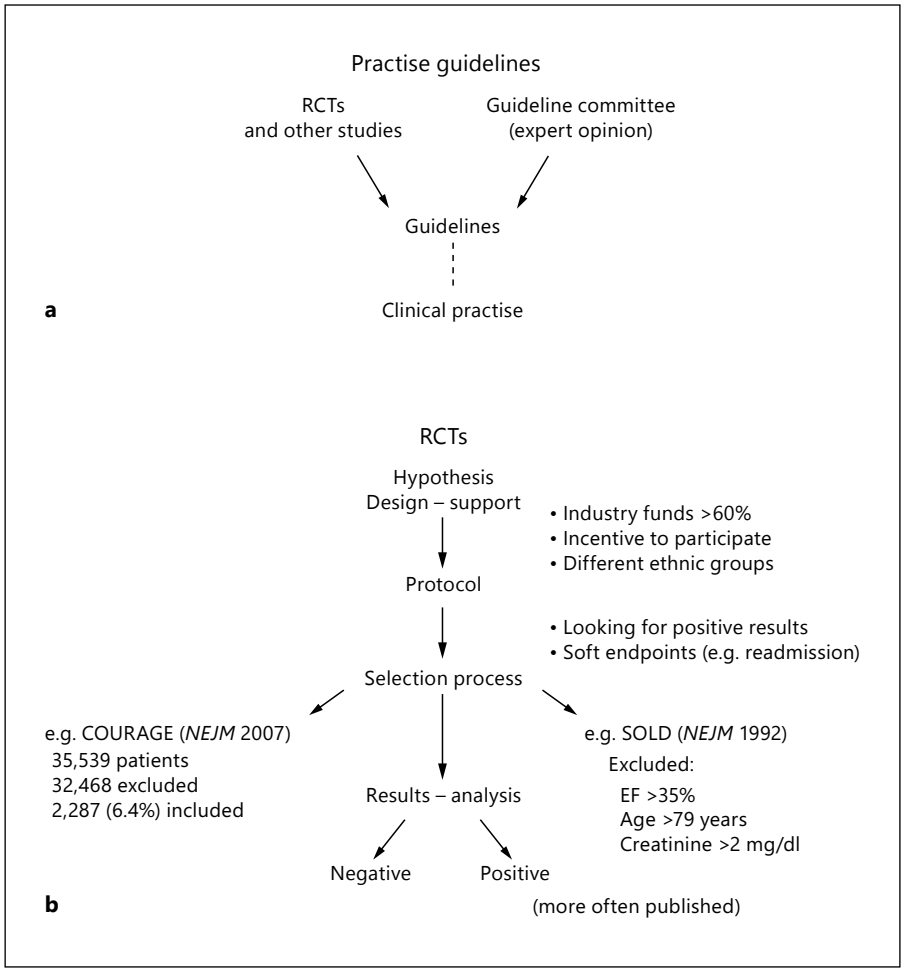

Fig. 1. a Members of the guideline committee using data from RCTs/non-RCTs produced the guideline documents. In the written guidelines, there is limited or no information on how to apply the guidelines to the individual patient (dotted line). **b** Schematic presentation showing how a RCT is typically conducted. EF = Ejection fraction; NEJM = *New England Journal of Medicine*.

Merits

The established standard for hard evidence of clinical effectiveness of a procedure or intervention is the blinded, randomized, multicenter controlled trial. Blinded randomization to a control group (placebo or proven effective agent) or to the intervention group under investigation in a multicenter format is the optimal means to generate hard data with the least bias on effectiveness and the adverse effects of a diagnostic or therapeutic intervention. The multicenter format reduces the isolated single center partiality and institutional bias. In general, the population under study is well defined [17–19].

Limitations

Financial Support

The greatest proportion of support for trials comes from the industry. Support from the industry is essential and without their support many important studies would never have been performed. However, industry has a vested interest; companies want to prove that their product is better than an approved agent or placebo and, thus, lean heavily toward 'positive' results. It is known that the way a protocol is designed may affect the results. For example, making an active control drug appear relatively unfavorable by selecting the wrong dosage of this agent is rather commonplace. Thus, it follows that industry involvement in clinical trials is associated with the risk of bias [17–25].

Patient Population

The blinded, randomized, multicenter, controlled trial is the ideal study to perform. But certain diseases and populations do not lend themselves easily to this format and, thus, studies with less stringent design and enrollment criteria are often employed. Needless to say, the risk for less reliable data, more distinct subgroups, and misinterpretation of results is higher than for the former model [26–29].

