

Pearls and Pitfalls of Clinical Practice Guidelines

Rachel Proteau, PharmD Candidate and Megan Herink, Pharm.D, Drug Use Research & Management, Oregon State University College of Pharmacy

Clinical practice guidelines play an important role in optimizing patient care. They assist with interpretation of research, provide guidance for standard practice, and have the potential to improve patient outcomes. However, guidelines must also be critically evaluated. Commonly encountered limitations of guidelines include recommendations with low level of supporting evidence, potential bias due to conflicts of interest (COIs), and limited generalizability to real-world patients. These limitations must be considered when interpreting and applying guidelines in clinical practice.

Over recent decades, practice has moved increasingly towards evidence-based medicine. The quality of clinical practice guidelines has been a topic of increasing interest since the 1990's.¹ In 2011, the National Academy of Sciences Institute of Medicine (IOM) published a set of standards to promote development of guidelines with stronger, more transparent methodology (Table 1).² While these standards offer a useful framework, it is unclear how this has influenced development of recent guidelines. Evidence suggests that specialist society guidelines may be more concerning due to decreased transparency regarding guideline development and COI.^{3,4}

The purpose of this newsletter is to review the level of evidence (LOE) supporting current cardiovascular (CV) guidelines, explore the potential effects of COI, and provide tips for primary care clinicians to critically assess guidelines and their application to individual patients.

Table 1: Summary of IOM Standards for Developing Trustworthy Guidelines²

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| <ul style="list-style-type: none"> Standardize guideline development methodology | <ul style="list-style-type: none"> Establish evidence-based systems for rating strength of recommendations |
| <ul style="list-style-type: none"> Establish transparency and strategies for management of COI | <ul style="list-style-type: none"> Articulate recommendations to reflect the supporting LOE and need for action |
| <ul style="list-style-type: none"> Consider COI when establishing guideline development groups | <ul style="list-style-type: none"> Seek external review of proposed guidelines by relevant stakeholders |
| <ul style="list-style-type: none"> Maintain an ongoing interactive relationship between systematic review teams and guideline developers | <ul style="list-style-type: none"> Monitor literature and update guidelines when new evidence suggests need for clinically important modification |

Abbreviations: COI: conflict of interest; LOE: level of evidence

Level of Evidence Supporting Major Cardiovascular Recommendations

In March of 2019, a review published in the *Journal of the American Medical Association (JAMA)* examined the LOE supporting 51 current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines.⁵ The primary outcome was the percentage of recommendations supported by evidence graded as LOE A (i.e. multiple randomized controlled trials [RCTs] or a single large RCT). Among the 26 ACC/AHA guidelines examined, only 8.5% of recommendations had LOE A support. Fifty percent of recommendations were graded LOE B (observational studies or a single smaller RCT), and 41.5% were based on expert opinion alone (LOE C). An analysis of CV guidelines from the ESC was similar, with slightly more of the recommendations coming from LOE A (15%).

Publication of the 2011 IOM evidence standards has not changed the quality of evidence in the ACC/AHA guidelines. Comparing current guidelines to previous versions in 2009, the number of LOE A recommendations did not significantly differ (9% vs. 11.7%, respectively). However, the proportion of LOE B recommendations increased, corresponding to a decrease in LOE C support.⁶ A dearth of high quality evidence to inform guideline

recommendations is evident in other fields as well, including infectious disease, liver, and cancer.⁷⁻⁹

An additional classification of recommendations (Class I-III) conveys both level of consensus and benefit versus harm. ACC/AHA defines a Class I recommendation as a strong recommendation that the medication or therapeutic test is indicated and should be performed or administered, as the benefit greatly outweighs the risk. Yet among Class I recommendations in the examined ACC/AHA guidelines, only 14.2% were supported by LOE A, and 37% were based on expert opinion alone (LOE C).⁵ Making these recommendations based solely on expert opinion without real data remains controversial. These recommendations are more subject to bias and more likely to be reversed. An example of this comes from past CV guideline recommendations regarding perioperative beta blockers.¹⁰ In the late 1990's, two small trials were published that suggested pre-operative initiation of beta-blockers could reduce post-operative cardiac complications.¹⁰ These results were quickly adopted into recommendations in the ACC/AHA guidelines. However, larger trials were unable to replicate these benefits and ultimately the recommendations were reversed.

