Optimize treatment regimens to reduce cardiovascular disease events: Individualizing antihypertensive therapy

Dr. Johnson returned to his office to compose his post-visit notes. He had just finished a follow-up visit with a new patient — a young adult male cigarette smoker — whom Dr. Johnson just told had early-stage diabetes, stage 1 hypertension and, with a BMI of 26 kg/m^2, was overweight. Dr. Johnson wondered how motivated the patient would be to follow the medical regimens necessary to turn around this slow-motion train wreck.

Needs Assessment

The most prevalent healthcare problem facing us today is the morbidity and mortality caused by obesity, diabetes, and cardiovascular disease (CVD). The causal link between hypertension and CVD, and the importance of controlling hypertension are well established. [Wong 2007] Management guidelines have long acknowledged that reduction of cardiovascular and renal morbidity and mortality are the primary goals of hypertensive therapy. [Chobanian 2003] Yet, according to the Institute of Medicine (IOM), hypertension is a "neglected disease." [IOM 2010] Hypertension remains a challenge in part because healthcare providers fail to apply treatment strategies that aggressively reduce metabolic and cardiovascular risk factors to prevent or delay progression to a CVD event. [IOM 2010; Feldman 2009]

The other half of the challenge, of course, is patient behavior and lifestyle. Despite increased awareness of the consequences, individuals continue to follow unhealthy lifestyles that contribute to the prevalence of CVD, and poor adherence that undermines its treatment. At the request of the Centers for Disease Control and Prevention (CDC), the IOM just released a strategic plan that outlines a population-based and systems approach to promote healthy lifestyle choices that will reduce the prevalence of hypertension in the United States. [IOM 2010]

At the same time, pharmaceutical management of hypertension continues to evolve. Some experts, in an effort to reduce CVD events, are calling for an expansion of the clinical criteria that identify candidates for antihypertensive therapy. [Giles 2009] As older drugs fall out of favor, clinical studies report potential pleiotropic benefits for others. But newly identified strategies are not being implemented in clinical practices, management of hypertension remains suboptimal, and deaths from CVD are rising. [IOM, 2010; Feldman

2009] ***Providers are challenged to stay abreast of current evidence-based findings that inform optimal treatments of hypertension, and to employ individualized strategies that reduce the incidence of CVD events in candidates for intervention.***

Gap Analysis

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
HCPs who manage HTN lack **knowledge** of, and **competence** and **performance** in consistently identifying indicators for treatment and appropriately individualizing treatment regimens	*Literature review; Expert opinion*	Review literature for patient differences in indicators for treatment, responses to agents, and target goals; present NIDDKD, ACCORD, INVEST outcomes	3 (Knowledge); 4 (Competence); 5 (Performance)
HCPs who manage HTN lack **knowledge** of, and **competence** and **performance** in applying recent evidence-based outcomes shown to reduce CVD events	*Recent survey; Literature review; Expert opinion*	Present recent evidence-based outcomes in reducing CVD [ACCOMPLISH, ASCOT-BPLA]	3 (Knowledge); 4 (Competence); 5 (Performance)
HCPs who manage HTN lack **knowledge** of, and **competence** and **performance** in managing all candidates for pharmaceutical intervention	*Literature review; Expert opinion*	Present recent evidence-based outcomes in patients previously not considered candidates for intervention [NIDDKD ASCOT-BPLA, HYVET]	3 (Knowledge); 4 (Competence); 5 (Performance)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
HCPs who manage HTN lack **knowledge** of, and **competence** and **performance** in translating guideline updates into clinical practice	*Literature review; Expert opinion*	Present recent updates to management guidelines [JNC-8 2010; Llyod-Jones 2010 586; Giles 2009]	3 (Knowledge); 4 (Competence); 5 (Performance)

HCPs = healthcare providers; HTN = hypertension; ACCORD = Action to Control Cardiovascular Risk in Diabetes; INVEST = International Verapamil-SR-Trandolapril
ACCOMPLISH = Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm; NIDDKD = National Institute of Diabetes and Digestive and Kidney Diseases; HYVET = Hypertension in the Very Elderly Trial

