

Clinical Practice Guidelines: 'To Treat, or Not to Treat, That is the Question'

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HEALTHCARE PROVIDERS are assailed with a steady flow of "new and improved" clinical practice guidelines (CPGs) designed to impact the quality of patient care but which can be confusing, conflicting, difficult to apply in patient settings and challenging to gain physician acceptance and patient adherence. Nowhere is this more prevalent and complex than in the arena of cardiovascular disease where the combined American College of Cardiology and American Heart Association (ACC/AHA) have 26 current guidelines (averaging 121 recommendations/guideline), including the management of blood pressure (BP) and elevated blood cholesterol, impacting not just cardiologists but internists, family medicine physicians, endocrinologists, pediatricians and other primary care providers.

According to the Institute of Medicine, "Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances."¹ Commonly issued by subspecialty organizations like the ACC and the AHA, CPGs define the role of specific diagnostic and treatment modalities and contain recommendations based on a systematic review and synthesis of the published medical literature and an assessment of relative risks and benefits. Guidelines are suggestions, not rules, intended to help clinicians take better care of patients. While they



identify and describe generally recommended courses of intervention, they are not presented as a substitute for physician judgement in the treatment of an individual patient.

The rationale behind current CPGs correlates to the increasing difficulty to stay current with the volume of medical literature and the rapidly expanding knowledge bases related to healthcare. The number of randomized controlled trials (RCTs) published in MEDLINE grew from 5,000 per year from 1978–1985 to 25,000 per year from 1994–2001.² Furthermore, much of the RCT literature is focused on individual subsets of target populations which may not be reflective of broader clinical settings and thus are difficult to apply in daily practice. As a consequence, critically appraised and synthesized scientific evidence has become a valuable tool of modern clinical practice.

Levels of Evidence (LOEs)

Most CPGs rely heavily on RCTs' results to validate and support their recommendations and employ levels of evidence (LOE) to support particular guideline recommendations. Three well-defined LOEs are commonly utilized in CPGs: LOE A, supported by data from multiple RCTs or a single, large RCT; LOE B, supported by data from observational studies or a single RCT; and LOE C, supported by expert opinion only. Across the 26 current ACC/AHA guidelines, only 8.5% of

the recommendations were classified as LOE A, while 50% were LOE B, and 41.5% were LOE C. Thus, among recommendations in major cardiovascular society guidelines, only a small percentage were supported by evidence from multiple RCTs or a single, large RCT.³ Nevertheless, this represents the best current available evidence from which to base guideline recommendations.

Evolving Guidelines

CPGs are not meant to be static documents and evolve over time as new scientific knowledge is acquired. One of the most striking examples of this comes from review of 50 years of AHA guidelines for the prevention of infective endocarditis (IE).⁴ The earliest guidelines were complicated, difficult to remember, ambiguous, and inconsistent. Reflective of the times, they had an overemphasis on antibiotic prophylaxis based predominately on case reports, limited data and expert opinion. Over the course of 50 years, however, the recognition that there were no RCTs demonstrating an increased incidence of IE following dental or other (GI, GU) procedures and more importantly no demonstrable benefit from antibiotic prophylaxis in actually reducing the incidence of IE, have changed the guidelines considerably. Antibiotic prophylaxis is no longer recommended for dental and other procedures, nor for the majority of patients including those with mitral valve prolapse, congenital heart disease or rheumatic valve disease. Current guidelines stress the importance of regular dental hygiene for the majority of the population and limit use of prophylactic

antibiotics to a small subset of patients with the highest risk of adverse outcomes from IE (complex congenital heart disease, prosthetic heart valves and prior IE).

Conflicting Guidelines

Occasionally, differing societal guidelines conflict and while these differences are typically minor, they can lead to substantial confusion for providers. This is most evident in the controversy surrounding recent BP guidelines. In 2017, the ACC/AHA published new guidelines for the management of high blood pressure⁵ which contained much valuable information regarding best practices for measuring BP, the relevance of home BP monitoring and the important role of diet and exercise as first-line therapy for hypertension. Perhaps most striking however, the recommendations redefined hypertension as a BP of 130/80 mm Hg or greater. Underpinning this guideline was the belief that achieving this target BP would lower a person's risk of CVD events, including the large group of adults younger than 75 years who are at low to moderate risk of CVD. Nine trials contributed to the ACC/AHA meta-analysis on which the guideline was based. Trials selectively enrolled persons at high risk of cardiovascular disease, with follow-up ranging from 2 to 5.7 years. No statistically significant benefit was found for all-cause mortality, CVD mortality, heart failure, or renal events when the lower BP cutoff was used, and the difference for fatal or nonfatal myocardial infarction was borderline nonsignificant. Only composite major CVD events (6.2% vs. 7.3%; RR = 0.84; number needed to treat = 91) and the combination of fatal and nonfatal stroke (2.4% vs. 2.9%; RR= 0.82; number needed to treat = 200) were significantly

decreased when the lower cutoff was used.