In order for the population to be more homogeneous, stricter inclusion criteria are often used, and this maneuver necessarily excludes many of the patients encountered in real-life practices. For example, in SOLVD (Studies of Left Ventricular Dysfunction), which involved patients with left-ventricular systolic dysfunction and heart failure, those with left-ventricular ejection fraction greater than 35%, serum creatinine higher than 2 mg/dl, and age older than 79 years were excluded. But many patients with heart failure (>50%) do not have these characteristics, and, thus, data from that trial cannot be applied to patients who do not meet the rigorous inclusion criteria [18]. Similarly, in COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), 35,359 patients were evaluated, but only 2,287 (<7%) were included in the final study. Thus, highly selected patients were included in the trial and data cannot be applied to all patients (as many as ≥90%) with the same disease [30]. Dr. Barry Greenberg, a former associate editor of the *Journal of the American College of Cardiology*, compares trials to muzak (i.e. monotonous background music that is usually played in elevators or through telephones on hold); however, clinical practice is more like music of Mozart, which has a large variety of musical notes. Patients seen in everyday clinical practice represent a wide spectrum of cases from mild to severe, from acute to chronic, and from simple to very complicated with multiple medical problems. As one cannot compose Mozart's music from muzak, likewise it is difficult to apply the results from select homogeneous populations in trials to complicated patients with complex diseases [4]. Thus, the merits and strength of a RCT, which make it possible to test the effect of only one intervention (diagnostic or therapeutic) on the outcomes of a disease in a homogeneous population (restricted by definition), often become its inherent limitation. A recent report by the US Department of Health and Human Services/AHA/ACC is making an initial attempt to address this concept (the complex patient with comorbidities) [31].

Surrogate endpoints for various outcomes have now shown their limitations and unreliability. CAST (Cardiac Arrhythmia Suppression Trial) is one of the examples in which therapy with anti-arrhythmic drugs in postmyocardial infarction patients with cardiac arrhythmia reduced the frequency of ventricular ectopy, but increased the incidence of sudden cardiac death [17]. Other examples include acute hemodynamic measurements in heart failure to guide therapies and formal lipid parameters to prevent the expression and outcomes of atherosclerotic cardiovascular disease.

In order to include more patients in a study, incentives including monetary or related inducements can be involved, which may result in patient selection bias. A study may also include patients from various ethnic groups; differences in ethnicity may alter the effect of pharmacologic agents via underlying physiologic mechanisms, pharmacokinetics, or different effects at the receptor level (pharmacodynamics) [28, 29].

Withheld Information

After completion of a study and analysis of its data, the results could be negative (outcomes related to an intervention are worse than control), unchanged or the same as control ('noninferiority'), or positive (better results than control). Studies with negative results are often not published at several decision levels for various reasons, but, generally, the medical industry does not want to release negative information related to its product(s). It is well established now that investigators, journal reviewers, and publishers are less enthusiastic to publish a study with unremarkable or negative results [32, 33]. Thus, studies supported by the industry demonstrate positive results in more than 80% of published articles compared to the published reports funded by federal services in which positive results were reported approximately 50% of the time, perhaps a number closer to reality [32]. In other instances and for a variety of reasons (e.g. lack of support or if preliminary data do not appear promising), a study can be discontinued prior to its completion [34, 35]; the results of this incomplete study are often not published, and the scientific community is not aware that such a study was even conducted. In other instances, the pharmaceutical companies do not provide all the data available from a study or trial. For example, there is evidence to suggest that if the plasma levels for dabigatran (Pradaxa) were measured and the dose of the drug was adjusted according to blood levels, major bleeding could be reduced substantially. The pharmaceutical company, however, withheld this information and the approval of the drug was based on the theme that a fixed dose of dabigatran was sufficient and the need to monitor drug plasma levels was not necessary; available information perhaps suggests otherwise [36, 37].

Practice guidelines are based only on published information and, thus, evidence-based medicine is, at best, based only on some of the evidence [38, 39]. Several attempts to force the medical industry to publish all the available information to date have been unsuccessful [40–42]. This creates a huge problem since our gold standard (i.e. controlled RCTs) is often inadequate to generate a guide-

line recommendation at a level of evidence A. More recently, certain pharmaceutical companies have started to provide the requested data with some restriction to the scientific community and to the public. This obviously is a step in the right direction, but even if this approach is started today from the entire medical industry, it would take a substantial amount of time to evaluate and assimilate the accumulated information and thus, would not likely influence the practice of medicine in the foreseeable future [43].

A study with negative results does not necessarily mean that the intervention is ineffective. The smaller the effect of therapy is on the reduction of events, the larger the number of patients needed for study and/or the longer the intervention time necessary to prove efficacy. For example, in the ISIS 2 (Second International Study of Infarct Survival) [19], 17,187 patients with suspected acute myocardial infarction were analyzed; however, if only 1,700 had been studied, the study would have turned out to be negative. In contrast, the larger the difference between the intervention and the control in preventing adverse events, the smaller the number of patients needed to be studied to prove efficacy (fig. 2a).

On occasion, a trial loses its impact during its performance. It is not uncommon for a large, well-designed pharmacologic or surgical trial to become 'outdated' during the course of its performance because of new clinical developments that have altered the patient population under study or made the intervention relatively irrelevant [44]. The results of the DIG trial, performed before patients with heart failure were treated with β-blockers, may have little relevance today except for the few patients with heart failure not receiving or tolerating β-blockers.

