The Shortcomings of Clinical Practice Guidelines

Harisios Boudoulas, MD, Dr, Dr Hon.
Professor of Medicine/Cardiovascular Medicine and Pharmacy (emeritus)
The Ohio State University, Columbus, Ohio, USA
Honorary Professor, Academician (an. mem.)
Biomedical Research Foundation, Academy of Athens
Related Publications


Basis for Practicing Medicine Until Recent Past

- To practice medicine the physician had to understand the basic mechanisms of disease, the basic principles of clinical pharmacology, and then apply the knowledge and experience to the individual patient.

(active process – thinking)
Factors Contributed to the Development of Guidelines

- Knowledge increased dramatically over the last 5 decades
- Difficult to follow all the information even for the scholar who is dealing with only one major disease
- Natural course of diseases and outcomes had altered
- Difficult for one physician to evaluate the long-term effects of a particular treatment on hard end points (death, MI, stroke, other)
Development of Guidelines

• In 1984, the first set of clinical practice guidelines was published by the ACC/AHA in response to the USA government’s request to review evidence concerning the use of cardiac pacemakers (cost was a factor).

• For over 30 years the ACC/AHA has developed more than 30 clinical practice guidelines with “updates” and additional modifications at intervals.
Guidelines: A Homogeneous Approach to All Patients

Guidelines:

• Facilitate a more homogeneous approach to all patients with the same disease in order to decrease cost and eventually improve outcome.

• Assist in facilitating the translation of new research discoveries into clinical practice.

• Despite the updates and modifications, there are still several major issues related to the guidelines and their clinical application and often appear “lost in translation”.
Practicing Medicine: A Transition from Tradition to Guidelines

The guidelines gradually shifted:

• The emphasis from a sick individual to that of a sick population.

• From pathophysiology and the understanding of basic disease mechanisms (i.e. thinking) to memorizing fast changing facts and outcomes.
Pathophysiology

Response to Agonist

Active Receptor → Resting Cell

Agonist (isoproterenol)

Guidelines

Level of evidence
A, B, C

Class
I, II, III
Practice Guidelines

Randomized clinical trials
Other studies
Guidelines Committee (expert opinion)

Guidelines

Clinical Practice
Practice Guidelines

Randomized clinical trials
Other studies

Guidelines Committee (expert opinion)

Guidelines

Clinical Practice
Randomized Clinical Trials

Hypothesis Design – Support

Industry > 60%
Incentive to participate
Different ethnic groups

Protocol

Looking for positive results
Soft end points (readmission)

Selection Process

e.g. COURAGE (NEJM 2007)
35,539 patients
32,468 excluded
2,287 (6.3%) included

Boudoulas KD, et al. Cardiology. 2015; 130: 187-200

e.g. SOLD (NEJM 1992)
Excluded
EF > 35%
Age >79
Creatinine > 2 mg/dl
Randomized Clinical Trials: Limitations

• Epidemiologic approach
• Financial support (>80% positive results funded by industry)
• Many exclusion criteria
• Withheld information (e.g. dabigatran or Pradaxa)
• Publication and presentation of data (negative results, % reduction)
• Subgroup analysis and meta-analysis
• Information does not provide insight into pathophysiologic mechanisms
Practice guidelines are based only on published information. Thus evidence based medicine is, at best, based only in some of the evidence.
## Randomized Clinical Trials: Absolute Difference and % Reduction in Events

<table>
<thead>
<tr>
<th>Therapy / Disease</th>
<th>Follow-up</th>
<th>Events</th>
<th>% Decrease Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (unstable angina)</td>
<td>24 mos</td>
<td>Control: 17.0  Treatment: 8.6  Difference: 8.4  Event: 51</td>
<td></td>
</tr>
<tr>
<td>Aspirin (normal)</td>
<td>57 mos</td>
<td>Control: 1.71 Treatment: 0.94 Difference: 0.77 Event: 47</td>
<td></td>
</tr>
<tr>
<td>Streptokinase (AMI)</td>
<td>21 days</td>
<td>Control: 13.0 Treatment: 10.7 Difference: 2.3 Event: 18</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Weissler, Miller, Boudoulas. *JACC* 1989; 13: 764
No Insight Into Pathophysiologic Mechanisms

In trials:

• A single molecule (i.e. study medication) in a complex disease process is studied.

