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Rethinking our Guideline System: Returning to Evidence Based Medicine as it was Originally Intended

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The scientific literature is burgeoning at an alarming rate, making it impossible for physicians to integrate, let alone read even a miniscule portion of publications. The STM, a global organization whose aim is to disseminate results of high-level research and publications, recently assessed the magnitude of the literature boom. In 2012 they reported that 1.8 to 1.9 million papers were published in 28,100 active scholarly journals [1]. With regulatory demands equally explosive, how are physicians to find time to remain current with medical science and still provide quality care for their patients? One solution has been the creation of evidence-based guidelines. Guidelines offer medical practitioners easily accessible, carefully considered distillations of the literature, with associated recommendations. Theoretically such guidelines should ensure consistency of care. Pragmatically though, the lack of harmonization among guidelines has left doctors more confused than supported. The 2013 ACC/AHA cholesterol guideline exemplifies this problem. Based solely on Randomized Controlled Trial evidence (RCT) it flipped lipid management upside down. It is important to recognize that the decision to rely exclusively upon RCT evidence was not made in a vacuum; it was influenced by The Institute of Medicine's 2011 Book, *Clinical Practice Guidelines We Can Trust* [2]. By abolishing specific cholesterol targets, and presenting a paradigm in direct conflict with other reputable guidelines - such as those from the NLA, AACE, EAS, IAS, and ESC - the ACC/AHA confused physicians and patients alike [3-8]. Though borne of good intentions, the guideline's restriction of evidence to simply RCTs (eliminating even expert opinion), led to recommendations that failed to resonate with many lipid experts, cardiologists, and internists here and abroad. Instead of simplifying patient care, the 2013 ACC/AHA cholesterol guideline threw the cardiology and internal medicine world into a tailspin. A similar phenomenon recently rocked the realm of hypertension. Clearly it is time for us to reevaluate the construct and purpose of our guidelines. A closer look at the hypertension dilemma will help us understand why.

Hypertension is a major risk factor for the development of coronary artery disease and stroke. According to the Centers for Disease Control (CDC) 740,083 Americans died in 2013 from these two pathologies. "At least 65 million U.S. residents have blood pressures (BPs) that place them at significantly higher risk of coronary artery disease, heart failure, renal failure, thoracic and abdominal aneurysms, myocardial infarction, and stroke. Hypertension is also associated with cognitive dysfunction, erectile dysfunction, and loss of vision. The higher the pressure is, the greater is the risk of complications" [9]. Hypertension, like cholesterol, has occupied center stage in clinical medicine. In a similar vein, so too have its guidelines, especially with regard to older adults. JNC-8's loosening of BP cut-points in the elderly raised more than a few eyebrows. JNC-8 was published in 2014 and advised that in the general population, pharmacologic treatment should be initiated when blood pressure is 150/90 mmHg or higher in adults 60 years and older, or 140/90 mmHg or higher in adults younger than 60 years. In patients with hypertension and diabetes, JNC-8 recommended initiation of pharmacologic treatment when blood pressure is 140/90 mmHg or higher, regardless of age [10]. JNC-8 recommendations differed significantly from the prior 2007 ESH/ESC Guidelines [2], which, in consensus with other hypertension guidelines, recommended two distinct BP targets, < 140/90 in low-moderate risk hypertensive's and < 130/80 mmHg in high-risk hypertensive's (those with diabetes, cerebrovascular, cardiovascular, or renal disease) [11]. JNC-8 explained their shift in the following manner, "While there is high-quality evidence to support a specific systolic blood pressure (SBP) threshold and goal for persons aged 60 years or older (See recommendation1), the panel found insufficient evidence from good- or fair-quality RCTs to support a specific SBP threshold or goal for persons younger than 60 years. In the absence of such evidence, the panel recommends a SBP treatment threshold of 140 mmHg or higher and a SBP treatment goal of lower than 140 mmHg…" [10]. In accord with the aforementioned ACC/AHA Cholesterol Guidelines, the upward shift of a SBP threshold to 150 mmHg in those > 60 years was made solely on the basis of RCT data. Paralleling the fallout from the ACC/AHA cholesterol guideline's reliance on exclusively RCT evidence, many hypertension experts were more than dismayed by this change.