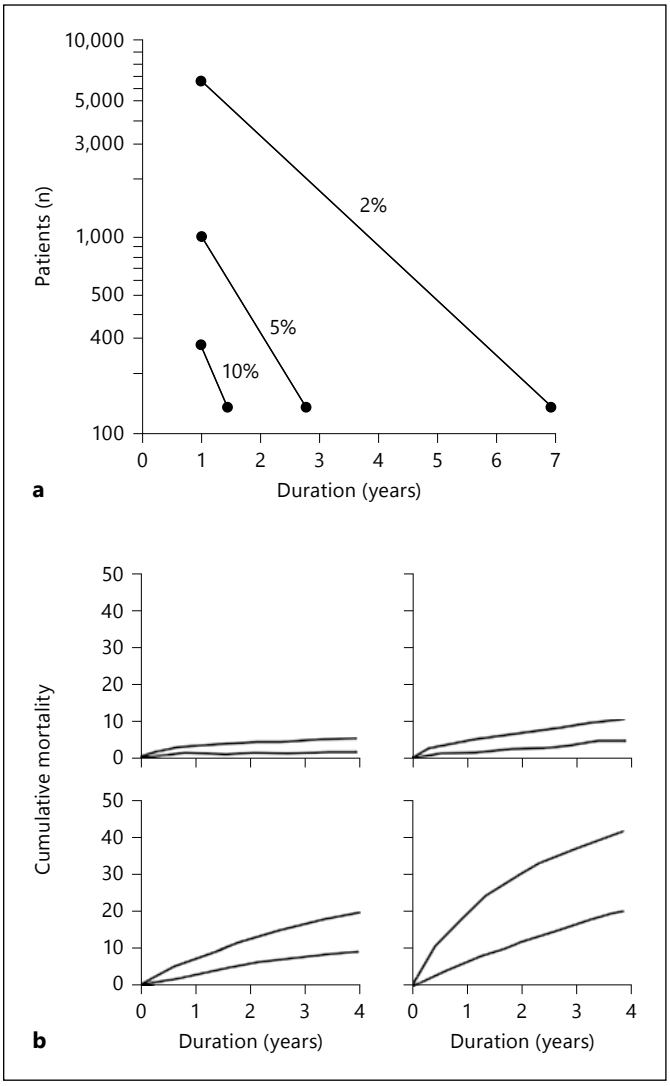

Fig. 2. a When the difference between two groups is small, larger numbers of patients and longer follow-ups are needed for the results to be statistically significant. The number of patients needed to be studied (vertical axis) and the duration of follow-up (horizontal axis) in order to demonstrate a statistically significant difference between groups are shown schematically; note that much larger numbers of patients and longer follow-ups are required when the difference between two groups is small (e.g. 2 vs. 10%) [51]. **b** The absolute and relative percent reduction in mortality in RCTs in relation to control is shown schematically; note that 2, 6, 8 and 20% difference in absolute mortality can all be expressed as 50% relative reduction in mortality [51].

Publication and Presentation of the Data

The results of RCTs are usually published in high-impact journals. The results are also made available on a public clinical trial registry (ClinicalTrials.gov).

Almost all reports had at least one substantial discrepancy between these two publications (i.e. medical journal and clinical trial registry), including the discrepancy in primary endpoints; these discrepancies in certain instances can lead to ambiguity [45, 46]. The way results are presented may also give false impressions. Results from clinical trials are typically reported in tables or illustrations/figures showing the differences between the two groups, often based on analytic methods introduced by Berkson [47], Kaplan and Meier [48], and Mantel and Haenszel [47–49]. More recently, a novel and now seemingly popular measure of the difference between treatment and control groups has been used; it is now most commonly referred to as percent risk reduction and has been termed percent reduction in mortality or relative event reduction [50]. The percent risk reduction, however, reflects the relative frequency of events between the treatment groups rather than their absolute difference. In

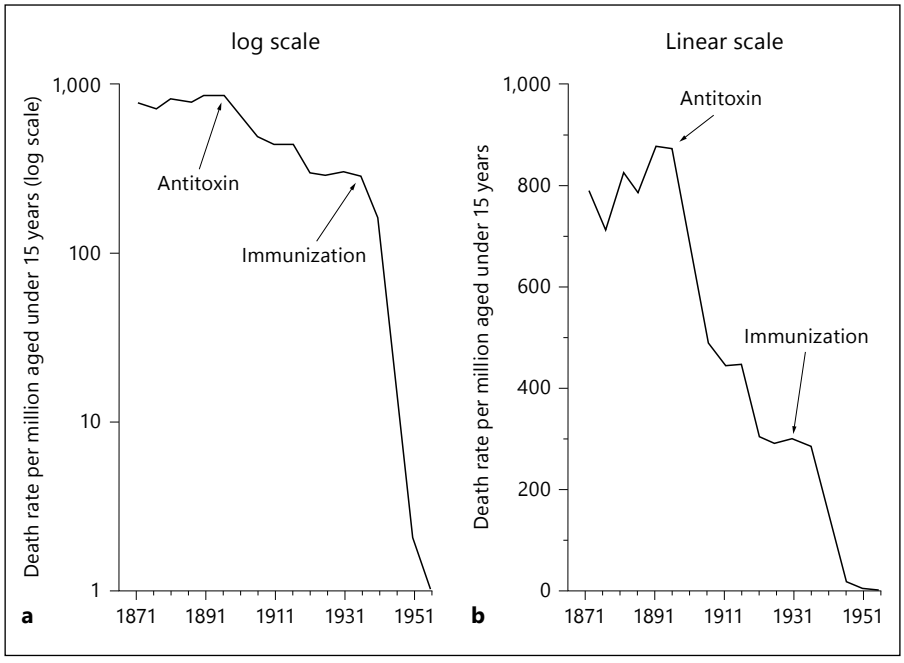

Fig. 3. Statistics and ethics in medical research: childhood mortality from diphtheria from 1871 to 1971 on a logarithmic scale (**a**) and a linear scale (**b**). It can be seen that the visual effect and the interpretation are quite different. It is obvious on the linear scale that the mortality from diphtheria had started to decline well before immunization, but in the logarithmic scale the deep drop appeared to occur with immunization [52].

