Brief Review

Observational Studies May Be More Important Than Randomized Clinical Trials

Weaknesses in US Preventive Services Task Force Recommendation on Blood Pressure Screening in Youth

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On behalf of the Atherosclerosis, Hypertension, and Obesity in Youth committee of the American Heart Association (AHA), we appreciate the opportunity to comment on the recently published US Preventive Services Task Force (USPSTF) recommendation statement on Screening for Hypertension in Children and Adolescents (Table).1

Since the 1970s, the National Heart, Lung, and Blood Institute has recommended measurement of blood pressure (BP) in healthy children as part of routine health maintenance.2,3 The American Academy of Pediatrics4 and the AHA also advocate this approach.5,6 Recently, the USPSTF concluded that the "current evidence is insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease (CVD) in childhood or adulthood."7 The USPSTF approach, which limits the allowable evidence, primarily to randomized controlled trials, and additionally fails to address important questions on pediatric BP, may lead to an undervaluing of pediatric BP measurement and may contribute to practitioner confusion.

The USPSTF performed an evidenced-based review to address the use of BP screening in childhood. The task force developed 8 key questions and performed a literature review that netted 6435 potentially relevant articles. After abstract review, 1059 articles were selected as applicable to the key questions, and they underwent full text review. Only 35 articles (describing 34 studies) were included in the statement. The others were excluded as wrong population, intervention, outcome, study design, language, duration, no original data, inadequate duration, or inadequate reference standard. The search strategy, key questions, and references can be found at http://www.uspreventiveservicestaskforce.org/uspstf/uspsphyechld.htm. The evidence considered (34 articles in all) was, in our opinion, unnecessarily restrictive. For example, the evidence used to address the question “Is screening for hypertension in children/adolescents effective in delaying the onset or reducing adverse health outcomes related to hypertension?” gave little weight to important observational data. Unfortunately, there are no randomized controlled trials comparing CVD outcomes in children screened versus not screened for hypertension (HTN); such a study would require following up children to the point of clinical events 40 to 50 years later. However, multiple observational studies have shown that BP levels in childhood have some (although not perfect) use in predicting adult HTN. The Muscatine study reported significant correlations between childhood and adulthood BP levels after 17 years of follow-up as early as 1989.8 This finding was replicated in the Bogalusa Heart Study with additional Bogalusa data showing clinically diagnosed HTN as an adult was 4 times higher with BP level above the 80th percentile as a child. If elevated BP was identified on multiple occasions as a child, the prevalence of adult HTN was even higher.9 Recent analyses from the CV Risk in Young Finns study examined subjects up to 27 years since baseline childhood measures were obtained. Higher childhood BP level increased the odds for adult HTN significantly even after adjustment for childhood obesity, family history of HTN, and genetic risk score (odds ratio, 1.65; P<0.0001).10 This is relevant because adult HTN is a well-proven risk factor for CVD events.11,12 Although a randomized, controlled trial data would be ideal, considering observational studies allows the reasonable clinician to infer that identification and treatment of HTN in youth may prevent future CVD events.

Important evidence links childhood BP measures to intermediate outcomes in adults such as carotid intima-media thickness (cIMT). Observational data from the CV Risk in Young Finns Study showed that higher BP measured in youth was associated with greater cIMT in adulthood,13 an important finding because cIMT is strongly correlated with coronary artery disease.14 The Task Force disputed the strength of this evidence because a Bogalusa Heart Study article found adiposity and lipids to be more important than BP levels.15 However, the Bogalusa article included a much smaller sample (486 versus 2229 subjects). Furthermore, a recent article pooling data from Bogalusa, Young Finns, Childhood Determinants of Adult Health (Australia), and Muscatine Study (n=4380) observational data found a significant effect of BP measured at age 12 years and adult carotid thickness.16