• Information obtained usually does not provide insights into the basic mechanisms of a disease; tell us what happened (the final event) and little on why it happened.
Proposal to Facilitate Randomized Trials and Registry Data Into Clinical Practice

• Minimize exclusion criteria (e.g. GISSI, ISIS 2)
• In multinational trials only patients with the same origin (e.g. European, African, Asian, other) should be included
• Hard end points should be emphasized with less attention to soft end points as final events
• Give absolute and not only % difference in events
• All trials with negative results or that have been discontinued must be published
• Eliminate or minimize sub-group analysis or meta-analysis
• Obtain data from registries (e.g. catheterization laboratory of the ACC, electronic medical records, other [no placebo])
Practice Guidelines

Randomized clinical trials

Other studies

Guidelines Committee (expert opinion)

Guidelines

Clinical Practice
Guidelines Committee Members: Merits

- Mostly members of a major scientific society
- World leaders in their field
- Know the major current and future projects of medical industry and government programs
- Individuals from several countries offering diversity of opinion and awareness of problems facing each nation
Guideline Committee Members: Limitations

- Many professional activities (scientific societies, teaching, administration, university committee members, other)
- Many professional trips
- Extremely busy
- Relationship with biomedical industry
- Conflict of interest
- Subconscious influence
# Guideline Committee Members: Relationship with Pharmaceutical Companies

<table>
<thead>
<tr>
<th>Relationship</th>
<th>% of Authors</th>
<th>Mean No. of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any relationship</td>
<td>87</td>
<td>10.5</td>
</tr>
<tr>
<td>Travel funding</td>
<td>53</td>
<td>5.4</td>
</tr>
<tr>
<td>Speaker honorarium</td>
<td>64</td>
<td>7.3</td>
</tr>
<tr>
<td>Educational program support</td>
<td>51</td>
<td>4.7</td>
</tr>
<tr>
<td>Research support</td>
<td>58</td>
<td>6.7</td>
</tr>
<tr>
<td>Employee/consultant</td>
<td>38</td>
<td>5.7</td>
</tr>
<tr>
<td>Equity</td>
<td>6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Choudhry NK et al. *JAMA* 2002; 287: 612-617
Proposals for Improvement of Guideline Committees

• Physicians with good clinical experience in one or two areas
• Pharmacologists and researchers may also be participants
• No individual should participate in more than two guideline committees
• Individuals with any financial interest related to medical industry should be excluded
• Members of the guidelines committee should not give lectures related to their guidelines topic, especially if honorarium is involved
• Members of a committee should not be more than 6 or 7 (each member assumes more responsibility)
Practice Guidelines

Randomized clinical trials

Other studies

Guidelines Committee (expert opinion)

Guidelines

Clinical Practice
Written Guidelines: Merits

• Are directly linked to merits of randomized clinical trials and to the structure of the guidelines committee

• Small difference on hard end points (death, MI, stroke, other) due to therapeutic intervention can be detected (e.g. CAST, hormone replacement therapy, other)

• Very useful in the assessment of preventive measures (e.g. vaccination, colonoscopy, other)

• Provide focused and concentrated information on one condition with an extensive supporting bibliography
Written Guidelines: Limitations

- Related to the limitations of randomized controlled clinical trials and to the structure of the guidelines committee
- Written document ("inert ideas", expert opinion)
- Limit personalized medicine; ignore variability in biology
- Lack of consideration for pathophysiology; do not stimulate thinking
- Lack of incorporation of clinical experience; do not facilitate the development of the superior physician
- Limited follow-up; “get with guidelines” is not a direct measure of their effectiveness
- Other
### Practice Guidelines: Presentation of Inert ideas

“Education with inert ideas is not only useless; It is, above all things, harmful…”

Alfred North Whitehead

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
</table>
| A                 | More than 1 randomized controlled trial (RCT)  
                  | Meta-analyses of RCTs |
| B – R             | Single randomized or non randomized studies |
| B – non R         | Information obtained from non-randomized studies |
| C                 | Expert opinion |

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strong evidence; benefit &gt;&gt;&gt; risk</td>
</tr>
<tr>
<td>IIa</td>
<td>Moderate evidence; benefit &gt; risk</td>
</tr>
<tr>
<td>IIb</td>
<td>Effectiveness less well established</td>
</tr>
</tbody>
</table>

Practice Guidelines: How Strong is the Information?