paired groups of equal size, the same 50% relative risk reduction could be reported for such widely varying event differences (absolute) between treatment and control groups as 0.1 versus 0.2, 1 versus 2, 2 versus 4, 6 versus 12, 8 versus 16, 20 versus 40, and so forth (fig. 2b) [51]. Without reference to the absolute event incidence in the control group, the clinical impact and significance of such a 50% relative reduction in risk cannot be appreciated. When the absolute difference in events is not provided and when quoted out of context, one can have an inflated view of an effect, even when there is a relatively minor difference in events (e.g. 0.1 vs. 0.2). Thus, there are clear limitations in the reporting of percent or relative risk reduction. It seems that the popularity of reporting the percent or relative reduction lies simply in the appeal of a higher percentage value (a percent relative risk reduction of 50% vs. a 0.1% reduction in absolute terms). When applied in such a way in professional journals or in the public media, it is simply designed to promote immediate application of clinical trial results. The deviation from the basic data that are reported in the form of the percent or relative risk reduction, particularly when quoted out of context, can lead to obfuscation of results [50].

Visual display is a particularly effective way of presenting results. Figure 3 shows mortality from diphtheria from 1871 to 1971 on a logarithmic scale (fig. 3a) and on a linear scale (fig. 3b) [52]. It can be seen that the visual effect and the resulting impression are quite different. It is obvious that over the period of 1871–1971 mortality from diphtheria had started to decline well before immunization (reality), but in the logarithmic scale the deep drop occurred with immunization. The authors, in many instances, will often choose the visual display that best fits its intended purpose and renders a particular impression.

Subgroup Analyses and Meta-Analyses

In certain instances, subgroup (post hoc) analyses or meta-analyses are performed. After the completion of the parent trial, a subgroup analyses without a previous determination statistically may be incorrect, and the results of such an analysis may be not valid. In the ISIS 2 study [19], the effect of aspirin on reducing mortality during an acute myocardial infarction was found to be related to the zodiac of the patient in a post hoc subgroup analysis. Thus, in certain instances, subgroup analysis may lead to erroneous conclusions and should be viewed only as 'hypothesis generating' [53, 54].

As mentioned previously, a study with negative results has much less of a chance to be published compared to one with positive results, especially if the study was funded by the industry. As a result, studies with negative data may not be included in a meta-analysis. The inaccuracy is even greater when studies were performed at different time periods, particularly if different therapeutic modalities were available and used to manage the studied population (different background medications or procedures) [10, 32].

Information Does Not Provide Insights into Pathophysiologic Mechanisms

In trials, the effect of a single molecule (i.e. study medication) in a disease process is studied. Thus, despite all the efforts and the large costs to perform these trials, the information obtained usually does not provide insights into the basic mechanisms of a disease. Information from trials tells us what happened (the final event) and little information on why it happened [1, 2, 10].

Proposal to Facilitate Translation of RCT Results and Registry Data into Clinical Practice

In order for the results of trials to be applicable to a larger patient population, the exclusion criteria should be minimized. Good examples are GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) and ISIS 2, where all patients with suspected acute myocardial infarction were included [16, 19]. Since differences in the effect of pharmacologic agents may exist between different ethnic groups, only patients with the same ethnic origin should be included in a particular study [28, 29]. All trials that have been discontinued during the course of study and/or studies with negative results should be published [32]. For now, hard endpoints (e.g. death, myocardial infarction, and stroke) should be emphasized with less attention rendered to softer endpoints (e.g. readmission and quality of life) or surrogate data (e.g. cholesterol reduction and blood pressure levels) [10, 32].

The results of blinded, well-controlled RCTs are quite evident with the direct expression of results on the primary endpoint events. As noted, stretching the basic data as percent or relative risk reduction, when quoted out of context, can lead to misrepresentation of these results. If the reporting of relative risk reduction is to be continued, the data must be accompanied by confidence limits and the absolute values, and presented only in the appropriate context of the event. This practice should be the rule in all published academic and educational documents and, finally, in commercial advertisements delivered to physicians, medical staff, and the general population. It is time to tighten our clinical reporting standards. To avoid additional erroneous conclusions, subgroup analyses or meta-analyses should be limited only to generating hypotheses [10, 50, 51, 53, 55].

Clinical data are also available from well-conducted patient registries like the ACC catheterization laboratory registry. With electronic medical records that are widely available worldwide, registries that include real-life scenarios can readily be reported and accessed. Further, differences between drugs of the same group of pharmacologic agents can be compared (e.g. one particular statin or angiotensin-converting enzyme inhibitor vs. another). The choice for each treatment obviously would be the preference of the physician who is taking care of the patient. However, since randomization of treatment to placebo is not involved, registries are at greater risk for physician and center bias, and, if funded or promoted by the industry, the registry can inappropriately influence (encourage) the monitoring and administration of a particular drug [56, 57].

Writing Committees for Guidelines

Merits

The committees responsible for writing the guidelines consist mostly of academic members of major scientific societies of the United States of America and/or Europe (fig. 1). They are typically world leaders in their field and usually know the major current and future projects of the medical industry and of government-sponsored programs. Occasionally, members of a committee are individuals from several countries offering diversity of opinion and awareness of the problems facing each nation. It is of great importance that most committee members have actual clinical experience in the field under review.