Considering additional data also sheds light on other Task Force statements. First, poor accuracy of BP measurement, and associated risks of false positives, was concerning to the
USPSTF: Other ways of measuring BP, aside from BP screening in well child visits, may help reduce risks of false positives because ambulatory\textsuperscript{17} and home BP monitoring\textsuperscript{18} better characterize the true BP level of a patient when compared with the office, and can be performed in pediatric patients. Second, the Task Force felt studies addressing the effectiveness of therapy for primary HTN were inadequate. There are several studies showing that diet,\textsuperscript{19} weight loss with increased exercise,\textsuperscript{20} and antihypertensive drugs\textsuperscript{21} are effective in reducing BP in youth. Although these small studies did not demonstrate significant adverse effects, there have been $>20$ years of pediatric usage of these drugs in clinical practice, and no new systematic adverse class-effects have been identified. However, these data were given less importance because many of the trials were of short duration, perhaps so as not to leave placebo patients untreated for too long. Recent studies included year-long open-label extension periods demonstrating sustained BP reductions in pediatric patients with drug treatment.\textsuperscript{21} The Task Force report did not include consideration of these data.

Other important key questions were simply not addressed by the USPSTF. For example, “what is the evidence that identification and treatment of HTN in youth can prevent target organ damage?” such as left ventricular hypertrophy (LVH). Cross-sectional studies show an association between childhood BP and concurrent target organ damage, including LVH, increased cIMT, and arterial stiffness.\textsuperscript{22} Intervention studies in hypertensive youth demonstrate that antihypertensive therapy leads to regression of LVH,\textsuperscript{23,24} reduction in carotid thickness,\textsuperscript{25} and reversal of microalbuminuria.\textsuperscript{26} Reversal of target organ damage in adults is associated with reduction in hard CVD events,\textsuperscript{27} suggesting that treatment in youth may modify adult event rates, even if long-term follow-up data from randomized, controlled trials are not available in adolescent HTN.

Another important issue not considered in the USPSTF guidelines was whether screening for and treatment of HTN in youth may indeed lead to additional positive outcomes beyond BP reduction, resulting in reduction in clustering of CV risk factors. The identification of prehypertension (before progression to sustained HTN) may lead to positive lifestyle changes that could contribute to improved short-term (target organ damage) and long-term (reduced CVD mortality) outcomes. Most importantly, BP screening identifies the small but significant number of children with severe secondary HTN who would otherwise have been missed.

In summary, we believe that the Task Force’s I (inconclusive) recommendation is flawed because the evidence was too narrowly selected, and available shorter term and observational studies were not considered. In the absence of perfect data, the practitioner must use common sense, not ignore research that is given a lower grade where superior evidence does not exist. “What is the evidence that adult HTN can be prevented or modified by earlier intervention” will never be answered if we do not continue screening for BP in youth. Ongoing collaboration among the world’s largest childhood CV studies (http://i3cconsortium.org/index.html) may soon provide answers. The International CV Childhood Cohorts Consortium is gathering and harmonizing data from the largest international children’s cohorts that contain measurements of major CV risk factors in childhood with follow-up through adulthood. The 7 cohorts (Bogalusa Heart Study, CV Determinants of Adult Health, Minneapolis Childhood Cohorts Studies, Muscatine Study, National Growth & Health, Princeton Lipid Research Study, and CV Risk in Young Finns) have data on $>40000$ participants who are now reaching 50 years of age when CV events are beginning to occur. Continued follow-up of these cohorts will provide data on the independent effects of childhood and early adult levels of CVD risk factors on subsequent CVD occurrence. However, the restrictive exclusion criteria in the USPSTF approach would preclude consideration of even these robust data. Until the consortium can complete their work, our group continues to recommend routine screening for HTN at all well child visits, with the goal of achieving the AHA’s 2020 goals for CV Health.\textsuperscript{28}

Disclosures

E.M. Urbina is consultant, Midmark Medical, Inc. The other authors report no conflicts.

References


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