- **Level of Evidence A**: ~ 11%
- **Level of Evidence C**: ~ 50% (expert opinion)
Problems Related to Expert Opinion in Guidelines


• 2001-2010 authors reviewed articles of NEJM
  – 2044 original articles
  – 1344 clinical practice
  – 363 tested on established practice
  – 146, 40.2%, reversed that practice

• Women's Health Initiative randomized controlled trial (estrogen replacement therapy) JAMA 2002; 288: 321-333

• A randomized controlled trial of the use of pulmonary artery catheter in high-risk patients. NEJM 2003; 348: 5-14

• Optimal medical therapy with or without PCI for stable coronary artery disease. NEJM 2007; 356: 1503-1516

• Effects of intensive glucose control in type 2 diabetes. NEJM 2008; 358: 2545-2559

• Other
Guidelines are directed at populations with a particular disease and not to the individual patient.

Lack of Consideration for Pathophysiology

Circulation is Continuous with Multiple Interactions

Different Stages of a Chronic Disease that Continuously Evolves: CAD as a Paradigm
Lack of Consideration for Pathophysiology: Does Not Stimulate Thinking

“The Master said, He who learns but does not think, is lost. He who thinks but does not learn is in great danger!”

- Confucius

<table>
<thead>
<tr>
<th>Factors (n)</th>
<th>Probabilities (2^n-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>1,023</td>
</tr>
<tr>
<td>20</td>
<td>1,048,575</td>
</tr>
</tbody>
</table>
Written Guidelines: Lack of Incorporation of Clinical Experience

- The “thinking physician” based on clinical experience, pathophysiology and basic principles of pharmacology, can effectively manage a patient who does not “fit” within the description of guidelines (> 50% of patients) as compared to a physician who base his/her primary practice to guidelines
Importance of Clinical Experience

“A new idea comes suddenly and in a rather intuitive way. But intuition is nothing but the outcome of earlier intellectual experience.”

– Einstein

• Medical, angioplasty or surgery study (MASS II Trial)

• Two experienced cardiologists determined their preference prior to randomization

• Patients randomized to the treatment favored by the cardiologists did better
Guidelines Do Not Facilitate the Development of the Superior Physician

“He is skeptical toward the data of his own profession, welcomes discoveries which upset his previous hypothesis, and is still animated by human sympathy and understanding.”


“…the secret of the care of the patient is in caring for the patient.”

- F. W. Peabody

- Family Medical History
- Medical History (multiple diseases)
- Psyche
- Other
Written Guidelines: Proposals for Improvement

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

• Keep it simple, clear, short and to the point (3-4 pages)
• Give information related to evidence level A and perhaps B.
• Give 1-2 pages related to basic mechanisms of the disease
• Correlate therapy with pathophysiology
• Guidelines should facilitate the development of the superior physician
• Information should be mostly related to hard end points
• Emphasize variability in biology
• This approach allows the guidelines to stimulate thinking and provide the necessary flexibility
Written Guidelines: Proposals for Improvement: Stable Post-MI Patients as a Paradigm

- Smoking cessation, therapy with statins and aspirin increase survival in all patients
- Therapy with β-blockers and angiotensin converting enzyme inhibitors increase survival in patients with LV dysfunction
- Coronary bypass surgery increases survival in patients with 2-3 vessel disease (LIMA to LAD) and LV dysfunction; patients with left main disease
- PCI is indicated only in patients who continue to have chest pain while on maximal medical management and myocardial ischemia and/or large area of myocardium at jeopardy
- Give 1-2 pages related to pathophysiology of myocardial perfusion and development/progression of atherosclerosis
- Relate therapy to pathophysiology
Written Guidelines: Proposals for Improvement - CAD as a Paradigm
(All information should be applied to the individual patient)