Limitations

It is not uncommon that individuals of the guideline committees, in addition to their activities related to scientific societies, have other professional responsibilities in their institution/university, such as teaching, research, clinical/committee work, and administrative and other activities. In other words, they are extremely busy individuals. Due to the nature of their academic position, these individuals are often found traveling on professional trips and often have close relationships with the industry (pharmaceutical and/or devices) leading to the potential for conflicts of interest when working with guideline documents. According to some reports, more than 80% of the guideline committee members have some financial association with the medical industry, including travel funding, speaker honoraria, educational program support, research support, consultant service, and equity. Furthermore, members of the guideline committee may be associated with multiple medical industries [10, 32, 58–61]. This close association with the industry may subconsciously affect decisions when providing expert opinions in guideline documents. Reveal-

ing and listing one's relationship with industry is an effort to mitigate this problem, but does not come close to solving it.

Unfortunately, due to the great demand of their time to numerous other responsibilities, many committee members may have limited time to deal with the direct patient care needed to acquire and/or maintain clinical experience and clinical expertise absolutely necessary to provide an 'expert opinion' in the guidelines. Being an excellent, up-to-date clinician is a continuous day-to-day, week-to-week, month-to-month, and year-to-year process [1, 2, 10].

Proposal for Improvement of Guideline Committees

Committees must include a variety of qualified participants. While primary scholars generally known as 'academicians' are probably important, physicians with extensive clinical experience in areas under review must be included in the committees. Pharmacologists and basic researchers that are most familiar with the latest developments in a certain area and understand the pharmacokinetics and pharmacodynamics of pharmacologic agents should also be included in the committees. To avoid overextending certain individuals and to facilitate the selection of available experts with extensive clinical experience, no individual should simultaneously serve on more than two guideline committees. Individuals with a financial relationship to the medical industry with a product under review should be excluded. Members of guideline committees should not give lectures related to their guideline topic, especially if a honorarium is provided by the industry. Finally, the number of members of a committee should not exceed six or seven, thus allowing each member to assume more responsibility and depth rather than spreading the same responsibility among twenty or thirty members.

Written Guidelines

> Education with inert ideas is not only useless;
> it is above all things harmful
> (Dialogues 1954)
> *A.N. Whitehead*

Merits

The merits of guidelines are directly linked to the merits and prowess of well-controlled, RCTs and the committee generating the guidelines. Thus, even a small difference in survival or other hard endpoints (e.g. stroke or myocardial infarction) due to a therapeutic intervention can be incorporated into the guideline documents. Guidelines are also extremely useful in the assessment of preventive measures, such as vaccination, colonoscopy, and mammography. Furthermore, guidelines generally provide focused and concentrated information on one condition or intervention with an extensive supporting bibliography.

Limitations

Limitations of guidelines are directly related to the limitations of controlled RCTs and available credible studies, the interpretation of these data, and the structure of the guideline committees as mentioned above. Further, it is not known if results of a well-conducted, RCT obtained 10–20 years ago are applicable today. For example, there are no studies today to indicate that therapy with β-adrenergic blocking agents are effective in postmyocardial infarction patients with normal left-ventricular systolic function in the era of percutaneous coronary intervention; most of the studies were conducted prior to the myocardial reperfusion era. The same is true for studies comparing medical versus percutaneous coronary intervention versus coronary bypass surgery in patients with stable coronary artery disease [55]. Further, it is not clear what to do with trials that are internally inconsistent and have two large subsets with positive and negative results. Such disparities have occurred in trials where major differences in the results were noted for the American and European populations.

Written Guideline Documents

The members of the committee produce the written guideline documents based on the publications of RCTs, other studies, and their own experience under the heading of expert opinion. The guidelines are based on the class of recommendation (I, II, and III) and the level of evidence (A, B, and C) as follows: class I – strong evidence that the benefit of the treatment or procedure is much greater than the risk; class IIa – moderate evidence that the treatment or procedure is useful and that the benefit is greater than the risk; class IIb – the treatment or procedure may be useful and that the benefit may be equal or greater to the risk, and class III – the treatment or procedure may not be useful and may be harmful; A – information obtained from more than one high-quality RCT or valid meta-analyses of all available data from high-quality RCTs; B-randomized – information obtained from one or more moderate-quality RCT or meta-analyses of available data from moderate-quality

Practice guidelines	
Level of evidence	
A	More than one high-quality RTC or meta-analyses of high-quality RCTs
B-R	One or more moderate quality RCT or meta-analyses of moderate-quality RCTs
B-NR	One or more nonrandomized studies or meta-analyses of such studies
C	Expert opinion, case studies or standard of care
Class	
I	Strong evidence; benefit >>> risk
IIa	Moderate evidence; benefit > risk
IIb	Effectiveness less well established
III	Treatment or procedure not useful: risk > benefit

Fig. 4. The presentation of guidelines is based on class and level of evidence [modified from ref. 3]. R = Randomized; NR = nonrandomized.

