Best Pharmaceuticals for Children Act (BPCA)
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)**
National Institutes of Health (NIH)
in collaboration with the U.S. Food and Drug Administration (FDA) and National Heart, Lung, and Blood Institute (NHLBI)

Primary Pediatric Hypertension Workshop: Epidemiology and Treatment Gaps
September 25, 2017

Welcome and Introductions

Perdita Taylor-Zapata, M.D., began by welcoming participants and presenters to the workshop. Dr. Taylor-Zapata briefly described the BPCA mandate—including supporting research to improve therapeutics for children and teens. She reviewed the background and development of the workshop within the context of that mandate. Dr. Taylor-Zapata explained that the workshop was the result of efforts from within NIH and FDA to improve clinical trials and clinical research concerning children and young people. She noted that the workshop came about largely due to interest in a retrospective study published by David Kaelber, M.D., Ph.D., and associates on how pediatric hypertension (HTN) is diagnosed and treated in primary care settings. That study was the impetus for establishing a BPCA Primary Hypertension Working Group (WG) to provide a forum for further discussion of study findings. As a result of their dialogue, WG members from throughout NIH, including NICHD and NHLBI, and their colleagues from FDA recommended conducting a workshop to engage in a broad discussion of the gaps in diagnosis and treatment of primary pediatric HTN and how those gaps might be addressed.

Purpose

Dr. Taylor-Zapata introduced Anne Zajicek, M.D., who thanked participants for their interest. Dr. Zajicek emphasized that the alarming rates of adult obesity, and conditions associated with obesity such as HTN, in the U.S. and internationally are now also increasing in pediatric populations. She also noted that while the effects of HTN in adults are clear, the meaning of elevated blood pressure (BP) on pediatric patients is less clear.

In referring to the report, "Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study,"[1] Dr. Zajicek pointed out that in the study, only 2,813 of the approximately 12,000 children with HTN were diagnosed. Of those diagnosed, only 158 were being treated for the condition with antihypertensive medications within 12 months of diagnosis, which was obviously problematic. Dr. Zajicek also noted that the most common types of treatment included diuretics, beta blockers, and ACE-I-channel blockers. Each of these treatment types involves issues that could potentially compromise compliance, for example diuretics resulting in frequent bathroom visits, beta blockers and exercise tolerance, or ACE-I and possible teratogenicity. She also briefly described other relevant issues that warrant discussion. For example, Dr. Zajicek referred to studies conducted by WG member, Danny Benjamin, M.D., and associates that concluded that some of these studies failed because of insufficient dose ranging. [2]

Another issue of concern is the effect of off-label use of antihypertensive agents. She then discussed the issue of lack of identification of clear biomarkers of HTN in children. While increased BP is a surrogate biomarker for myocardial infarction (MI)/heart failure and death in adults, that relation is less clear for pediatric cases. Dr. Zajicek concluded her remarks noting that the goal of this workshop was to discuss some of these issues and define next steps in addressing these issues and closing the gaps in effective and proper treatment of primary HTN in children.

Gilbert Burckart, Pharm.D., welcomed participants on behalf of the FDA. Dr. Burckart emphasized that FDA is working to make science-based decisions as much as possible. He noted that those decisions depend on feedback from groups like this one and from NIH colleagues to define studies that answer the difficult questions that arise during the course of identification of, and research on, new diseases and conditions. He reiterated that the FDA looks forward to the science that results from these studies.

Dr. Taylor-Zapata briefly described the workshop format. She explained that the WG decided to structure presentations and discussions in three modules, with questions and answers at the end of each module as well as within and across the modules.

Dr. Taylor-Zapata next introduced Brian Kit, M.D., M.P.H., representing NHLBI, as the moderator for Module 1.

Module 1: Primary Pediatric Hypertension—Epidemiology and Current Diagnosis Criteria
Moderator: Brian Kit, M.D.

What Do We Know? Overview of Hypertension in Pediatrics, Epidemiology and Diagnosis
Presenter: Carissa Baker-Smith, M.D.

Dr. Kit next introduced Dr. Carissa Baker-Smith, who began her presentation by noting that the prevalence of primary HTN is approximately 2-4% in all children, and that clinical data indicate that HTN prevalence is approximately 3.5 % among children, when based on elevated BP readings at three separate office visits. These findings are based largely on data compiled from National Health and Nutrition Examination Survey (NHANES) data. Dr. Baker-Smith also noted that clinical studies that have recorded elevated BP also have shown a decline in BP by the third reading.

She noted that among U.S. adults diagnosed with high BP, only half were aware of their diagnosis and that only half had controlled HTN. Dr. Baker-Smith pointed out that there have been no studies of awareness of HTN among healthy youths, but among youths with diabetes, only 1/3 were aware of their BP status, and only 40-60 % achieved good BP control. She emphasized that small studies have indicated that lifestyle modification and medications are effective in controlling elevated BP in youths.

Dr. Baker-Smith next reviewed several dynamics that are key variables in the diagnosis of primary HTN:

- Devices used in making diagnosis
- Repeated measure

- Where diagnosis is made (office visit vs. home monitoring vs. ambulatory measurement)
- Metrics such as age, height percentile, and gender.

She also described barriers to accurate BP measurement, including lack of appropriate/accurately sized BP cuffs and improper technique for taking BP; she discussed the effect of "cumbersome" BP tables on accurate measurement. Dr. Baker-Smith cautioned that because of the lack of BP and cardiovascular (CV) endpoints in children and teens, since 1987, HTN has been defined based on BP distribution in healthy children. Normative data in children are based on auscultatory the BP measurements.

Dr. Baker-Smith referred to the recently issued American Academy of Pediatrics 2017 Clinical Practice Guideline for Screening and Measurement of High Blood Pressure in Children and Adolescents (CPG), noting that diagnosis of HTN continues to be based on BP measurement and assessment. She did point out that the 2017 CPG definition of HTN refers to BP > the 90^{th} percentile as "elevated" BP.

Dr. Baker-Smith emphasized that the importance of proper technique for measuring BP cannot be minimized, and that BP should be measured over three visits. She briefly reviewed the various types of BP measuring devices.

Dr. Baker-Smith reported that BP measurement should begin about age 3 years among healthy children. This recommendation did not change in the 2017 CPG. She did note that there is a greater awareness of "masked" HTN, and briefly discussed Ambulatory BP Monitoring (ABPM). Dr. Baker-Smith next discussed "White Coat Hypertension" (WCH). The WCH phenomenon is defined as BP $\geq 95^{th}$ percentile in the office or clinical setting but $<95^{th}$ percentile outside the office or clinical setting. It is estimated that as many as half of children who are evaluated for elevated office BP have WCH. Children and adolescents with WCH should have screening BP measured at regular well-child care visits with consideration of a repeat ABPM in 1 to 2 years.

Dr. Baker-Smith next discussed masked HTN. Described in 5.8 % of children, masked HTN is defined as normal office BP with elevated out-of-office BP on ABPM. Associated with increased risk of hypertensive target-organ damage, masked HTN is more commonly found in patients with obesity, chronic kidney disease (CKD), and other secondary forms of HTN. She also discussed BP measurement in children with obesity.

Dr. Baker-Smith described other challenges to accurate BP measurement, including at-home measurement. She pointed out that pediatric studies do not show that BP measurements obtained in settings other than the office or by ABPM are sufficiently reliable to establish a diagnosis of HTN by themselves. However, this recommendation should not discourage home or school BP measurement for screening or monitoring purposes.

Dr. Baker-Smith summarized other issues regarding BP measurement:

- Lack of normative data
- Only a few devices validated for children
- Limited cuff sizes for children
- Lack of consensus about how many measurements across what period of time are needed to evaluate BP.

Dr. Baker-Smith again noted that full BP tables are complicated and cumbersome to use, which likely contributes to under-recognition of childhood HTN. She briefly discussed the BP Diagnosis Algorithm and revised BP tables included in the 2017 CPG.

She then discussed the primary and secondary causes and risk factors for HTN in children greater than 6 years of age, including positive family history of HTN and obesity/overweight. She described secondary causes, including renal/renovascular disease, environmental exposures, and aortic coarctation. She noted that those clinical conditions associated with greater risk for hypertension or elevated BP include:

- Obesity
- Sleep-disordered breathing (SDB)
- CKD
- Type 1 and type 2 diabetes
- History of low birth weight
- Children with aortic coarctation and other forms of aortic arch obstruction (e.g., middle aortic syndrome).

Dr. Baker-Smith discussed the prevalence of HTN in children with obesity, noting that the rate of HTN increases with increasing adiposity such that prevalence ranges from 3.8% in children who are overweight to 24.8% in children with obesity. She summarized a school-based BP Screening Program (Houston Public Schools) that followed 21,062 adolescents, 10 to 19 years of age. Study findings showed a Sustained Prevalence of HTN: 2.7% (with a 3.1 % prevalence among Hispanic students, compared with 2.7 % among African-American students, 2.6 % among White students, and 1.7 % among Asian students). She noted that the relationship between obesity status and HTN may differ by group.

Dr. Baker-Smith discussed the relationship between HTN and SDB, noting that children with SDB are at risk for systemic HTN. She noted several challenges in trying to determine the relationship between race and risk for HTN, pointing out that studies have found that the risk of HTN correlates more with obesity status than with ethnicity or race, although there may be some interaction. Currently, there are insufficient data to support the use of race, sex, or ethnic factors to inform the evaluation or management of HTN in children.

In discussing the relationship of HTN and the risk for future cardiovascular disease (CVD), Dr. Baker-Smith pointed out that elevated BP in childhood increases the risk for adult HTN and metabolic syndrome. She also noted that measuring BP on routine well-child visits allows for identification of both primary and asymptomatic secondary HTN.