The American Academy of Family Practice (AAFP) and the American College of Physicians (ACP) were not involved in the development of these guidelines and based on a review of the scientific merits elected not to endorse them. Instead, these groups continue to follow the 2014 Eighth Joint National Committee (JNC-8) guidelines on managing hypertension in adults,⁶ which calls for treatment to lower BP to 150/90 mm Hg in those age 60 and older, and to 140/90 for adults less than 60. In patients with diabetes and chronic kidney disease (CKD), the guidelines recommend initiating drug treatment to a goal of <140/90mmHg. The AAFP and ACP did acknowledge that there might be a small benefit of lower treatment targets in reducing cardiovascular events and recommended treatment for some patients as part of a shared decision-making process.

Cholesterol Management Guidelines and the Risk Calculator

In 2013, the ACC/AHA published Guidelines for the Management of Blood Cholesterol⁷ which, among other recommendations, included use of a Pooled Cohort Risk Equation to estimate 10-year risk of ASCVD events and provide a guide for who should receive statin therapy and at what level (low, moderate or high intensity). Commonly referred to as the CV Risk Calculator

(RC), it was designed for individuals aged 40–75 years of age, with or without diabetes, with an LDL-C between 70 and 189 mg%, not on statin therapy. It is based upon 8 data elements including age, gender, systolic BP, Total and HDL cholesterol, active treatment of HTN and/or DM and current smoking. Individuals with an estimated 10-year risk of >7.5% were recommended to receive moderate to high intensity statin therapy. The 7.5 % value was deemed to be a moderately elevated risk although earlier risk calculator models defined 10-20% as moderate risk and >20% as high risk. The RC continues to be an important element in the updated 2018 ACC/AHA Cholesterol Management Guidelines as well as in the 2017 ACC/AHA Blood Pressure Guidelines (where a risk level of 10% instead of 7.5% is deemed moderate risk).

Use of the RC has markedly increased the pool of potential individuals who would require therapy and has sparked considerable controversy and debate as to its ability to accurately predict risk. The RC is heavily driven by age and gender such that men 65 and older and women 70 and older almost always fall into a moderate risk category (Figure 1). In addition, the RC does not include key information such as history of ASCVD events, family history of premature coronary artery disease or stroke, diet and activity level (healthy lifestyle), BMI and other elements that physicians routinely take

Figure 1. Estimated 10-year ASCVD Risk for a Patient with a BP of 120/75, Total Cholesterol of 150 mg% and HDL-C 55mg%, Not Diabetic, Nonsmoker and Not on Statin Therapy

AGE	Male	Recommendations	Female	Recommendations
50	1.9%	No indication for Statin	0.7%	No indication for Statin
55	3.3%	No indication for Statin	1.3%	No indication for Statin
60	5.5%	No indication for Statin	2.3%	No indication for Statin
65	8.9%	Moderate to High Dose Statin Therapy	4.2%	No indication for Statin
70	13.6%	Moderate to High Dose Statin Therapy	7.7%	Moderate to High Dose Statin Therapy
75	19.9%	Moderate to High Dose Statin Therapy	13.9%	Moderate to High Dose Statin Therapy
79	26.2%	Consider Moderate Dose Statin Therapy	21.9%	Consider Moderate Dose Statin Therapy

*ACC/AHA Pooled Cohort Risk Equation and estimated 10-yr. risk of ASCVD events.

into account when assessing risk and recommending treatment. In 2013, the Kaiser Permanente health group compared the observed risk of ASCVD to the RC predicted risk in a large pool of their patients.⁸ Among 307,591 eligible adults without diabetes between 40 and 75 years of age, there were 2,061 ASCVD events during 1,515,142 person-years. The observed 5-year ASCVD risk was substantially lower than the predicted risk, sometimes by as much as 50% lower risk. Thus, in this large, contemporary “real-world” population, the ACC/AHA Pooled Cohort Risk Equation substantially overestimated actual 5-year risk in adults without diabetes, overall and across various socio-demographic subgroups. For patients with DM, the observed and predicted risk was more closely correlated.