RCTs; B-nonrandomized – information obtained from one or more nonrandomized studies or meta-analyses of such studies, and C – expert opinion (fig. 4) [3]. Unfortunately, this type of presentation does not stimulate in-depth thinking and, in fact, consists of relatively inert thoughts and ideas [62]. Due to the nature of biology, complexity of the disease(s), the difficulty and often impossibility to properly control, and due to the fact that many studies are designed to test the effect of one molecule or drug in a complex disease/syndrome, such as coronary atherosclerosis and heart failure, approximately half of most guidelines are based on level C evidence (fig. 5). Available information indicates that reversal of expert opinion in the guidelines is not uncommon [63]. In addition, guidelines are often presented in great detail, making them difficult for the physician to efficiently unravel and apply to an individual patient. Further, extensive reviews are often required to generate the written guideline documents and, thus, it can take some time to render the guidelines after the completion of a well-performed clinical trial(s) [7, 64–67].

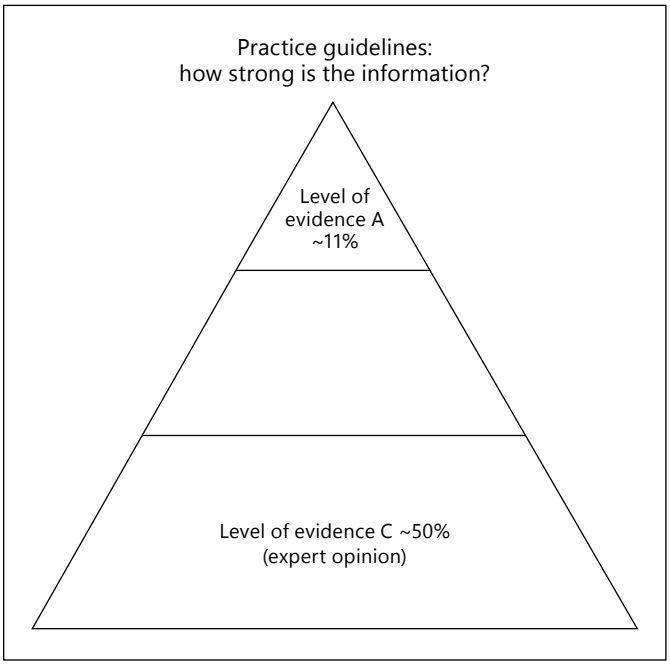

Fig. 5. Approximately 50% of the guidelines are based on level of evidence C (expert opinion) with only a small proportion based on level of evidence A (schematic presentation).

Guidelines Limit Personalized Medicine

Guidelines infrequently do not consider such important issues as family history, coexistent diseases, and many other relevant factors. Importantly, guidelines do not take the variability in patients and their diseases into consideration, which is the rule rather than the exception in biology. This variability is impossible to address in guidelines (fig. 6). Guidelines also do not reflect the variable effects of pharmacologic agents from patient to patient and the drug-drug interactions commonly seen in patients treated with multiple drugs. Thus, guidelines are directed at *populations* with a particular disease and *not at the individual* patient. Only the patient's physician is

Factors (n)	Probabilities ($2^n - 1$)
5	31
10	1,023
20	1,048,575

Fig. 6. Mathematical formula showing how the combination of several basic pathophysiologic mechanisms can lead to millions of new ideas and conclusions.

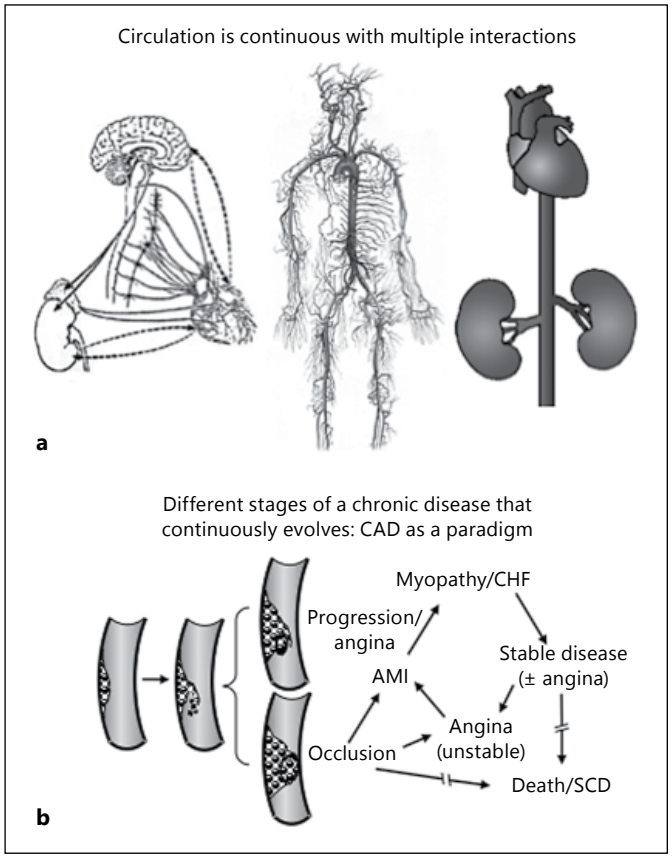

Fig. 7. a The guidelines do not take the continuity of the circulation and its multiple interactions (central nervous, cardiorenal, or other systems) into account. **b** In the guidelines, a continuously evolving disease [e.g. coronary artery disease (CAD)] with multiple clinical presentations is 'artificially' divided into multiple different stages. AMI = Acute myocardial infarction; CHF = congestive heart failure; SCD = sudden cardiac death.

in the position to determine the variability and multiple aspects of each patient and to apply the most appropriate treatment towards them. In an attempt to address this known variability, efforts have been made over the last couple of decades to develop 'personalized medicine'. Guidelines are counter to this effort and appear to be a step backwards. Strict adherence to guidelines without appropriate individual adjustment can be viewed as 'anti-personalized medicine' [1, 2, 6, 31, 68–71].