Dr. Baker-Smith concluded her presentation by noting:

- Hypertension in youth is not uncommon.
- Current guidelines no longer rely only on the presence of elevated BP in the office for recognizing HTN but also incorporate ABPM. However, appropriate in-office technique is important for diagnosis.
- Children with obesity, a history of prematurity, SDB, and other risk factors need to be screened more frequently and represent a higher risk group.

- Race and ethnicity- based differences in the prevalence of HTN in youth appear to be less prevalent than in adults.
- HTN in youths may be a risk for HTN in adulthood, allowing for greater risk of CVD in adulthood.

Epidemiology of Elevated Blood Pressure Among US Children and Adolescents: An Overview of the NHANES Experience
Presenter: Brian Kit, M.D.

Dr. Kit began his presentation by referring to NHANES data on the prevalence of HTN in U.S. adults aged 18 or older. He pointed out that these data indicate that the prevalence of HTN has remained somewhat stable during 1999 to 2014, noting that approximately one-third of U.S. adults have had HTN. Dr. Kit also pointed out that NHANES data indicate that the prevalence of HTN among U.S. young adults between the ages of 18 and 39 was actually lower than the national average, but also remained somewhat constant (7.6 in 1999 versus 7.3 in 2014).

Dr. Kit next presented data results from assessing awareness of HTN among those diagnosed with HTN in the 18-39-year-old age group. He pointed out that approximately ¾ of the young adults assessed were aware of their condition compared with ¼ that were not aware of their condition; 50% were being treated for their HTN.

Dr. Kit reviewed the definitions for HTN used in the NHANES analysis:

- Adult: Systolic BP≥140 mm Hg, or diastolic BP ≥ 90 mm Hg, or currently taking medication to lower blood pressure
- Pediatric: Statistically defined, not outcomes based; Systolic or diastolic-≥ 95th percentile ("high"); ≥90th percentile or >120/80 but <95th percentile ("borderline").

Dr. Kit noted that the reference data used were from the Fourth Report. He also briefly described NHANES sample recruitment and data collection procedures. He pointed out that this national population-based study uses randomly selected subjects. BP readings are collected in mobile examination facilities, as part of a comprehensive examination that collects data on height, weight, etc.

Dr. Kit reviewed data on BP among U.S. youth 8-17 years, from NHANES 1999-2012, noting that BP in > 95th percentile showed a small decline. He called attention to NHANES 1988-2012 data for BP in U.S. youths in the 8-17 age group. There was greater variability among those in the > 90th percentile. He also mentioned that NHANES also collected data that examined BP in U.S. youth 8-17 years of age, by race/ethnicity 2011-2012, which allowed investigators to derive data for Asian populations.

Dr. Kit next reviewed NHANES 2011-2012 data on BP among U.S. youth 8-17 years, based on weight status. Not surprisingly, these data support the conclusion that weight status is related to BP. He also noted that other populations in NHANES included children younger than 8 years of age, as well as those with chronic medical conditions, such as diabetes and renal disease.

Dr. Kit closed his presentation by echoing the point underscored in previous presentations emphasizing the importance of measuring BP over the course of multiple visits.

Research Activities to Address Knowledge Gaps Related to Blood Pressure Screening and Control in Children
Presenter: Carrie Klabunde, Ph.D.
Presenter: Iris Mabry-Hernandez, M.D., M.P.H.

Dr. Kit next introduced Dr. Carrie Klabunde, who in turn, introduced co-presenter, Dr. Iris Mabry-Hernandez.

Dr. Klabunde described the role of the NIH Office of Disease Prevention (ODP) in addressing prevention research gaps. The ODP carries out its prevention research mission in collaboration with a number of stakeholders; this includes a partnership with the Agency for Healthcare Research and Quality/U.S. Preventive Services Task Force (AHRQ/USPSTF) Program. She presented a brief overview of the NIH ODP reiterating ODP strategic priorities:

- Identify prevention research areas for investment or expanded effort by NIH.
- Work with stakeholders to identify needs in prevention research.
- Compare those needs to the current NIH portfolio to identify gaps in prevention research.
- Work with the NIH Institutes and Centers to identify promising/feasible prevention research gaps for investment or expanded effort.

Dr. Klabunde also briefly described the USPSTF role, as an independent, volunteer panel of non-Federal experts in prevention and evidence-based medicine. She explained that ODP is the NIH liaison to the USPSTF. She also explained that the USPSTF makes evidence-based recommendations about clinical preventive services in primary care. The Task Force assigns a letter grade (A, B, C, D, or I) based on the strength of the evidence and balance of benefits/harms of a preventive service. AHRQ convenes the Task Force and provides scientific, administrative, and dissemination support for that letter grade.

Dr. Klabunde explained the USPSTF I Statement, in which the USPSTF has concluded that the current evidence is insufficient to assess the balance of benefits and harms of the service. She also discussed the ODP Annual USPSTF I Statement Reporting Survey, which identifies and documents NIH involvement in activities to address the research gaps reflected in USPSTF I statements. She noted that the 2017 survey covered 49 I statements that included screening for BP in children and adolescents and interest in expanding the NIH portfolio to address screening for pediatric HTN evidence gaps.

Dr. Mabry-Hernandez explained that in 2013, the USPSTF concluded that the evidence was **"**insufficient to assess the balance of benefits and harms of screening for primary HTN in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood."

She explained that the Task Force had developed a detailed Analytic Framework for Blood Pressure in Children and Adolescents that included several key questions that were asked in determining the Task Force recommendations and the I letter grade. These questions focused on the effectiveness of HTN screening in children/adolescents in delaying the onset of or reducing HTN-related adverse health outcomes. The Task Force also looked at the diagnostic accuracy of tests screening for elevated BP in children and adolescents, as well as the association of HTN in children and HTN in adults. Other questions addressed adverse effects of screening for HTN in children/adolescents, including labeling and anxiety. The Task Force questioned the

effectiveness of drug, nondrug, and combination interventions for treating primary HTN in children/adolescents, as well as the effectiveness of drug, nondrug, and combination interventions initiated for treating primary HTN in children/adolescents for reducing BP in adults, as well as reducing adverse health outcomes in adults.

Dr. Mabry-Hernandez presented an overview of the evidence that informed the Task Force determination of the I designation:

- Limited information about the accuracy of the BP cuff in diagnosing high BP in children and teens
- Limited information about screening intervals
- Difficulty in predicting which children and teens will continue to be hypertensive as adults
- Lack of evidence about potential harms of screening
- Unclear evidence as to whether lowering BP in youth leads to improved cardiovascular health in adulthood
- Interventions designed to improve healthy habits and medications have been used to lower BP
- No available evidence on whether treatments are effective over the long term.

Dr. Mabry-Hernandez reviewed several evidence gaps identified by USPSTF Blood Pressure Screening in Children and Adolescents and that there is a need for studies that examine:

- Effectiveness and comparative effectiveness of pharmacologic and lifestyle interventions to achieve sustained reductions in BP and longer term modification of adult HTN and cardiovascular risk in children with primary HTN
- Accuracy and reliability of BP screening tools and protocols in primary care among children and adolescents of varying ages and characteristics
- Adverse effects of screening
- Comparative accuracy studies of different types of devices to measure BP
- Screening strategies that reduce the rate of false-positive diagnoses of hypertension
- Cohort studies that include BP measures and other cardiovascular risk factors (CRFs) in children and adolescents with long-term follow-up
- Studies that elucidate the association among childhood HTN, adult HTN, and surrogate measures of CVD in childhood and adulthood, as well as adult clinical CVD
- Treatment trials examining surrogate or subclinical cardiovascular outcomes during adolescence or young adulthood
- Trials in high-risk adolescent populations that include longer term follow-up with future HTN and subclinical cardiovascular outcomes
- Medication harm, measures of long-term compliance, and individual components of multifactorial interventions.

In summary, Dr. Mabry-Hernandez noted that there are many evidence gaps related to BP screening and control in children, and thus many opportunities for new research studies.

Clinical Decision Trees - Particularly in Primary Care, Can it be Done and How?
Presenter: David C Kaelber, M.D., Ph.D., M.P.H.

Dr. David Kaelber began by discussing the Clinical Decision Tree as a tool for how to transition to guideline-based care as the standard of care implemented "all" of the time. He pointed out that the typical primary care visit is usually between 15–20 minutes, although ideally that visit should be closer to 30 minutes. He discussed the pediatric decision tree as a tool to improve care, noting that the challenge is how to transition to guideline-based care as the standard of care implemented all of the time.

Dr. Kaelber differentiated the primary care pediatric HTN diagnosis decision tree from the primary care pediatric HTN management decision tree, focusing on how to improve BP measurement technique, and how to quickly evaluate normal versus abnormal BP in "real time." He also emphasized the need for three separate measurements for diagnosis; and how to track BPs over time. He also pointed out that BP measurements are usually taken by office staff, as part of patient check-in procedures. It is important that these non-physician staff are trained to immediately recognize an abnormal reading and be prepared to take a follow-up reading before the patient sees the primary care physician. The challenge is how to improve BP measurement technique.

Dr. Kaelber noted the importance of provider recognition of HTN, explaining that at least ¾ of abnormal BP in pediatric patients goes undiagnosed. He also pointed out that electronic health record (EHR) alerts doubled the recognition of abnormal BPs. At the same time, "real-time" EHR alerts eliminated 1/3 of "false positive" BPs. He suggested that organizations with EHRs used in an office setting should consider including flags for abnormal BP values, both when the values are being entered and when they are being viewed. Dr. Kaelber also questioned whether three lifetime elevated BP readings is the right cut-off for diagnosis.

Dr. Kaelber discussed the Management Decision Tree, based on several factors, including:

- Effectiveness of lifestyle
- Counseling for most patients
- Ambulatory BP monitoring (ABPM) availability
- Comfort level for starting treatment
- Subspecialty availability.