‘To Treat, or Not to Treat’

It is fairly well accepted that patients with hypertension, DM and/or a history of vascular events should be on aspirin, statin and antihypertensive therapy. But when considering primary prevention, the RC can be a source of confusion for clinicians and their otherwise healthy and older (> 65) patients with no or little evidence of significant vascular disease. In our hypothetical patient from **Figure 1** with normal BP and an unremarkable lipid profile, the predicted CV risk for men doubled between the ages of 65 and 75 years and for women it almost doubled every 5 years, all other elements being equal. In the absence of other risk factors we are left in a quandary whether to initiate statin therapy, especially when the patient is reluctant. A recent meta-analysis of all large statin trials (those recruiting at least 1,000 participants with a treatment duration >2 years) evaluated the effects of statin therapy on major vascular events and cause-specific mortality for 6 subdivided age groups: >75 years, 71–75 years, 66–70 years, 61–65 years, 56–60 years, and ≤55 years.⁹ Although statin therapy significantly reduced the number of major vascular events regardless

of patient age, there was less direct evidence of the benefits of statin therapy for patients >75 years old who did not already show evidence of occlusive vascular disease. Thus, while the evidence supports the use of statin therapy in older people considered to have a sufficiently high risk of occlusive vascular events, “there is less definitive direct evidence of benefit in the primary prevention setting among patients older

than 75 years.”⁹ The importance of shared decision making in informing patients and gaining their acceptance cannot be overstated.

Barriers to Physician and Patient Acceptance of CPG Recommendations

Physician adoption and patient adherence to CPGs can be challenging and numerous barriers exist.¹⁰ There are

The Edwin Smith Papyrus



NEW YORK ACADEMY OF MEDICINE COLLECTION/WIKIPEDIA

Earliest CPG buried for 3,000 years in Egyptian tomb

Clinical practice guidelines (CPGs) are not new and have been around since the beginning of recorded time. The earliest reported medical guidelines, the Edwin Smith Papyrus, written in Egypt c.1600 BC, a surgical treatise, describes in great detail the clinical findings, diagnosis, treatment and prognosis of some 48 different ailments.

The Papyrus was brought to light by Egyptologist Edwin Smith of Connecticut, who purchased the scroll while in Egypt in 1862. It lay buried in a Thebes tomb for 3,000 years. After his death in 1906, the scroll was donated to The New York Historical Society by his daughter. It was translated in 1930 by Egyptologist James Henry, along with the medical interpretation prepared by Chicago physician Dr. Arno Luckhardt.

The Papyrus is now at the New York Academy of Medicine, and can be viewed online, with an updated translation, in an interactive scroll at the National Library of Medicine (NLM) website: <https://ceb.nlm.nih.gov/proj/tp/Nash/smith/smith.html>

In the introduction to the archival material, NLM Director Donald A.B. Lindberg, MD, said, “The Smith Papyrus is extremely important because it showed for the first time that Egyptians had a scientific understanding of traumatic injuries based on observable anatomy rather than relying on magic or potions.”

provider barriers which include lack of awareness or lack of familiarity with current guidelines. The recent ACC/AHA blood pressure guidelines include more than 700 pages; an encyclopedic reference but difficult for any clinician to wade through. Lack of agreement with specific recommendations and lack of outcome expectancy (whether the recommendation will lead to an improved outcome) are underscored by the controversies surrounding the ACC/AHA BP and cholesterol guidelines and the RC. Guideline-related barriers also occur when they are perceived as inconvenient and not easy to use. Elimination of an established behavior may be more difficult to follow than guidelines that recommend adding a new behavior (such as recent ACC/AHA guidelines which no longer recommend aspirin for primary prevention). External barriers include time limitations (during a routine office visit), lack of a reminder system and lack of other office and hospital-based resources and facilities. Finally, and perhaps most limiting

of all, are patient-related barriers to guideline acceptance including pharmaceutical cost and insurance coverage. Among the more challenging barriers are patient resistance to medications in general and statins in particular, frequently based on real and perceived concerns regarding side effects. In addition, intermediate and long-term adherence to statin therapy can be surprisingly low. Women, younger patients and minorities tend to have lower adherence rates. Poor adherence to statin therapy also cuts across different degrees of cardiovascular risk. In one study, two-year adherence was 40.1% for patients prescribed a statin after an acute coronary event and 25.4% in patients being treated for primary prevention.¹¹