Plaque
- Smoking cessation
- Statin
- Aspirin
- β-blockers
- ACEI
- Other

Myocardial Oxygen
<table>
<thead>
<tr>
<th>Supply</th>
<th>Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Ca++ blockers</td>
<td>±</td>
</tr>
<tr>
<td>Nitrates</td>
<td>↑</td>
</tr>
<tr>
<td>CABG</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>PCI</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Other</td>
<td>—</td>
</tr>
</tbody>
</table>
Concluding Remarks

“We can be knowledgeable with other men’s knowledge, but we can’t be wise with other men’s wisdom”
- Montaigne, 1533-1592

• Clinical practice guidelines as currently written represent only an extensive accumulation of “inert information” that ignore pathophysiology variances of patients’ diseases and personal clinical experience

• Guidelines should be simple, clear, short and to the point

• In order to practice effective medicine and “personalized” medicine, a physician not only needs information, but importantly clinical wisdom and knowledge related to basic pathophysiology

• The wide implementation of guidelines today put at risk the clinical wisdom of the physician that is acquired only by following patients over time

• This perhaps is the major risk associated with the wide application of clinical practice guidelines as used today
“Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?”
- T.S. Eliot
Practicing Medicine: Requirements

Appropriate training
  - Medical school
  - Post graduate (specialty, sub-specialty, other)

Medical examinations

License from medical boards
Randomized Clinical Trials: Withheld Information

- Studies with negative results often are not published (missing in action!)
- Studies supported by industry demonstrate positive results in > 80% of published articles, while published reports funded by federal services positive results reported ≈ 50% of the time
- Results of studies that discontinued prior to completion were not published
- Pharmaceutical companies do not provide all available information (e.g. dabigatran or Pradaxa)
- Practice guidelines are based only on published information. Thus, evidence based medicine is, at best, based only in some of the evidence.
Importance of Clinical Experience

- EAST, *NEJM* 1994; 331: 1044-1050

After randomization some patients did not participate in the trial. The personal physician of those patients decided for the final therapy. Outcome of these patients was better compared to randomized.
Guidelines – Definition
(Institute of Medicine, 2011)

• “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."

Jacobs AK, et al. Circulation 2014; 130: 208-17
Clinical Practice Guidelines

- Merits and limitation of randomized clinical trials
- Issues related to guidelines committees
- Presentation of guidelines
- Proposals for improvement
“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: 12-13_
Randomized Clinical Trials: Merits

- 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 on the adverse effects of a diagnostic or therapeutic procedure.

- The multicenter format reducing the isolated single center partiality and institutional bias.

- In general the population under study is well defined.
A Trial with Negative Results: What Does it Mean?

ISIS-2 – 17,787 patients
(If 1,700 patients were used the study would be negative)

Boudoulas H et al. Diagnostic Procedures in Cardiology; Year Book 1985. p 378

Differences in Absolute Mortality 2%, 6%, 8%, and 20% are Expressed as 50% Reductions in Mortality

Boudoulas H et al. *Diagnostic Procedures in Cardiology; Year Book* 1985. p 378
Statistics and Ethics in Medical Research
Childhood Mortality from Diptheria

Log Scale

Linear Scale

Altman DG. Lancet 1980; 28: 1542-44
Subgroup Analysis and Meta-analysis

- Subgroup analysis without a previous determination statistically may be incorrect (e.g. ISIS 2)
- Studies with negative results (usually not published) may not be included in the meta-analysis
- Inaccuracy is even greater if studies were performed at different time periods (different therapeutic modalities, etc.)
Written Guidelines: Other Limitations

• It is not uncommon for a large well conducted trial to become “out dated” because of new developments

• Are results of trials conducted 15-20 years ago applicable today? (e.g. β-blockers in post-MI, medical vs PCI vs CABG, DIG study, other)

• It is not clear what to do with trials that are internally inconsistent and have two large subsets with positive and negative results (e.g. major differences in the results were noted for American and European populations)