He also noted that there may be significant practical barriers to obtaining ABPM in many pediatric care settings.

Dr. Kaelber pointed out that most pediatricians do not have training or experience with antihypertensive medications, and that there is no clear evidence regarding what medication to use. He also pointed out that parental and provider concerns are not unusual about starting "life-time" medication (for an asymptomatic disease), and if there will be a need to treat or refer for persistent uncontrolled HTN.

Dr. Kaelber pointed out that pediatric HTN is among the top five chronic diseases in pediatrics, and that 1.5 million children in the United States are undiagnosed for HTN, and approximately 1.8 million children in the United States are undertreated. He concluded by emphasizing that addressing these gaps and concerns can be accomplished in a primary care setting, noting that

American Academy of Pediatrics (AAP) HTN guidelines are clear, and simple to follow. He also urged for the need for efforts from local organizations and stakeholders, as well as systemic/national efforts from agencies such as the Centers for Disease Control and Prevention (CDC) and NIH, as well as EHR vendor engagement, for continued research/funding to study and address pediatric HTN.

Questions, Comments, Discussion

Question 1 (Ingelfinger): There is a need for more data, especially prospective data, for example, that which will derive from a current study, SHIP AHOY (Study of High Blood Pressure in Pediatrics: Adult HTN Onset in Youth) data, as well as additional research. How can we make ABPM doable, scalable, and verifiable?

Response (Kaelber): Both 2017 Pediatric CPG and the forthcoming CPG for adults, increased the call for ABPM. European countries have already adopted ABPM procedures. While the U.S. is behind in incorporating ABPM as a standard of care, we should be able to do this fairly easily, especially if we address reimbursement sooner rather than later.

Response (Baker-Smith): The issue of cost is real; not only the cost (and availability) of ABPM devices, but also the costs associated with elevated BP work-ups and tracking. However, given the recognition of WCH, which will be discovered through the use of ABPM devices, it may take some time but ABPM as a standard is doable. It will require a shift in approaches from the primary care provider and their staff in how they go about identifying HTN in kids.

Response (Portman): The ABPM process is cumbersome. With the help of technology, we should be able to move on from this cumbersome process.

Response (Kaelber): There are areas of Research and Development (R&D) and current/future technologies that present possibilities to use to more accurately measure BP, but to facilitate BP monitoring. For example, there are cell phone "apps" that record BP, but there are proprietary issues among "app" developers/providers.

Response (Baker-Smith): With most kids so at ease with today's technology, we encourage teenagers to test BP at home to take away the white coat effect. Collaborating with Apple or other industries would be a good way to move forward to validate measurements and establish normative values.

Response (Urbina): There are no ABPM devices that have associated apps, but there is a whole BP monitor called Qardio. Patients can use their cell phones to activate it and send data to their physicians.

Response (Kaelber): This idea is not simple due to the proprietary nature of some of these apps. If we could agree on oscillometric standards, that would help with a lot of things.

Question 2 (Daniels): Are studies of BP in children feasible? Are the costs of these studies prohibitive?

Response (Mabry-Hernandez): ODP and the Task Force will look at evidence, and factors that indicate a relationship, as well as surrogates that demonstrate a link.

Comment: (Higgins): For low birthweight babies (LBW) babies, it is unclear what is done for neonates in the NICU (both term and pre-term) babies regarding nephrotoxic drugs, PDA, etc.

This points to an epidemiological gap in knowing how those factors contribute to a diagnosis of kidney disease and development of HTN.

Question 3: Are home-and school-based measurements valid for monitoring (in addition to initial diagnosis) elevated BP?

Response (Kaelber): It is very unclear regarding the quality of these measurements, whether ABPMs are used for diagnosis and for ongoing monitoring.

Response (Flynn): Getting FDA approvals needs to be addressed; there is a need to streamline process for device validation.

Response: (Kevin McBryde): BP devices are approved based on established certain standards, reproducible, but not necessarily precise. To change regulations on how BP devices are reviewed and approved, requires FDA approval. Also, the BP monitoring makers will not share information among themselves, all of which is problematic.

Question 4 (from Webinar/Ward): Can't we collaborate with European colleagues with large long-term databases for HTN data?

Response (Urbina): There is already collaboration with a number of international organizations, all of which have been collecting data from populations that are now close to 50 years of age. These groups and a number of U.S. organizations are collaborating, including sharing mortality and morbidity data.

Question 5 (Kit): What are the barriers for calculating percentiles and other information from EHR vendors?

Response (Kaelber): Not every EHR has the same capability. We need to "think outside the box" on how to facilitate and tailor information to a specific requirement. There is an opportunity for NIH (or other organization) to direct and influence the format and content of information collected on EHRs.

Comment/Question 6: Discuss 2017 Guidelines-population-based approach for healthy weight as a strategy for reducing HTN.

Response (Kaelber): One of the challenges of an evidence-based report is that there is still the need for more evidence. Some studies have documented evidence of non-traditional approaches to BP control, but these are large, long-term studies.

Response (Baker-Smith): As part of the study's evidence review for the Guidelines, investigators looked at daily sodium intake, and looked at the DASH Diet, as well as potential non-traditional approaches to BP control. Whatever evidence there was, they did include in informing the Guideline.

Comment (Pratt): It seems that there are racial differences that are more obese driven. Can you comment on that?

Response (Baker-Smith): There is a notion that there are race-based differences in prevalence of obesity in certain groups, especially in the adult population. It is clear that the more obese the child, the higher the BP. Several studies have reported those results. However, more information

needs to be gathered. Self-defined race may be more of a social construct. Environmental constructs may have more of an impact.

Module 2: Hypertension Pathophysiology—What Do We Know? Where Are the Gaps?

Moderator: Stephen Daniels, M.D., Ph.D.

Mechanisms of Elevated Blood Pressure and the Rationale for Treatment
Presenter: Julie R. Ingelfinger, M.D.

Dr. Daniels opened this module by introducing Dr. Ingelfinger, who discussed what we currently understand about the pathophysiology of primary HTN. She reiterated that there are numerous documented reasons for studying HTN, noting that essential HTN affects 20 to 30 % of the world's population, and that HTN contributes to cardiovascular morbidity and mortality. The heritability of elevated BP is approximately 15 to 40 %. Over time, there is a progression of disease in patients with primary HTN. Vascular changes are part of established HTN, but it is unclear how or when these changes occur. She reviewed the numerous factors associated with HTN and many of these factors have been known and studied for decades. The structure and function of blood vessels in the heart change over time in persons with HTN, and the effects of these changes on various organ systems lead to end-organ damage. The mechanisms of end-organ damage are incompletely understood, particularly in children.

Other areas to consider in studying the physiology of HTN include the relation of inflammation to HTN, as well as the role of autoimmunity in primary HTN. Another new area that warrants further consideration is the evolving role of sodium, which is now recognized as retained in the extravascular space. The mechanism of such retention is incompletely understand, as is how this recently recognized role of sodium is involved in primary HTN. Dr. Ingelfinger also briefly discussed microbiota and how they interact with antibiotics, which could modulate BP. She next discussed perinatal programming and critical periods in human gestation in organ development. In concert with the role of perinatal programming, Dr. Ingelfinger next reviewed the association of birthweight with elevated BP and the prevalence of HTN. She also pointed out that epidemiologic studies in humans and animal models strongly suggest that the *in utero* and perinatal environment affect predisposition to CVD, HTN, adult obesity, and type II diabetes. Dr. Ingelfinger emphasized that further research offers the possibility of studying the impact of reduction in long-term risk via focused intervention in early life.

She also discussed that it is widely assumed that BP is controlled by a large number of genes, each of which has only relatively mild effects. It is difficult to discover the genes that contribute to BP variation using traditional approaches, including candidate gene studies and linkage studies.

Dr. Ingelfinger cautioned that while identification of a gene associated with a Mendelian HTN is approachable, for non-Mendelian forms of high BP, which have multiple genetic determinants, the situation is more challenging. A number of recently developed tools are available to reveal genes involved in primary HTN, and a number of studies have identified associations with essential HTN, which is widely viewed as a polygenic disorder. She also noted the importance of proper controls and validation sets when such studies are carried out.

Role of Obesity in Pediatric HTN: Implications for Treatment
Presenter: Aaron Kelly, Ph.D.

Dr. Kelly focused his presentation on:

- Pediatric obesity prevalence and tracking
- Pathophysiology and mechanisms of HTN in the context of obesity
- Excess adiposity as a target for HTN treatment
- Gaps and opportunities for future research.

He briefly reviewed pediatric body mass index (BMI) percentile cutoffs, which are based on age- and gender-specific cutoffs to categorize overweight, obesity, and severe obesity. Dr. Kelly noted that in the past several years, there has been increased focus on severe obesity, with general consensus that this condition has become increasingly prevalent. He reported that the prevalence of pediatric obesity in the United States among children and young adults 2-19 years of age is 17.4 % for Class I, 6.3% for Class II, and 2.4% among Class III obesity cutoffs. Dr. Kelly explained that severe obesity (classes II and III) affects between 4-5 million youths in the United States alone. He also noted that the prevalence is increasing despite leveling-off of overweight/obesity rates in children and adolescents.

Dr. Kelly next discussed tracking, noting that not every child who manifests HTN or elevated BP in childhood will go on to have poor health outcomes as an adult. He presented data from studies that tracked severely obese children, noting that BMI is currently the strongest tracker from childhood to adulthood. He explained that these studies indicate that most of those followed throughout the course of these studies remained in the severe obese category in adulthood. Dr. Kelly referred to an Israeli study that looked at the relation between BMI and CVD mortality.

Dr. Kelly pointed out that prevalence of HTN in all children/adolescents in the United States is approximately 3.5%, whereas in overweight or obese children/adolescents, the prevalence is notably higher, ranging from 4-25%.