Conflict of Interest in Clinical Guidelines

A COI is a set of conditions in which professional judgement concerning a primary interest may be unduly influenced by a secondary interest. This may be intellectual or financial. Commercial COI seems to have the most potential to influence guideline recommendations and introduce bias.¹¹ COIs within guidelines may arise from any level of industry involvement, such as contributions to organizations authoring guidelines, and/or significant funding of pivotal trials. It is important to consider COI during guideline development, as bias in clinical practice guidelines can have a widespread negative effect on patient care.

COIs are common among guideline authors and vary significantly.¹¹⁻¹³ A study concluded that 56% of individuals involved in the ACC/AHA guidelines reported a COI.¹⁴ This is problematic since it is known that a substantial number of ACC/AHA guideline recommendations are based on expert opinion. COIs appear to be particularly prevalent in guidelines considering expensive specialty medications.¹⁵

Ideally, authors of clinical guidelines would not have any COIs. Since that is a difficult standard to meet, IOM standards include strategies for managing COIs. These include, at a minimum, full disclosure of COIs for all potential members of the guideline development group.² Additional strategies include: excluding members with COIs from leadership roles (chair, vice-chair), limiting the proportion of members with any commercial COI to less than 50%, and fully excluding members with COI from panel participation and/or limiting their participation to very few, specific recommendations. Lastly, industry sponsors should not be involved in guideline development.

A recent evaluation of the ACC/AHA cholesterol management guidelines and a hepatitis C guideline found that neither guideline fully met the IOM standards for COI management.¹¹ Three-fourths (72%) of the hepatitis C virus guideline committee members and two-thirds of the co-chairs disclosed commercial COIs.¹¹ Although the ACC/AHA cholesterol guideline performed better, there remained discordance between COIs reported by authors during guideline publication and those disclosed by the same authors in other articles published around the same time.

Generalizability of Guidelines to Real World Patients

Guidelines are often viewed with a one-size-fits-all approach, but the translation of guideline recommendations to the care of an individual patient is complex. Clinical trial populations are more likely to include “ideal patients” – often younger, healthier, and more adherent than the average primary care patient. A 2014 review of 22 National Institute for Health and Care Excellence (NICE) primary care guidelines found that only 38% of the recommendations cited research derived from a primary care or community-based population.¹⁶ In the real world, patients have co-morbidities and other factors (social, cultural, financial, etc.) that influence care decisions. These situations are under-represented or ignored in practice guidelines.

Table 2: Tips for Applying Guidelines to Clinical Practice

- Look for the level of evidence supporting guideline recommendations
 - RCTs and meta-analyses provide the highest LOE
 - Observational studies can be helpful when RCTs are not available, however recommendations based on observational data are not as reliable
 - Expert opinion is the lowest LOE. In the absence of any data these statements can provide helpful perspective, but should not be treated as evidence-based medicine
- Consider, “Are these recommendations appropriate to my patient?”
 - Do the guidelines offer any information on age, comorbidities, or contraindications that make the recommendations less applicable?
 - What modifications to guideline care are necessary for each individual patient?
- Look for a clear COI policy and try to determine if there are significant COIs, particularly when recommendations support the use of high-cost or specialty medications
 - All COIs should be disclosed. Committee chairs and co-chairs should not have any commercial COIs
 - Only a minority of committee members (<50%) should have a commercial COI.
 - If COIs are present, consider that bias may be present and critically evaluate the evidence behind the guideline recommendations

Conclusions

Clinical practice guidelines provide a needed resource to approach complex medical decision-making, enhance healthcare quality and safety, and accelerate the translation of research into clinical practice. Progress has been made since the IOM released standards for guideline methodology and transparency. Many organizations have since moved towards increased COI transparency and improvement in policies and procedures to manage COIs.^{5,16}

Nevertheless, guideline reliability varies, and many suffer from significant methodological flaws, limitations in scientific evidence, and presence of COIs, making the recommendations difficult to apply to clinical practice. Tools are available to help guideline users assess the quality of guidelines, including the AGREE instrument (<https://www.agreetrust.org/>). However, these tools can be too time intensive to incorporate into a busy clinical practice. General awareness of fatal flaws in clinical practice guidelines and application of simple tips (Table 2) when reading guidelines can help clinicians quickly assess and apply guidelines more appropriately.

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