The European Guidelines on CVD Prevention also altered their BP targets in 2012. They recommended a target of < 140/85 mmHg for patients with diabetes. The reason for easing their guidelines in even high risk patients according to the ESH/ESC was that re-appraisal of ESH/ESC Guidelines from 2009 revealed that RCT evidence had not been available to support the prior recommendations to lower BP to < 130/80 mmHg in patients with diabetes or a history of CV or renal disease [12]. Again, RCT evidence was the sole driver of this guideline change and was outlined in the society's official guideline publication, a weighted system built on the hierarchical level of evidence considered [13].

The recently published SPRINT trial confirmed the concerns of many who believed the elderly required tighter BP control than that which was specified in JNC-8. SPRINT was a randomized, controlled, open-label trial conducted at 102 clinical sites. Participants were

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required to meet all of the following criteria: an age of ≥ 50 years, a systolic blood pressure of 130 to 180 mmHg, and an increased risk of cardiovascular events. Eligible participants were randomized to a systolic blood-pressure target of either < 140 mmHg (the standard-treatment group) or < 120 mmHg (the intensive-treatment group). The primary hypothesis was that treatment to reach a systolic blood pressure target of < 120 mmHg, as compared with a target of < 140 mmHg, would result in a lower rate of the composite outcome of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Secondary outcomes included the individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome and death from any cause. A total of 9361 participants were enrolled between November 2010 and March 2013. The trial was prematurely halted after a median follow-up of 3.26 years because of a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65 % per year vs. 2.19 % per year respectively; hazard ratio with intensive treatment, 0.75; 95 % confidence interval [CI], 0.64 to 0.89; P < 0.001). All-cause mortality was also significantly lower in the intensive treatment group (hazard ratio, 0.73; 95 % CI, 0.60 to 0.90; P = 0.003). Rates of serious adverse events including hypotension, syncope (without injurious falls), electrolyte abnormalities, and acute kidney injury or failure were higher in the intensive treatment group than in the standard-treatment group. As anticipated, a price was paid for improving the hard outcomes included in the primary endpoint [14]. Thus SPRINT, an excellent RCT, conflicted with the findings of JNC-8-which was based strictly on RCT data.

Reviewing the various guidelines noted above, as well as the data on which they are based, clinicians and researchers must recognize and accept two facts: First, RCT evidence will always be limited and conflicting. It is in large part for this reason that evidence based medicine was meant to include multiple forms of evidence-observational data, current understanding of pathophysiology, RCT data, and yes, even clinical acumen [15]. Evidence Based Medicine (EBM) was never intended to be one-dimensional, relying solely on RCT evidence. Such a concept is a dangerous distortion of the intent of EBM and has led to the confusion described in this commentary. Second, every patient is unique. Thus, some will experience adverse events from our therapies while others will simply enjoy benefit. It is difficult to sort these patients, but it is the duty of the clinician to do his/her best. Success depends not only upon a clinician's familiarity with guidelines and RCT evidence, but also broad-based knowledge, and clinical acumen as well.

As the data mount and cardiovascular disease remains the number one cause of death in the United States, where does this leave clinicians? Unquestionably medicine's evolution is rapid and profound and our guidelines must attempt to keep pace. However, it is dangerous and misleading to elevate guidelines - or any RCT data for that matter - to the level of infallibility. Guidelines also should not deviate from the prudent intent of EBM by being limited to RCT data. In fact, RCT-dependent guidelines should for clarity probably be dubbed, "RCT Guidelines."The fluid nature of medical understanding itself is proof that guidelines are and will always be inherently flawed. Instead of looking to them as immutable doctrines, we must do the following. We should adhere to the fundamentals of clinical care and practice in a patient-centric manner. Each patient is unique. Optimal results demand the utilization of every piece of data at hand, the understanding that medical knowledge is evolving, and the recognition that guidelines must remain a guide, not a dictum.

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