Dr. Kelly next briefly reviewed several of the known mechanisms of obesity-induced HTN, including adipocytes, leptin, and adiponectin. He also discussed the effects of inflammation and oxidative stress as biomarkers, as well as vascular interactions, such as circulating endothelial cells.

Dr. Kelly emphasized that some studies have found that adults who had obesity in childhood, but not in adulthood, were equally as healthy as their adult peers who never experienced obesity. It is, therefore, reasonable to conclude that long-term, cumulative exposure to obesity (and its co-morbidities) will lead to poor health outcomes.

Dr. Kelly next discussed the question of how much weight loss is necessary to reduce BP. He referred to the U.S. Preventive Service Task Force 2017 report recently published on screening and management of childhood obesity, which noted that achieving even modest weight loss through lifestyle changes alone is extremely difficult. He also pointed out that this type of dietary and lifestyle counseling requires considerable time and is extremely resource- and time-intensive, requiring between 26 to 51 hours of dietary modification counseling to be effective,

and some would argue that at least 52 hours of behavioral counseling is necessary. Dr. Kelly cautioned that this approach may not be generalizable and that families may not be willing (or able) to take on this time commitment.

He also discussed the important relationship between physical activity and BP. Dr. Kelly turned to pharmacotherapy to treat adolescent elevated BP. He discussed a study of GLP-1 Receptor Agonist in a randomized, controlled trial in adolescents 12-19 years old, which reported a 3% BMI reduction at 3 months with 10 mcg dose twice per day.

Dr. Kelly also discussed findings from studies that looked at the use of various medications to reduce weight and BP. Dr. Kelly reported that these agents have been approved for treating adults:

- A combination of Phentermine and Topiramate administered orally once daily resulted in 1-year weight loss of 7-9% among adults, with a BP reduction commensurate with degree of weight loss.
- A combination of Naltrexone and Bupropion administered orally twice daily resulted in a 1-year weight loss of 3-4% among adults, with a BP reduction less than expected for degree of weight loss.
- Liraglutide administered once daily by subcutaneous injection resulted in a 1-year weight loss of 5-6% among adults, with a BP reduction greater than expected for degree of weight loss.

Dr. Kelly concluded his discussion by describing several issues to consider in determining the future direction for studying childhood obesity and HTN. He strongly emphasized that a combination of therapies is the best approach to achieve long-term and lasting outcomes. He also discussed the need for chronic treatment, and urged that the potential risks of treatment should be weighed against known risks of persistent obesity. Dr. Kelly urged that there is a need to look at predictors of response to try to understand what is working best, with increased attention to how BP and heart rate variability are measured, and the BP-altering effects of obesity.

Role Markers of Atherosclerosis Relevant to Pediatric HTN
Presenter: Elaine Urbina, M.D., M.S.

Dr. Urbina discussed whether there is proof that atherosclerosis is related to high BP. She summarized several studies that indicated subjects with plaque had higher ante-mortem BP and thicker renal arteries. Results were gathered from non-invasive studies that used echocardiography as well as from autopsy results from people who passed away due to unrelated/external causes. Dr. Urbina noted that some of these studies examined the use of MRI results as well as systolic strain as predictors of coronary events. Dr. Urbina focused her presentation on addressing several key issues:

- Proof that atherosclerosis is related to high BP
- How to measure atherosclerotic target organ damage (TOD) non-invasively
- Studies that have linked adult HTN to non-invasive measures of TOD
- Data linking BP in childhood to TOD in adulthood.

Dr. Urbina discussed the time course for development of atherosclerosis, pointing out that atherosclerosis is a slow process that begins early in life. She also noted that atherosclerosis development is accelerated in youth with adverse levels of CVRFs.

She described studies that found that subjects with plaque had higher ante-mortem BP. Dr. Urbina also noted that studies have shown that those subjects with high BP had thicker renal arteries, with histology like that seen in adults with HTN. Also, the mean intima-medial thickness of the left anterior descending (LAD) artery is greater in persons with elevated levels of CVRFs, including BP.

Dr. Urbina pointed to several non-invasive markers of atherosclerotic TOD:

- Cardiac structure and function
- Vascular structure
- Arterial stiffness
- Endothelial function.

She explained that studies have indicated that subjects with left ventricular hypertrophy (LVH) were at four times greater risk of a cardiovascular event during 10 years of follow up, even after adjustment for age. Dr. Urbina discussed HTN as a predictor of cardiac abnormalities, noting that the prevalence of LVH and systolic dysfunction is higher with HTN and/or diabetes. She described cardiac structure and function assessed through MRI, noting that myocardial perfusion measured by MRI was lower in subjects with CVRFs, including those with higher BP, and lower perfusion predicated incident coronary heart disease events. She also noted that the incidence of stroke or myocardial infarction in adults increases with increasing carotid Intima-Media Thickness (cIMT). She next discussed brachial artery distensibility (Brachd), derived using the technique of pulse dynamic analysis of arterial pressure signals obtained from a standard mercury cuff. She explained that Brachd decreases with increasing numbers of CVRFs including, higher BP.

Dr. Urbina emphasized that there are many modalities being used to measure atherosclerotic function, including MRIs, ultrasound, oscillometry, and tonometry. She also pointed out that Brachd ankle pulse wave velocity (PWV) and rate of change increased with the number of CVRFs, including HTN. She described a review of 77 articles that demonstrated that BP is a consistent independent predictor of PWV, even in healthy cohorts.

Dr. Urbina next summarized a meta-analysis of 11 longitudinal studies that followed more than 5,000 subjects for 45 months. These studies found an increased risk for CV events (RR 1.32) in only 10% increase in Augmentation Index (AIx). Flow-mediated dilation (FMD) was lower in adults with HTN compared to normotensive controls. She also discussed decreased reactive hyperemia ratio in hypertensive adults.

Dr. Urbina also noted that data from the Northern Manhattan Study showed reduced endothelial function is a predictor of CV events, and that BP is related to endothelial function. She described several non-invasive devices that are used to measure endothelial function, in particular, peripheral arterial tonometry. This method can be performed by a non-sonographer; it controls for baseline arterial tone, and quantifies quality. She also mentioned laser flow Doppler as another method for measurement.

Dr. Urbina discussed the relation of childhood BP and obesity with increased risk of coronary calcification, noting that eBCT performed at mean age 33 years of age found 30 % of men and 16 % of women had a raised CAC score associated with higher childhood obesity. A total of 62% of men with both high BP and BMI had increased CAC compared with 10 % with normal BP and BMI. She reported that higher BP in childhood is associated with carotid stiffness in adulthood.

Dr. Urbina next summarized data from five studies beginning in 1980 that indicate that subjects with persistently elevated BP across the lifespan and those with incident HTN as adults had increased risk of high carotid IMT versus consistently normal BP or resolved childhood high BP, even after controlling for age and gender. She emphasized the need to be cautious about the age of measurement of CVRFs, noting that a higher CVRF score was independently associated with greater cIMT in adulthood only when measured at or after 9 years of age.

Dr. Urbina urged the adoption of "primordial" prevention, pointing out that studies have found that youth with low levels of CVRFs in childhood had lower carotid IMT as an adult. She closed by reporting that persistently high levels of consumption of both fruits and vegetables have been associated with lower PWV after 27 years.

CV Outcomes: Short-term and Long-term Impact of Pediatric HTN
Presenter: Stephen Daniels, M.D., Ph.D.

Dr. Daniels opened his presentation with a brief discussion of adult HTN, pointing out that heart disease is the number 1 cause of death for adults in developed countries around the world. He cited data from the Framingham Heart Study, listing CVRFs:

- Obesity
- High blood pressure
- High LDL-C (Bad cholesterol)
- Low HDL-C (Good cholesterol)
- Diabetes
- Cigarette smoking
- Male sex (for CVD at a young age)
- Strong family history.

Dr. Daniels emphasized that high BP is a well-established risk factor for cardiovascular disease (CVD) in adults, noting that clinical trials in adults have consistently demonstrated that pharmacologic treatment of HTN results in lower CVD morbidity and mortality. What is less clear is what level of BP requires treatment. Dr. Daniels also noted that it is unclear about what should be the goal level of BP reduction.

He noted that high BP affects virtually every target organ, and that HTN in children is often asymptomatic. Unless HTN is severe (usually secondary HTN), children and adolescents do not suffer morbidity or mortality from cardiovascular outcomes. This is why intermediate markers of the impact of HTN on the cardiovascular system are important. A number of cross-sectional studies have related BP level to target organ damage (TOD) in children and adolescents.

Dr. Daniels explained that LVH is an independent risk factor for sudden death and myocardial infarction and important in the pathophysiology of HTN-induced CVD. He noted that in addition to LV mass, LV geometry is also important. He described the factors influencing LVH geometry in hypertensive patients in the progression of hypertensive heart disease.

Dr. Daniels discussed a study to evaluate the prevalence and severity of LVH, in particular the distribution by sex and race for percentile category of left ventricular mass index. From these results, it can be concluded that severe LVH is relatively common in children with HTN. This suggests that recognition and early treatment of HTN may be important in childhood. He also discussed a 2013 Study of 1st year collegiate football players at the beginning and at the end of the season, across 6 study years. Dr. Daniels reported that at pre-season, most of those studied had normal BP. At post-season, SBP and DBP increased significantly, with most meeting the criteria for pre-HTN (47%) or Stage 1 HTN (14%), with concentric hypertrophy increasing from pre-to post-season.

Dr. Daniels referred to a recent study (*Hypertension* 2017, in press) that evaluated cardiac function in pediatric patients with HTN compared to normotensive controls by echocardiography using Doppler and speckle tracking. Ventricular volume and ejection fraction were similar between normotensive and hypertensive individuals. Hypertensive children had impaired LV relaxation and systolic function compared to normotensive children. This study also pointed to a potential dose-response relationship between higher BP level and lower measures of diastolic function.