Despite medical advances and public awareness campaigns, hypertension remains one of the leading causes of death in the United States, responsible for 1 in every 6 deaths annually. [IOM 2010] Uncontrolled hypertension contributes to the fact that cardiovascular disease (CVD) continues to be the number one cause of preventable death in developing countries. [CDC 2010; WHO 2010] Analysis of National Health and Nutrition Examination Surveys (NHANES) data found that the prevalence of hypertension has remained unchanged from 1999 to 2006 [Ostchega 2008]; from 2003 to 2006 the prevalence of hypertension in all US adults (≥20 years of age) was 33.6%. [Lloyd-Jones 2010 e46]

In 2005 and with a 2009 update, a consortium of hypertension specialists, the American Society of Hypertension (ASH) Hypertension Writing Group, proposed a paradigm shift in the management of hypertension. Their position is based on the assumption that elevated blood pressure is a disease marker that frequently coexists with other compelling markers for CVD. [Giles 2009] These experts assert that hypertension is "a progressive cardiovascular syndrome, the early markers of which may be present before

blood pressure elevations are observed." [Giles 2009] According to this position paper, initiation of treatment should be individualized and guided by CVD risk and target organ damage rather than blood pressure thresholds. [Giles 2009] They state further that clinical awareness of SBP and pulse pressure (SBP minus DBP) levels, more accurate measures of CVD risk than DBP, should translate into more aggressive management. [Giles 2009] Dissenters who eschew aggressive intervention state that claims of reduction in CVD events are yet not proven. [Staessen 2010; Mancia 2009]

Support for aggressive intervention can be found in the WHO records that report 62% of blood pressure-related CVD events are attributable to SBP as low as just above 115 mmHg. [WHO 2002] Based on the WHO Global Burden on Disease database, approximately half of CVD attributed to blood pressure occurs in patients with an SBP <140 mmHg. [Rodgers 2004] The implication is that the threshold for intervention is not an SBP >140 mmHg, but rather the presence of risk factors for CVD, such as history of a prior CVD event; conditions highly associated with CVD, such as diabetes or renal disease; and multiple risk factors, such as cigarette smoking and advanced age. [Chalmers 2009] ***Healthcare providers need to update their knowledge of the risks for a CVD event and appropriately identify candidates for antihypertensive therapy.***

Based on analysis of NHANES database 2003-2004, nearly three-fourths of patients with conditions associated with CVD risk were hypertensive (defined as ≥130/90 mmHg), yet of the approximately 75% receiving treatment only one-third to one-half were controlled to target goals. [Wong 20087] Alarmingly, the incidence of death attributed to hypertension has risen 25% from 1995 to 2005. [IOM 2010] ***Healthcare providers need to improve their competence in implementing intervention strategies shown to reduce the incidence of CVD events.***

Application of clinical outcomes and treatment guidelines must incorporate each patient's individual clinical circumstances, particularly the thresholds for intervention, underlying causes of hypertension, comorbid conditions, and ability to tolerate known side effects of therapy. The four podcasts outlined below present examples of distinct clinical profiles that require awareness of appropriate interventions to reduce CVD events. ***Healthcare providers need to increase their performance in individualizing regimens shown to reduce the incidence of CVD events.***

Learning Objectives

- Discuss clinical thresholds for initiation of pharmaceutical intervention to reduce the risk of CVD events.
- Evaluate the impact of new study outcomes on therapeutic choices for optimal intervention in patients with hypertension.
- Recognize the potential for earlier onset of vascular aging in African Americans and outline strategies to address differences in response to antihypertensive agents.
- Identify treatment regimens that improve control in resistant hypertension.
- Evaluate study outcomes that suggest visit-to-visit variability in blood pressure is a marker for CVD risk.
- Discuss the threshold for intervention in pediatric hypertension.
- Identify differences in the treatment of hypertension complicated by metabolic syndrome or diabetes mellitus.
- Discuss the risks and benefits of antihypertensive treatment of the very elderly.