Conclusion

CPGs provide a synthesis of the best and most currently available data, in spite of their apparent limitations. ACC/AHA CV guidelines are complex and at times controversial in a rapidly changing scientific environment with

emerging new technologies and pharmacotherapies. As Dr. Harlan Krumholz stated,¹² "CPGs should inform and not dictate, guide not enforce, support not restrict. They can provide options and recommendations to improve quality of care and can highlight points of uncertainty. But they should not reduce physicians to automatons and patients to passive recipients of guideline dictums. The idea of there being a 'right answer' has entangled guidelines in controversy rather than focusing on providing recommendations and promoting choice. There will always be opinions about how to interpret the evidence, whether to recommend therapy based on risk, but it may feel differently if the guideline is not assumed to impose practice." ❖

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Care New England - Brigham health deal will benefit Rhode Island's health care system

This opinion editorial is signed by Care New England Board Chairman Charles Reppucci; Maribeth Williamson and Gary Furtado, Vice Chairpersons; Douglas Jacobs, Treasurer; James Botvin, Secretary; Joseph McGair, Cynthia Patterson, Mario Bueno, Sharon Conard-Wells, Kent Gladding, William Kapos, Patrick Murray, Christina Paxson, George Schuster, James Fanale, MD, President and CEO; Kevin Baill, MD; Jason Boudjouk, MD; Tolga Kokturk, MD.

The proposed acquisition of Care New England by Boston's Brigham Health will enhance Rhode Islanders' quality of care and provide easier, affordable access to health care in Rhode Island, and will have a significant influence on our state's economy.

We are very proud of the many fine local hospitals, doctors and other clinicians Rhode Islanders have as a resource for health care. The principal benefit of the proposed acquisition is the ability to keep patients close to home, as evidenced by the Kent Hospital - Brigham cardiology and colorectal surgery partnership.

The premise of the CNE-Brigham affiliation is to import an enhanced level of health care to Rhode Island. Brigham Health ranks at the top of the list in regional and national performance metrics, in health care as well as in medical education and research. Excellence in these spheres translates into cutting-edge clinical services and new medical technology being available to those who reside within Rhode Island.

A major part of what Brigham Health will bring to Rhode Island is an infusion of medical talent that would be

immediately accessible to our community. Not to be ignored, however, is the financial strength of the Partners system, which will lower borrowing costs and provide needed access to capital to renovate our existing facilities and build new, easily accessible patient centered facilities for those requiring less than inpatient hospital care. New capital will provide the means to purchase technologically advanced software and cutting-edge medical equipment.

Hospital costs in the proposed acquisition would remain completely subject to negotiations with Rhode Island health insurers as well as the regulatory oversight of the RI Office of Health Insurance Commissioner (OHIC). Medical decisions in Rhode Island are currently and will continue to be made by physicians licensed in Rhode Island. This is not only good medicine, it is required by law.

The Care New England - Brigham affiliation will safeguard medical education in Rhode Island. The Brown University Program in Medicine has recently renegotiated a new three-way partnership agreement with Care New England and the Brigham.

Also, of note is that there are already three out-of-state health care systems operating in Rhode Island. The Yale - New Haven System with Westerly Hospital, Prospect - Charter Care owning St Joseph and Fatima hospitals and Prime Healthcare owning Landmark in Woonsocket.

The focus of remaining regulatory review of Care New England's proposed acquisition should be on the merits of the transaction and the benefits that will be achieved by expanding CNE's relationship with Brigham Health. The primary questions important to the citizens of this great state are: Does this merger improve the quality and access to health care in Rhode Island? The answer is an unequivocal yes. Will there be any negative impact on the affordability of care in Rhode Island? The answer is clearly no.

We, the Care New England Board of Directors, believe the proposed acquisition of Care New England by Boston's Brigham Health will support high-quality, affordable and accessible care for Rhode Islanders and benefit our state economy. ♦

[Editor's note: See earlier statements from Lifespan, CNE, Brown, In the News, page 52]