Dr. Daniels discussed other cross-sectional studies that have related BP to TOD, including the SHIP AHOY Study (Study of High Blood Pressure in Pediatrics: Adult HTN Onset in Youth). He described this American Heart Association (AHA)-funded study to better clarify clinic BP level associated with TOD, and determine which ambulatory BP patterns and metabolic phenotypes are markers of risk for TOD.

Dr. Daniels discussed studies that have indicated that in addition to cardiac structural and functional abnormalities, vascular abnormalities are associated with HTN in children and adolescents, and that elevated BP is associated with increased carotid IMT in children.

Dr. Daniels also noted that there is a clear relationship between clinic BP and carotid stiffness in children. He noted that HTN in children is associated with increased PWV and decreased Brachd, increased AIx, and an assessment of arterial wave reflection representing increased arterial stiffness. Furthermore, youth with both Pre-HTN and HTN had higher PWV indicating greater central arterial stiffness than their normotensive counterparts.

A large study of the cardiovascular effects of obesity and Type II diabetes (T2DM) found that even pre-HTN subjects had lower BrachD than their normotensive counterparts. Dr. Daniels emphasized that vascular dysfunction matters because it damages the heart, and that arterial stiffening matters because it causes TOD.

Dr. Daniels also discussed studies that used data from NHANES and screens such as the Wechsler Intelligence Scale for Children regarding neurocognitive impairment in children with normal, high, and greater BP. These results are important, in and of themselves, but also because they probably reflect vascular function in the brain, reinforcing the widespread effects of high BP.

Dr. Daniels presented several conclusions, noting that HTN in children is associated with concurrent:

- Cardiac structural abnormalities
- Cardiac functional abnormalities
- Vascular structural abnormalities
- Vascular functional abnormalities
- Cognitive dysfunction.

These abnormalities appear to occur even at levels of blood pressure that have been considered borderline or pre-HTN. He suggested that we need to know more about the impact of treatment of high BP on improvement in these outcomes. Dr. Daniels challenged participants that putting together the evidence from adults and children, it appears that we should be working to prevent HTN development at a young age and treating it once it occurs.

Questions, Comments, and Discussion

Question 1 (Flynn): Should the focus be on treating the BP, not treating the results of diagnostic tests? Are you concerned about obtaining echocardiograms in hypertensive children?

Response (Daniels): A lot of time was spent in considering what diagnostics would work best for children. It was decided to look at the presence of LVH to determine the optimal approach. We really need a better understanding.

Response (Urbina): There were concerns about diagnostic accuracy; echocardiograms in clinics and echocardiograms in a research environment are very different. Study developers decided to be a bit more conservative in that respect.

Response (Baker-Smith): It was necessary to have a somewhat arbitrary cut-off value. Further studies will likely warrant adjusting those cut-off points and/or values.

Response (Daniels): Again, this points to the need to pay greater attention to the geometry.

Response (Urbina): There was also the problem of obesity; the obesity epidemic complicates how we interpret LVH.

Response (Baker-Smith): A retrospective chart review study found that 28% of children require more than a single agent to control their BP.[3]

Response (Daniels): Approximately 30% of adults have HTN, but current guidelines have defined only 2–3 % in children, and we are not totally sure that we can predict which children will eventually have HTN as adults. For those reasons, studies of the arteries will help us focus on those pediatric patients who may need more aggressive treatment.

Question 2 (Burckart): You mentioned several treatments. Which of those are responsive?

Response (Daniels): Preliminary studies have shown that BP reduction also resulted in reduction of left ventricular mass, but these are very small studies. We need to conduct more studies.

Response (Urbina): Certain classes of medications are better than others for vascular function; also there is a gap; we are limited in what we are measuring; we have not looked at the impact of

elevated BP in the very young. We have not progressed in looking at renal functional nerves, or the impact of small elevations of BP in kidney growth. Some of these things we could do now.

Module 3: Hypertension Treatment—Current Knowledge and Future Directions
Moderator: Charlotte Pratt, Ph.D.

Hypertension Diagnosis and Management in High-Risk Populations
Presenter: Joseph T Flynn, M.D., M.S.

Dr. Flynn explained that he would focus his discussion on presenting an overview of HTN frequency in aortic coarctation, CKD, and diabetes. He also would review new CPG recommendations on the diagnosis of HTN in children with these conditions, discuss the importance of BP reduction in high-risk conditions, and offer treatment recommendations.

Dr. Flynn noted that HTN in aortic coarctation is a narrowing of the aorta, most commonly near the ductus. Patients with this condition can present with HTN or absent/diminished femoral pulses; the condition is most commonly repaired in infancy but may present later in life. In discussing HTN in pediatric CKD, Dr. Flynn also explained that many childhood renal diseases are associated with HTN. However, the true prevalence of HTN among children with CKD is difficult to determine. It is important to point out that coarctation repair does not solve the problem. Several studies have demonstrated that HTN can occur later, even after successful coarctation repair.

In discussing HTN in pediatric CKD, Dr. Flynn reiterated that many childhood renal diseases are associated with HTN, but the true prevalence of HTN among children with CKD is difficult to determine. He reviewed the CKiD Study, which used the Fourth Report criteria for analysis. Using casual BP measurements, about 25% of participants had abnormal BP. Their analysis of baseline ABPM data in 315 CKiD participants showed that almost 60% of the children had abnormal ambulatory BP patterns. Dr. Flynn also discussed results from the SEARCH for diabetes study, which found that 6.1% of participants had HTN, with the highest prevalence in Asian Pacific Island, Native American, and Hispanic children, and the overall prevalence of HTN in youth with type 1 diabetes (T1DM) is estimated at 4-16%. The prevalence of HTN is much higher among those with type 2 diabetes.

Dr. Flynn then reviewed new CPG recommendations on diagnosis of HTN based on BP classification in the 2017 AAP CPG, which recommends that trained health care professionals in the office setting should make a diagnosis of HTN if a child or adolescent has auscultator confirmed BP readings $\geq 95^{th}$ percentile at three different visits. Dr. Flynn noted that the 2017 CPG recommend that oscillometric devices may be used for BP screening measurements in children and adolescents. The 2017 Guideline also notes that ABPM should be performed for confirmation of HTN in children and adolescents with office BP measurements in the elevated BP category for 1 year or more or with stage 1 HTN over three clinic visits. Routine performance of ABPM should be strongly considered in children and adolescents with high-risk conditions to assess HTN severity and determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage.

In those cases of aortic coarctation, the 2017 AAP CPG recommend measurement of BP in the arm and leg if the child has ≥ two BP readings at the elevated BP level or above. Also, children and adolescents who have undergone coarctation repair should undergo ABPM for the detection of HTN (including MH).

Dr. Flynn noted that regardless of apparent control of BP with office measures, children and adolescents with CKD and a history of HTN should have BP assessed by ABPM at least yearly. Children found to have high-normal BP (SBP or DBP ≥90th percentile for age, sex, and height) or HTN (SBP or DBP ≥95th percentile for age, sex, and height) should have BP confirmed on three separate days. He also noted that the 2017 CPG indicate that children and adolescents with T1DM or T2DM should be evaluated for HTN at each medical encounter.

Dr. Flynn next addressed the importance of BP reduction in high-risk conditions, noting that patients with repaired coarctation have increased vascular stiffness, increased rates of CAD compared to patients with other types of CHD. He also pointed out that untreated HTN in those with CKD increases the risk for development of CVD, in particular, LVH. Dr. Flynn discussed the association of HTN with the progression of CKD. He also discussed the CKiD Study, which examined the effects of HTN in diabetes, noting that HTN contributes to development and progression of microvascular complications of diabetes, including diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.

He summarized treatment recommendations, noting that at the time of diagnosis of elevated BP or HTN in a child or adolescent, clinicians should provide advice on the DASH diet and recommend moderate-to-vigorous physical activity at least 3 to 5 days per week (30–60 min per session) to help reduce BP. The 2017 AAP Guideline recommends that clinicians should initiate pharmacologic treatment in hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LVH on echocardiography, symptomatic HTN, or stage 2 HTN without a clearly modifiable factor). In children and adolescents diagnosed with HTN, the treatment goal with non-pharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to <90th percentile and <130/80 mm Hg in adolescents ≥13 years old.

Dr. Flynn noted that there is currently no specific BP target for coarctation. However, those children or adolescents with both CKD and HTN should be treated to lower 24-hour MAP <50th percentile by ABPM. This target is based on the ESCAPE trial, which he reviewed.

Dr. Flynn reviewed the ESCAPE Trial. He explained that study results recommend that in children with CKD ND, BP lowering treatment should be started when BP is consistently above the 90th percentile for age, sex, and height. He noted that it is recommended that children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE inhibitor or ARB. Those diabetes patients with BP >120/80 mmHg should be advised on lifestyle changes. Patients with confirmed BP>140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy. Dr. Flynn noted that ACE inhibitors or angiotensin receptor blockers should be considered for the initial pharmacological treatment of HTN.

Dr. Flynn concluded by reiterating the following:

- HTN is common in coarctation (post-repair), CKD, and diabetes.

- Diagnosis of HTN in high-risk patient should be based on auscultated BP w/ ABPM confirmation.
- Persistent HTN in each of these conditions has deleterious effects.
- Treatment includes lifestyle change and antihypertensive medications.

Trials of Hypertension in the Pediatric Population
Presenter: Jennifer Li, M.D., M.H.S.