Intended Audience

- Cardiologists
- Nephrologists
- Primary care physicians
- Nurse practitioners
- Physician assistants

Proposed Agendas (four 15-minute podcasts)

Podcast #1: Resistant hypertension

- Introduction to clinical challenge from first-person narrative of treating physician
  - After the initial intake interview with a referred patient, the physician wonders what the underlying cause is for her new patient's uncontrolled blood pressure
- Brief review of patient's relevant clinical status
  - Perimenopausal African American female
  - Sitting BP 145/90 mmHg, BMI 25 kg/m^2, eGFR = 70 mL/min/1.73 m^2, pre-diabetic
  - Currently treated with beta blocker and loop diuretic
- Relevant clinical issues

- Ethnic, gender differences in prevalence
  - ⇒ Subgroup with most uncontrolled hypertension (41%) in NHANES study was African American women [Calhoun 2008]
- Physiologic, genetic differences predispose African Americans to earlier, more resistant hypertension
  - ⇒ Microvascular damage associated with endothelial dysfunction and atherosclerosis seen in otherwise healthy young African Americans [Heffernan 2008]
  - ⇒ Intima media layer thickness, measure of vascular remodeling and vascular age, thicker earlier in African Americans [Labropoulos 2005; Brewster 2010]
  - ⇒ CYP3A5*1 allele prevalent in African Americans, associated with resistant hypertension; possible cause of abnormal sodium, water retention and volume overload [Ho 2005]
  - ⇒ Plasma aldosterone more predictive of hypertension than body weight in African Americans [Kidambi 2009]; 20% prevalence of primary aldosteronism in resistant hypertension [Gaddam 2008]
- Most resistant hypertension associated with volume overload, excess sodium intake/retention [Sarafidis 2008; Pimenta 2009]

- Prognosis
  - 96% reduction in CVD events with 3-drug treatment of severe hypertension in VA COOP Hypertension study [Calhoun 2008]
- Possible treatments
  - Full-dose, 3-drug regimen of agents with complementary actions
    - ⇒ Potential pleiotropic effects with newer agents: endothelial function repair with ARB olmesartan [Ferrario 2009]; with CCB amlodipine [Jamerson 2009]
    - ⇒ Match class of diuretic with renal status (with normal function, long-acting thiazide; with eGFR<40 mL/min/1.73 m^2, loop diuretic) [Sarafidis 2008]
      - Long-acting chlorthalidone more effective than hydrochlorothiazide [Calhoun 2008]
      - Aldosterone antagonists or other potassium-sparing diuretics
  - Ethnic differences in response to antihypertensive agents
    - ⇒ Double dose of valsartan effective African Americans [Weir 2010]
  - Combinations
    - That work: diuretic + CCB + ARB [Meka 2010; Calhoun 2009]; ARB + natriuertic peptide inhibitor [Ruilope 2010]

- That don't work: ACE inhibitor + ARB [ONTARGET 2008]

Podcast #2: Visit-to-visit SBP variability

- Introduction to clinical challenge from first-person narrative of treating physician
  - Physician expresses his concern that a regular patient with family history of stroke has risks factors for CVD, and a SBP that is partially controlled but variable
- Brief review of patient's relevant clinical status
  - Adult male with family history of stroke, cigarette smoker, with high-stress desk job (3 CVD risk factors)
  - Attempts to modify his lifestyle have not been successful
  - Hypertension, treated with beta-blocker atenolol**,** controlled to 130/90 mmHg with occasionally higher SBP readings; CVD risk treated with ASA prophylaxis
- Relevant clinical issues
  - Prognosis of treated hypertension with SBP variability versus stable hypertension: 6-fold increase in stroke risk [Sever 2010]
  - SBP variability may be a maker of arterial stiffness [Sever 2010]
- Relevant recent clinical studies
  - ACCOMPLISH [Jamerson 2009]
  - UK-TIA + ASCOT-BPLA [Rothwell 2010 Lancet]
  - MRC + ASCOT-BPLA [Rothwell 2010 Lancet Neurology]
  - ASCOT-BPLA (beta blocker + thiazide vs CCB + ACE inhibitor) [Sever 2010]
  - Meta-analysis of ASCOT-BPLA (prior-TIA cohort), ESPS-1, Dutch TIA [Webb 2010]
- Clinical implications of studies outcomes
  - Greater reduction in CVD morbidity/mortality with single-pill combination of benazepril (ACE inhibitor) + amlodipine (CCB) versus diuretic-based regimen attributed to pleiotropic actions of agents, not BP lowering efficacy [Jamerson 2009]
  - Reduction in stroke, coronary events in variable HTN greater with long-acting CCB amlodipine than with beta blocker atenolol [Rothwell 2010 Lancet]
  - Risk of stroke increased with ACE inhibitors, ARBs, beta blockers [Rothwell 2010 Lancet Neurology]
  - Rothwell "study findings could double the number of candidates for antihypertensive therapy" [Sever 2010]