Lack of Incorporation of Clinical Experience

Guidelines cannot take the clinical experience of a particular physician into consideration. Clinical wisdom is acquired by carefully following countless patients over an extended time. One can acquire knowledge from others, but unfortunately one cannot acquire direct clinical experience or clinical wisdom from others. Clinical medicine also requires attention to details; attention not only to the sick human, multiple conditions, and the disease in question, but also to a patient's psyche, wishes, and preferences, which cannot be garnered from a written guideline document [1, 6].

Several studies have demonstrated the importance of the clinical experience of clinicians. After randomization of patients in studies related to percutaneous coronary artery revascularization, many patients decided against participation in the trial; the personal physician of those patients determined the final therapy (percutaneous coronary intervention or medical management) and the outcome of those patients were better compared to patients who participated in the trial [72]. In MASS II (Medical, Angioplasty or Surgery Study II), two expert cardiologists determined their preference prior to randomization; patients who were randomized to the treatment favored by the cardiologists had better outcomes compared to the remaining patients [73]. The physician, on the basis of experience, may act intuitively in certain occasions. It is analogous to the 'Eureka' phenomenon described by Archimedes [4, 10]. Einstein stated, 'A new idea comes suddenly and in a rather intuitive way. But intuition is nothing but the outcome of earlier intellectual experience.'

Lack of Consideration for Pathophysiology

Guidelines do not take into consideration pathophysiologic mechanisms and the complexity of the circulation (and other systems) with its multiple interactions. Further, a continuously evolving disease is typically 'artificially' divided into different stages (e.g. coronary artery disease and heart failure; fig. 7).

Guidelines foster memorization rather than active, in-depth thinking. Memorization is a passive accumulation of knowledge, while thinking is an active movement of knowledge. Knowing and understanding basic pathophysiologic mechanisms can lead one to conclusions and

ideas that have not been previously determined or even discovered. From understanding 20–30 basic mechanisms, one can generate over a million combinations (fig. 6); the memorization of 20–30 guidelines is nothing more than that. Memorizing guidelines do not make a physician [1, 2, 10].

'Is That All There Is?'

Practice guidelines offer limited follow-up for the published suggestions. Is a particular set of guidelines effective in achieving the expected results? Reporting that institutions are now using the guidelines ('get with the guidelines') is not a direct gauge of their actual effectiveness, their cost-benefit ratio, and so forth [7, 11, 14, 21, 55].

The 'thinking' physician, based on clinical experience, awareness of basic mechanisms of disease and the principles of clinical pharmacology, can effectively manage a patient who does not 'fit' within the description of the guidelines (a very common scenario in clinical practice that includes the majority of patients) as compared to physicians who base their practice primarily on guidelines. The guidelines do not facilitate the development of the 'superior' physician, as described by Alfred N. Whitehead; he states, 'He is skeptical toward the data of his own profession, welcomes discoveries which upset his previous hypotheses, and is still animated by human sympathy and understanding'. This perhaps is the major risk associated with the wide application of clinical practice guidelines used today.

Proposals for Improvement in the Written Guidelines

I have made this (letter) longer than usual,
only because I have not had the time to make it shorter
Blaise Pascal

Cognizant of the fact that guidelines will never be able to address most of the issues mentioned above, guidelines should be concise and simple consisting of only a few pages. Information related to level of evidence A, and perhaps B, should be mostly included, while information related to level of evidence C should be limited to 1 or 2 paragraphs at the end of a section or the document. Information provided should be mostly related to hard endpoints (e.g. death, myocardial infarction, and stroke). Approach to the individual patient should be emphasized [1, 2, 6]. This approach allows the guidelines to stimulate thinking and provide the necessary flexibility in management. This in effect would encourage the physician to make the proper decisions and choices for the typically complicated patient. Importantly, a short document can be easily and almost immediately changed after a new major relevant trial or discovery.

As an example, current postmyocardial infarction guidelines should be summarized in a few pages as follows: smoking cessation; therapy with statins and aspirin increase survival in all patients; therapy with β-adrenergic blocking agents and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers increase survival in patients with left-ventricular systolic dysfunction, and calcium channel blockers and nitrates control angina, but do not increase survival. Coronary artery bypass surgery increases survival in patients with multivessel coronary artery disease and left-ventricular systolic dysfunction when there is a stenosis in the proximal left anterior descending artery and in patients with significant left main coronary artery disease; percutaneous coronary artery revascularization is indicated only in patients who continue to have chest pain while on maximal medical management and/or myocardial ischemia during the stress test that involves more than 10% of the left-ventricular myocardium. It should also be stated that therapy must be individualized: a patient's characteristics and preferences, physician experience for each procedure, and, importantly, outcomes for each procedure in each particular hospital should be taken into consideration [1, 6, 32, 55, 74]. Therapeutic interventions should also be related to the progression of atherosclerosis and to factors that determine myocardial oxygen supply and demand. In addition, one page related to pathophysiology (e.g. development and progression of atherosclerosis, myocardial perfusion, and myocardial oxygen supply and demand) should be given (fig. 8).