Dr. Li began by reviewing various regulatory initiatives, including initiatives that have been especially important for children, such as the FDA Modernization Act of 1997, which led to the FDA Safety and Innovation Act, 2012. She also explained the Written Request (WR) process for pediatric studies wherein the sponsor is potentially eligible for 6 months of patent extension if certain criteria are satisfied, resulting in more than 700 new pediatric labels, with more than 15 HTN labeling changes in children.
Dr. Li next presented a brief overview of the timeline for pediatric HTN trials, with new label indications. Most trials have completed Phase 1 and Phase 2 studies.

She then discussed the four HTN trial designs, explaining the characteristics, differences, and similarities among the four models. Dr. Li also explained when one model would be the preferred approach over the other three. The goal is to show an interpretable dose response. HTN response should have a negative slope when compared with a placebo. To be eligible for exclusivity, the results do not need to be a positive dose response, but must be interpretable. Of these designs, Type A is the most straightforward. However, many Institutional Review Boards (IRBs) and parents are not willing to have a child on placebo for any length of time. She also discussed strengths and risks in the other designs. Type C is interpretable, regardless of outcome, which makes it the most preferred for pediatric HTN studies.

She summarized the various WR criteria for pediatric HTN studies, noting that this process has undergone significant change:

- Demographic:
  - ≧50% pre-adolescent, ≧200 subjects ages 6-16 years
  - ≧50 subjects ages 1-5 years
  - 40-60% African American
  - Both genders
- Inclusion
  - ≧95%ile for age/gender/height or ≧90%ile if there is an existing comorbid condition
- Formulation
  – Expected to develop a commercially marketable formulation, and if attempts fail, must document reasons for failure and develop a compounding protocol.

Dr. Li next discussed dose range, noting that doses should result in blood levels from less than those achieved with the lowest approved adult dose to more than those achieved by the highest used adult dose. She explained that the primary endpoint should either be absolute or % change in SBP or DBP. She noted that for Trials A and B, the efficacy should be change from baseline to end of treatment plus the trough; for Trials C and D, efficacy should be a change in BP from last treatment visit to end of withdrawal period. Dr. Li noted that WRs require that

pharmacokinetic (PK) studies require either traditional or sparse sampling in various age groups for the compound and its metabolites.

Dr. Li next discussed safety, noting that an independent data safety monitoring board (DSMB) is now required. Subjects must be followed at least weekly. A 1-year open-label phase is required for evaluating adverse events, growth, and development. Dr. Li also described statistical requirements, including at least 80 % power to detect a 3-mmHg change in BP with $p<0.05$, two-sided significance. She reported that an interim analysis is allowable at >90% enrollment to assess variability. Reporting requirements include posting the WR on the FDA website; the study must be registered on ClinicalTrials.gov.

Dr. Li presented a list of 15 drugs that have been studied to date, noting that several products did not get a label change. Of note, there are several that have not demonstrated a dose response. These have been identified as "failed" studies, which could result in a negative label change.

Dr. Li discussed possible reasons for what appears to be so many negative ("failed") efficacy trials. She pointed out that these "failures" may be due to failure to demonstrate a dose response. With increased pediatric HTN trial experience, trial designs have been refined, and there is a better understanding of several factors that could affect trial success or failure. Dr. Li identified these factors:

- **Dose range:** The goal is to demonstrate a dose response, with a significant "negative slope." Many failed trials showed a 2- to 9-fold variation in dose between low and high strata. Successful trials showed a 20-to 32-fold variation in dose between low and high strata.
- **Dosing by weight:** Failed trials did not consistently incorporate individual subject weight in dosing.
- **Liquid formulation** development: There are challenges with bioavailability, bioequivalence, stability, and palatability. Failed trials did not develop or use a liquid formulation; dosing was not precise, often based on pill combinations in drug kits.
- **Primary endpoint:** Systolic HTN is more common; the use of SBP is based on feasibility, a common concern in pediatric trials.
- **DBP:** Most successful trials used DBP; for subjects more likely to have renal disease DBP measurements have less variability than SBP.
- **BP measurement:** Measuring methods (oscillometry vs. auscultation) varied, even within same trial. Measurement method should be specified within the trial design to ensure consistent methodology among study sites.

Dr. Li pointed out that generally trials have been very safe with few serious adverse events and no deaths, even during the placebo phase and in those with decreased renal function. There has been a favorable economic return to industry. She concluded that these factors—poor dose selection, failure to fully incorporate weight and pediatric pharmacology into trial design, lack of liquid formulation development, and use of SBP as the primary endpoint— likely led to the failure of several antihypertensive pediatric exclusivity trials.

Dr. Li offered several suggestions to help inform future directions and to help further reduce the number of failed trials:

- Better incorporation of PK data and simulations of exposure-response models from adult or pre-existing data prior to embarking on pediatric randomized trials
- Need for comparative effectiveness studies in children ("ALLHAT" for kids)
- Need for assessment of long-term safety and effects on growth and development.

Considerations in Assessing Short- and Long-term Safety of Medications for Pediatric Hypertension
Presenter: Ann W. McMahon, M.D., M.S.

Dr. McMahon explained that many antihypertensives have been approved in children with little-to-no long-term efficacy or safety data. She reiterated that her presentation would focus on both short- and long-term safety considerations. She presented a brief review of short-term (less than 6 months) risks of antihypertensive use in children among six drug classes:

- Calcium channel blockers
- Angiotensin receptor blockers
- Beta blockers
- Angiotensin Converting Enzyme (ACE) inhibitors
- Thiazide diuretics
- Potassium-sparing diuretics.

Dr. McMahon pointed out that no long-term safety studies of antihypertensive use in children were identified.

In discussing approaches to studying long-term safety in children, Dr. McMahon described examples of the various possible types of long-term studies that could be used, as well as their strengths and limitations:

- **Long-term randomized controlled trials (RCTs):** [Example: Childhood Asthma Management Program (CAMP)]. Strength of evidence. Limitation: Study might still be too short to capture long-term outcomes given the cost.
- **Prospective cohort studies** (Example: National Children's Study). Strengths: Large sample size of children with longitudinal data in U.S. Limitation: Effort was not sustainable.
- **Registries:** (Example: Long-term safety of pegvisomant in patients with acromegaly). Strength: Long-term follow-up, clinician case assessment. Limitations: No comparator; clinician assessment.
- **Observational studies:** [Example: Study of risk of cancer in patients with childhood onset inflammatory bowel disease (IBD) in childhood and adulthood]. Strengths: Large sample size; long-term follow-up was excellent, comparator group. Limitations: This model is not available for U.S.-based study given lack of data coordination.
- **Cohort study with chart review:** [Example: Population-based cohort (chart review) of IBD patients treated with infliximab]. Strengths: Large sample size, clinical detail with chart review. Limitations: No comparator group.

Dr. McMahon listed several factors that should be considered in designing future short-term antihypertensive safety studies in children:

- Sample sizes in short-term RCTs need to be large enough to detect safety signals.
- As an alternative, study designs other than an RCT should be assessed.
- Large, long-term RCTs or cohort studies may currently be the gold standard, but are usually not feasible and cannot be large enough to detect rare signals.
- Investigators should assess larger data sets to gather and interpret safety and efficacy data over the long term
    - Need very large sample sizes over years of follow-up
    - Combine large databases
    - Develop standard methods for data collection and analysis so that strength of evidence exists in these systems.

Dr. McMahon concluded her presentation by emphasizing that short-term safety of antihypertensives in children has been studied, but these have been small studies. Also, the long-term safety of antihypertensives in children has not been studied. She also recommended that long-term studies of efficacy and safety of antihypertensives with large sample sizes in children is the next step. The unanswered question remains: Does the short-term control of BP in children have an impact on long-term cardiovascular (and other) morbidity?

Hypertension Treatment (Pharmacologic): Novel Approaches and New Horizons
Presenter: Ronald Portman, M.D.

In a discussion of the epidemiology of pediatric HTN, Dr. Portman explained HTN is far less common than in adults at 1-4% of the population. Most of these cases are asymptomatic. Dr. Portman noted that the primary form of pediatric HTN is systolic HTN, but that it is more likely to be of secondary etiology than for adults. He also pointed out that despite the available medications that treat high BP, HTN remains uncontrolled in more than 50% of adult patients and among approximately 50% of children with primary and secondary HTN by ABPM.

Dr. Portman next discussed the effects of HTN in children. In cases of severe HTN, the effects are similar to those in adults. In mild-moderate HTN, the effects are unclear and difficult to detect; long-term follow up is needed to determine outcomes. Dr. Portman also pointed out that few data exist on HTN in newborns; the International Neonatal Consortium has established a hemodynamic adaptation workgroup to try to establish normal newborn BP values.

In reviewing the criteria for pharmacologic intervention, Dr. Portman noted that current therapy includes lifestyle modification: weight loss, exercise, stress reduction, and dietary approaches, such as the DASH diet. Dr. Portman also noted that of 17 pedantic hypertensive studies performed, 8 showed dose response. However, the results of these studies have been of limited value to practitioners, where current information does not demonstrate the best what drugs to use first in treating primary HTN, or the most-effective combinations, dose or duration of therapy. He cautioned that early concerns regarding placebo use likely have led to less-than-straightforward study designs. Dr. Portman listed several other issues that have affected pediatric antihypertensives development:

- Heterogeneous HTN etiologies in study populations confounded results.

- BP measurement has only been used as surrogate marker: end organ damage is subtle, difficult to measure, without symptoms, with long-term outlook unknown.
- ABPM data have not been used in most studies, nor has the effect of including white coat patients been assessed.
- Only one combination products has been evaluated as yet; however, combinations are often needed for adequate BP control.
- A new focus for drug development is treatment of underlying disease.

Dr. Portman noted that currently, two new antihypertensives are being developed for adults with resistant HTN. He reviewed a list of example compounds for conditions with BP-lowering effect that could potentially ameliorate the need for antihypertensives.

Dr. Portman reiterated that the goals of pediatric drug development programs are twofold—(1) to facilitate the development and availability of innovative, quality medicines according to the highest ethical and scientific standards, and (2) to help extend and enhance the lives of infants, children, and adolescents by fulfilling unmet medical need in pediatrics. He pointed out that pediatric research policies vary worldwide. These policies range from formal legislation mandating pediatric research within an evolving environment in the United States, European Union, and Switzerland to voluntary pediatric data submission with incentive or no incentive in countries such as Japan, Canada, Australia, New Zealand, and Taiwan to no pediatric policy in countries such as China, Turkey, Russia, Asia Region, the Middle East, and Africa.

Dr. Portman discussed the complex issues that must be considered in trial design, emphasizing the importance of timing of interactions with the Pediatric Committee (PDCO) of the European Medicines Agency (EMA) and FDA for pediatric plans. These considerations include:

- Need
- Comparators
- Type of drug
- Size of patient population
- Dose determination strategy
- Study and protocol feasibility
- Age groups to be studied
- Reverse age enrollment
- Inclusion of adolescents in adult trials
- Acceptable pediatric formulations
- Regulatory obligations and opportunities
- Innovative study design, including extrapolation
- Existence of validated biomarkers/end points
- Adult and pediatric disease versus pediatric only
- Juvenile toxicology and short- and long-term safety considerations
- Operational issues (e.g. invasive diagnostic procedures requiring sedation or radiation).

Dr. Portman pointed out that pediatric trials often fail due to unacceptable trial demands. Other reasons for failure include wrong dose, restrictive entry criteria, unrealistic sample size, adult-

style study design, and unqualified biomarkers, as well as un-validated pediatric end-points. However, he also emphasized that innovative trial design is critical, and he identified a number of "keys" to success:

- An in-depth epidemiological review must be prioritized early in developing strategic planning prior to health authority interactions.
- Consider pediatric-specific enrollment requirements, current standards of care, competing studies, and recruitment timelines.
- Form partnerships with practicing/academic community and pediatric networks to identify external pediatric experts who can inform pediatric strategy. These partnerships should be formed early in the development process.
- Establish and sustain collaboration with sub-specialty networks.

Dr. Portman summarized several innovative studies in early drug development, as well as examples of innovation in clinical trials. He next focused on extrapolation, explaining that "pediatric extrapolation" is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and adult or other pediatric population. He reported that extrapolation of adult efficacy data to pediatric studies is encouraged by the EMA and FDA, noting that studies using extrapolation have a >80% success rate in pediatrics compared with 3% when extrapolation is not used. Dr. Portman cautioned that this is an iterative process, and that as evidence builds, the acceptability of the proposed extrapolation approach will need to be re-assessed, and it may be appropriate to change the extrapolation approach.

Dr. Portman also described several key considerations:

- Operationalizing a pediatric clinical program is the most time-consuming, challenging, and expensive part of pediatric drug development.
- Early involvement of external experts is critical to both research and operational success.
- Identifying global experts is challenging; composition of experts versus clinicians may confound knowledge received.
- Building a new network for each study is expensive, time-consuming, and inefficient.
- Early identification and consultation with global pediatric networks is key to a successful pediatric program.

Dr. Portman discussed the types of pediatric networks that currently exist. These networks can be national, regional, or State-based. They may be disease/subspecialty-specific networks or foundation-based networks. They can be office-based networks or children's hospital networks or patient advocacy networks. He also described several new initiatives, such as public/private partnerships, including the Institute for Advanced Clinical Trials for Children (IACT), the International Neonatal Consortium, and the European Pediatric Clinical Trials Network.

Dr. Portman next offered several cautions and recommendations for future pediatric drug development:

- Off-label use of pediatric therapeutics remains commonplace, complicating research efforts.

- Small sample sizes lead to challenging study recruitment and highly competitive research environments.
- There is a need for smarter study design, innovation in technical research and development, extrapolation approaches, and pediatric-focused global regulatory pathways.
- Most pediatric drug development still depends on adult development.
- The role of pediatric drug development remains unchanged; current incentive structures are not necessarily addressing significant unmet need.
- There is a need for training for new investigators/ junior faculty in pediatric drug development.

Dr. Portman concluded by offering recommendations for bridging the gap between academia and industry, including new and expanded partnership of academia, regulatory authorities, and industry to determine how to best treat HTN in pediatrics. He also underscored the need for assessment more related to how drugs are used – in combination, taking advantage of multiple synergistic mechanisms of action. Dr. Portman also recommended the following:

- Routinely collect blood samples at informative time points to assess PK effects in subjects to ascertain exposure response analysis.
- Develop an exposure-response model using adult and pediatric data; use this model to perform clinical trial simulations and explore competing trial designs/analysis options.
- Explore the effects on vascular reactivity and the impact of PK treatment on outcomes.
- Continue research for treatment of underlying causes of HTN and focus therapeutic efforts there.
- Evaluate response on both SBP and DBP.

Dr. Portman concluded by emphasizing that future trials are needed to evaluate the differential effects of antihypertensive agents in patients of different racial and ethnic backgrounds. He also noted that larger scale trials are needed to evaluate comparative effectiveness of individual antihypertensive agents, as well as combination therapies. He emphasized the need for continued research in long-term safety and effects on growth/development.

Questions, Comments, and Discussion

Question 1 (Kelly): Elaborate on "standard of care" issues, which is lifestyle modification. Have children that were enrolled previously "failed" in lifestyle modification?

Response (Li): It is standard to try lifestyle modification prior, and medication only after lifestyle modification fails. The issue is less about safety, but more about the perception by IRBs and child's family of failure, especially in use of placebo. This is more an ethics issue.

Question 2: (Daniels): Regarding choice of SBP target, is there a possibility that there may be more variability in BP as part of failure? There may be other reasons contributing to the failure. BP may be more of a marker, and there may be other considerations.

Response (Li): We agree. FDA had an opportunity to review actual primary data; this was a large meta-analysis. At the same time, we don't want to target only BP; there are a lot of confounding factors.

Question 3 (Flynn): Technique of BP measurement is another issue that warrants attention.

Response (Li): BP measurement techniques are an important issue, and should be incorporated into study design.

DASH Approach to Treatment in Hypertensive Youth
Presenter: Sarah C. Couch, Ph.D., R.D.N.

Dr. Couch focused her presentation on summarizing the DASH-4-Teens Trial, which studied if the DASH Diet behavioral nutrition intervention lowers BP and improves vascular function in adolescents with elevated BP. She began by explaining that the DASH dietary pattern optimizes levels of nutrients suggested to affect BP in adults resulting in a dietary pattern that emphasizes fruits, vegetables, low-fat dairy products, whole grains, and lean protein sources, and that is lower in total fat and sodium intakes. She noted that results of clinical trials of adults with normal and elevated BP and cross-sectional and longitudinal studies in youth with normal BP indicate that a DASH-type dietary pattern lowers BP and may improve other CRFs. Dr. Couch pointed out that although current pediatric guidelines for managing elevated BP in youth advocate a DASH-type dietary pattern, the level of evidence for this recommendation is considered weak due to the lack of randomized clinical trial data in children and adolescents.

Dr. Couch reviewed a randomized control trial that she and colleagues conducted in 2007 that looked at the efficacy of a clinic-based behavioral nutrition intervention emphasizing the DASH diet versus routine hospital-based nutritional care on changing diet quality, BP, and vascular function in adolescents with elevated BP. She explained that investigators were interested in answering two key questions:

- Can a clinic-based behavioral nutrition intervention emphasizing the DASH diet favorably modify dietary quality over the long term in adolescents with elevated BP?
- Can the aforementioned intervention favorably modify BP and pre-clinical markers of adverse cardiovascular changes in youth?

Dr. Couch described the intervention inclusion/exclusion criteria, as well as format, for this 24-week intervention. She also explained that the intervention content included counseling and manual based on Social Cognitive Theory, with additional education to enhance food literacy. She also described the behavior modification component and the usual care aspects of the intervention.

Dr. Couch noted that outcome measures included dietary intake, BP, and vascular function. She noted other measures included demographics data, adolescent self-report of age, race/ethnicity, as well as parent self-reports of family income, highest level of education attained, and race/ethnicity. Weight was measured using calibrated equipment with standardized protocol. Age and gender-specific BMIz-scores were determined from the CDC growth charts, which used the lambda, mu, sigma (LMS) method to calculate BMI. Physical activity was measured using validated 7-day physical activity recall. Metabolic Equivalent (MET) was calculated as a sum of MET minutes for light, moderate, hard, and very hard activity and sleep per day.

Dr. Couch explained that statistical analysis looked at the differences in change in response to intervention from baseline to post-treatment and baseline to follow-up tested by repeated measures analysis of completers and intention to treat (ITT). She presented a participant flow chart that tracked key events, including recruitment and screening, noting that of 1,900 adolescents screened in the clinic, 290 were eligible to participate. Of those, 207 consented to participate. These subjects were then screened to confirm that were truly hypertensive. A total of 159 subjects were randomized to treatment; 81 in the DASH-4 Teens and 78 in usual care groups.

Dr. Couch presented an intervention attendance table with participant characteristics and outcomes by dietary intervention condition. Of those participating in the study, 72 % of the DASH-4-Teens group attended face-to-face visits with a registered dietician (RD), compared with 60 % of those in the usual care group.

Dr. Couch next discussed intervention outcome data by randomized group at baseline, 6-month post-treatment, and at 18-month follow-up. She also summarized data adjusted for gender, race, and income; change in daily METs for BMI and dietary variables; change in BMI z score; and energy intake for dietary variables.

Dr. Couch presented data on the percent of participants who met DASH Diet goals at baseline and immediately post-intervention. Although there was success in DASH food improvement, no group met DASH goals of more than 50 %.