Concluding Remarks

This brief review is not intended to be a comprehensive review of practice guidelines or their shortcomings, nor to suggest the elimination of these practice-educational tools. It addresses, however, several issues that should be taken into consideration in the development and presentation of clinical practice guidelines to facilitate the development of the 'thinking', superior physician.

Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?
T.S. Eliot

There is no question that clinical practice guidelines are important and that they provide significant help to the

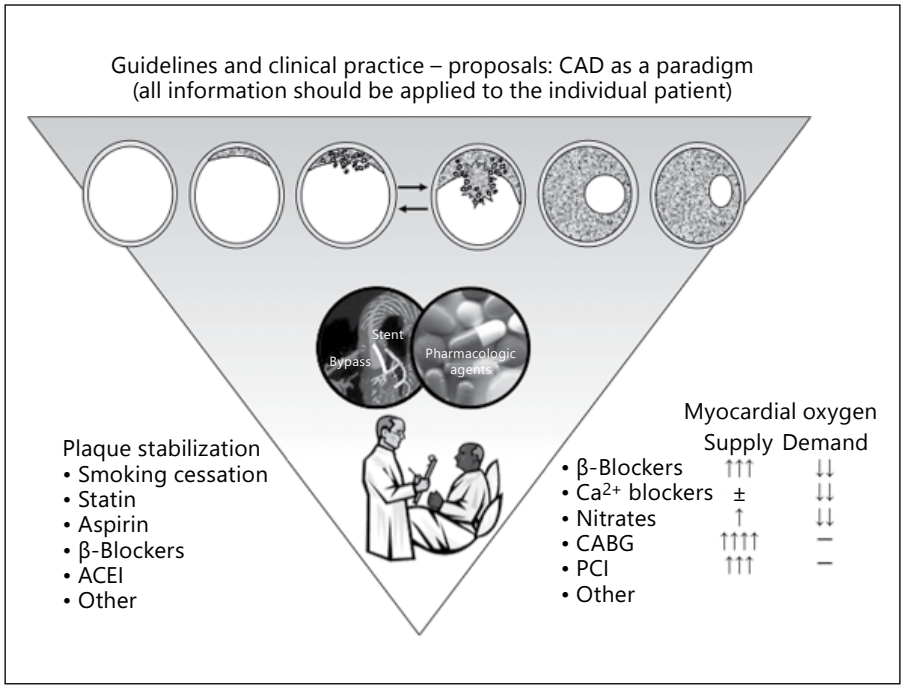

Fig. 8. Schematic presentation showing how guidelines in postmyocardial infarction patients can be summarized concisely (see text for details). ACEI = Angiotensin-converting enzyme inhibitor; CABG = coronary artery bypass grafting surgery; CAD = coronary artery disease; PCI = percutaneous coronary intervention; ↑ = increase; ↓ = decrease; – = no change; + = positive change.

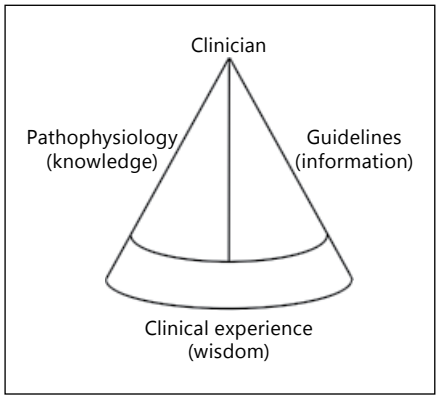

Fig. 9. Clinical practice should be optimally based on clinical experience and medical ethics (wisdom), pathophysiologic mechanisms (knowledge), and written guidelines (information).

busy physician, who often has to see 20–30 patients a day [3, 10]. Thus, clinical practice guidelines should be simple, clear, short, and to the point; this way, the busy physician can use them more effectively. It should also be emphasized that a short document can easily be modified to incorporate evolving information, yet maintaining brevity.

There are several pitfalls, however, related to controlled RCTs, nonrandomized data, and the guideline committees [10, 55]. In general, the clinical practice guidelines as currently written represent only an accumulation of 'inert information' that typically ignores basic pathophysiologic mechanisms, variances of patients' disease(s) and therapeutic effects, and personal clinical experience [4, 10]. Pathophysiologic mechanisms determine the foundation of knowledge in which all subsequent information accumulates, while clinical wisdom is acquired only by following patients over time [1, 2, 6]. Montaigne once wrote that, 'we can be knowledgeable with other men's knowledge, but we can't be wise with other men's wisdom'. The wide implementation of guidelines today put at risk the clinical wisdom of the physician, which is developed and maintained over time by solving clinical problems and facing clinical situations on a daily basis. In order to practice effective and 'personalized' medicine, a physician not only needs information as written in the guidelines, but, importantly, the clinical wisdom and knowledge related to basic pathophysiology (fig. 9). All these factors should be allowed (even at times emphasized) in the guideline documents. Thus, clinical guidelines, as applied or practicing documents, must be able to serve as a valuable tool to expediently assist the physician in providing the optimal care for each individual patient during the course of their disease well into the foreseeable future.

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