She summarized BP and vascular outcomes at baseline, 6-month post-treatment, and at 18-months follow-up by randomized group by ITT. Compared with the usual care group, there was a greater lowering of SBP and DBP in the DASH group in post-treatment. Similar effects were recorded for ITT analysis.

Dr. Couch reported that among participants prescribed medication, there was no significant difference in the DASH-4-Teens group compared with the usual care group. She also noted that that there was no significant difference among the two groups in the percent of participants with HTN status improvement. Although at 6 months, there was a tendency for greater improvement in the DASH-4-Teens group, at 18 months, both groups were close to identical.

Dr. Couch identified the following factors that likely limited study results:

- Potential self-reporting bias with dietary intake data collection
- Drop-in participant retention over time
- Weight change differences within and between groups.

Dr. Couch offered the following conclusions based on study findings:

- A clinic-based behavioral nutrition intervention with telephone and mail follow-up could be successfully integrated into the clinical operations of a hospital-based HTN treatment center achieving an 80% retention to treatment.
- The DASH-4-Teens approach was more efficacious in improving diet quality toward a more DASH-type dietary pattern than usual hospital-based nutrition care. A moderate adherence to DASH (58% of maximum DASH score) was achieved by DASH participants.

- Greater immediate post-intervention changes to SBP were seen in the DASH-4-Teens participants, and there was a tendency for these benefits to be sustained up to 1- year follow-up.
- A tendency for immediate and sustained vascular function improvement in DASH-4-Teens compared to usual care participants suggests that this program offers considerable cardiovascular benefit to adolescents with elevated BP.

She closed by emphasizing that the DASH-4-Teens intervention holds promise in providing an effective enhancement to usual hospital-based nutrition care for the treatment of elevated BP and CVRFs in adolescents. She also noted implications for future clinical studies:

- More frequent, sustained contact with a dietitian may be needed to prevent recidivism back to pre-treatment eating behaviors.
- Future studies should examine benefits of combining DASH-4-Teens with other remotely delivered lifestyle approaches such as physical activity programs for additional BP-lowering benefits.
- Studies designed to determine whether DASH-4-Teens may favorably impact blood pressure and pre-clinical markers of disease risk in adolescents receiving drug therapy are warranted.

Lifestyle Modifications in Hypertension Treatment
Presenter: Janet M. de Jesus, M.S., R.D.

Ms. de Jesus briefly reviewed lifestyle recommendations for HBP in children, including a summary of trends in nutrient intake and implementation of AAP HBP Clinical Practice Guideline recommendations. She noted that healthy lifestyles associated with BP control include:

- Following a DASH-style eating plan
- Moderate sodium intake
- Weight control
- Physical activity.

The AAP HBP Clinical Practice Guideline Recommendation suggests that at the time of diagnosis of elevated BP or HTN in a child or adolescent, clinicians should provide advice on the DASH diet and recommend moderate- to-vigorous physical activity at least 3 to 5 days per week (30–60 minutes per session) to help reduce BP.

Ms. de Jesus next reviewed dietary pattern scores between 1999 and 2010, and she also summarized data on adherence of the U.S. population ages 2 years and older to the 2010 Dietary Guidelines. Results indicate U.S. scores have improved from 49.1 in 1999 to 57.8 in 2010. Ms. de Jesus discussed fruit intake, vegetable intake, and dietary intake compared to recommended levels. She also pointed out that about 90% of U.S. children ages 6-18 years eat too much sodium daily, and that almost half of added sugars consumed are from beverages. Equally important, most U.S. children and youth do not meet physical activity guidelines.

Ms. de Jesus informed participants that the U.S. and Canadian governments have formed a dietary reference intake (DRI) working group. This recently formed DRI WG is co-funding the forthcoming AHRQ sodium and potassium review of the effects of dietary sodium and potassium

intake on chronic disease outcomes and related risk factors, as well as an examination of the effect of change in dietary sodium and potassium intake on cardiovascular kidney- related outcomes. This review also will help inform updated dietary reference intakes for sodium and potassium.

Ms. de Jesus explained that dietary reference intakes are evidence-based values for nutrient adequacy and safety. She also noted that DRIs inform recommendations for nutrient intakes for healthy populations, and that they are the basis for scientific nutrition policies, regulations, and guidance in Canada and the United States. DRIs are established by expert panels; this process is overseen by the National Academies of Science, Engineering, and Medicine.

Ms. de Jesus briefly described the need to assess strategies to increase delivery of guideline-based care to populations with health disparities, in particular:

- Strategies that focus on providers who care for clinical populations with excess burden of cardiovascular, lung, blood, and sleep diseases and disorders, in concert with the health care delivery systems.
- Test systems, infrastructures, and strategies to implement guideline-based care for NHLBI disorders in clinical care settings.

Ms. de Jesus concurred with Dr. Couch and other participants that lifestyle change is critically important in maintaining a healthy BP. She also emphasized that:

- A population shift is needed in dietary patterns.
- Prevention is key; it is critical to start with young children.
- Most Americans are not following recommended dietary patterns to control BP.
- Implementation research is needed to identify strategies for speeding up widespread adoption of clinical and dietary guidelines.

Questions, Comments, and Discussion

Comment 1: Please comment on why FDA has not accepted extrapolation of efficacy for antihypertensives for children less than 6 years of age.

Response (Burckart): There is no clear-cut answer, but often the youngest children may have problems with drug toxicity, or the disease is different for them.

Response (Flynn): Yes, there have been differences in studies that have been conducted on children less than 6 years of age.

Question 2 (Higgins): Is there any impact of maternal or paternal education or socioeconomic status, or if the study population had proximity to large grocery store as opposed to a convenience store?

Response (Couch): Yes, we did consider family income as a variable; we tried to consider socioeconomic status, and we built information into the Cincinnati school lunch program.

Question 3 (Ingelfinger): Dr. Couch alluded to recidivism and the difficulty of doing a study such as the DASH study. How does one encourage adherence to a healthy diet both during and after a study? How much were families involved in studies? Are there additional insights that we can share with pediatricians.

Response (Couch): Family involvement is critical to the success of the DASH diet, but involving parents that did not have a healthy diet during childhood was a considerable challenge. Creating a healthy food environment is critical.

Question 4 (Pratt): Should we be looking at social determinants of health, not only the home environment but also the school and neighborhood environments?

Response (De Jesus): FDA released sodium targets for individual food categories and some companies have voluntarily lowered sodium. The Childhood Nutrition Act covers school food, so legislature is gradually targeting areas of food consumption, but Congress has recently slowed those efforts.

Comment (Couch): A problem with the school lunch program is low quality of fruits and vegetables in school lunches.

Question 5 (Pratt): We don't really have a lot of studies in the area of long-term pharmacologic treatment. Have we considered different designs that acknowledge that kids are growing? At what point in time do you stop medication and switch to lifestyle medication, possibly going back to medication later on? What would you like to see in long-term PK treatment of HTN?

Response (McMahon): These studies were done in a slightly different way; observational databases are another possible way to collect data. It is important to look at additional ways to collect safety and efficacy data in the long run.

Response (Urbina): This approach has been relatively successful, especially in obese boys; their BMI decreases somewhat significantly.

Comment 6 (Flynn or Kelly): Other questions regarding what other types of long-term studies. Another approach might be a prospective registry, which might be a model for collecting and aggregating data.

Question (Pratt): Should we focus first on obesity treatment relative to HTN treatment, or should we combine both?

Response (Baker-Smith): There has been considerable discussion of what constitutes a "healthy" appearance, especially as perceived by a parent. While parents are alert in recognizing that their child is underweight, there is less awareness that the child is overweight. This is a big challenge.

Response/Comment (Kelly): We currently don't have good obesity treatments. There is still the need to develop studies that truly measure BP levels.

Question/Comment (Ingelfinger): Please comment on the role of bariatric surgery as a treatment option for the pediatric population.

Response (Kelly): Bariatric surgery is still relatively rare, and is reserved for those adolescents with the severest cases, even among those who qualify for the procedure. From a public health perspective, this is an interesting issue. The procedure clearly works, but there are third-party payer issues involved in this procedure. But we still need to face next steps: how to keep the weight off. Except for extreme cases, this surgery is not the answer.

Comment (Pratt): The American Heart Association speaks of ideal cardiovascular health with the "Simple 7" health behaviors and risk factors, one of which is BP. Looking at future research, we need to consider factors for ideal cardiovascular health in planning our studies.

Comment (Daniels): We need to think of cardiovascular health in terms of "primordial" prevention. We do better at achieving cardiovascular health through treatment, and medication is not as good as maintaining sound cardiovascular health. Most people are born with ideal cardiovascular health, which tends to devolve through lifetime. How we proceed on achieving ideal cardiovascular health diet changes in childhood; think about genetic component; that component is small; the major influence on cardiovascular health is lifestyle. A major challenge for pediatricians is to think about how to work with families.

Closing Comments and Discussion
Hypertension Research: Next Steps

Dr. Taylor-Zapata thanked participants for their interest and input. She also thanked them for their in-person and Webinar attendance, and for their participation from across a number of agencies, and from across multiple disciplines and areas of expertise.

Dr. Taylor-Zapata reminded participants that information is available online regarding funding opportunities and information sharing on future WG conversations. She encouraged participants to offer additional questions or suggestions for next steps.

It was noted that today's meeting brought together a discussion of topics that are not usually seen in one agenda. This roundtable offered the possibility of a possible larger future meeting to continue the discussion of achieving/maintaining cardiovascular health as a preventive approach to reducing primary pediatric HTN; today's meeting has been a great first step.

Dr. Taylor-Zapata also indicated that conversation would continue among NICHD and NHLBI on encouraging the Institutes to work together on funding opportunities, especially those regarding HTN biomarkers and gaps. The possibility of moving ahead on Dr. Portman's recommendation for exploring future collaboration with industry will also be a topic of cross-Institute conversation.

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