ACCOMPLISH = Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm
UK-TIA = United Kingdom-Transient Ischemic Attack
MRC = Medical Research Council
ESPS-1 = European Stroke Prevention Study-1
Dutch TIA = Dutch Transient Ischemic Attack

Podcast #3: Pediatric hypertension with obesity and metabolic syndrome

- Introduction to clinical challenge from first-person narrative of treating physician
  - After elevated blood pressure readings on 3 separate visits, growing clinical evidence of metabolic syndrome, and unsuccessful efforts to modify her young patient's lifestyle, the physician wonders if her patient now needs pharmaceutical intervention
- Brief review of patient's relevant clinical status
  - 16-year old boy, BMI 30 kg/m^2, BP on 3 separate visits 135-140/70-82 mmHg (>95th percentile for age, sex, and height), dyslipidemia, glucose intolerance, insulin resistance, hyperuricemia
  - Inactive lifestyle, unhealthy diet
  - Family history of type 2 diabetes, myocardial infarction
- Relevant clinical issues
  - Epidemic of obesity, hypertension, type 2 diabetes in children
    - ⇒ Prevalence of boys 12-19 years old in BMI ≥95th percentile is 19% [Ogden 2010]
    - ⇒ Lack of PCP awareness of pediatric hypertension [Flynn 2008]
    - ⇒ Need for treatment guidelines [Lurbe 2009]
  - Modification of lifestyle should be first-line intervention
  - Threshold for pharmaceutical intervention is lower in obese children with hypertension and metabolic syndrome [Lande 2009] because there is an increased risk for target organ damage [Redon 2009]
  - Recent antihypertensive agents approved for pediatric use
- Relevant recent clinical studies
  - Paucity of studies in pediatric population
    - ⇒ NIDDKD [Franks 2010]
  - In adults with type 2 diabetes

    - ⇒ ACCORD [Cushman 2010]
    - ⇒ INVEST [Cooper-DeHoff 2010]
- Clinical implications of studies outcomes
    - Obesity, glucose intolerance, and hypertension in children is strongly associated with increased rates of premature death [Franks 2010]
    - Beta blockers, diuretics have significant diabetogenic potential; they are no longer recommended by European Society for Hypertension/European Society of Cardiology guidelines, or for first-line therapy in uncomplicated hypertension by NICE or British Hypertension Society [Karnes 2009]
    - ACE inhibitor-, ARB-based regimens reduce risk of diabetes development [Karnes 2009]
    - Intensive antihypertensive treatment in adults with type 2 diabetes to a SBP target <120 mm Hg increases the risk of stroke [Cushman 2010]
        - ⇒ The correlation between SBP and CVD risk is not a direct continuum in type 2 diabetes as it is in non-type 2 diabetes [Cushman 2010]
    - Reducing SBP to <115 mmHg in patients with type 2 diabetes plus coronary artery disease increases the risk of CVD mortality [Cooper-DeHoff 2010]

NIDDKD = National Institute of Diabetes and Digestive and Kidney Diseases
ACCORD = Action to Control Cardiovascular Risk in Diabetes
INVEST = International Verapamil-SR-Trandolapril

Podcast #4: Hypertension in the very elderly

- Introduction to clinical challenge from first-person narrative of treating physician
    - At the follow-up to an annual check-up visit, an elderly patient continues to demonstrate mild isolated systolic hypertension and cognitive deficit in executive function; the physician wonders if her patient can tolerate therapy with an antihypertensive regimen
- Brief review of patient's relevant clinical status
    - Mild isolated systolic blood pressure
    - History of transient ischemic attack; possible early-stage vascular dementia
    - Osteoarthritis of hip, knees managed with daily over-the-counter NSAIDs
- Relevant clinical issues

- Prevalence of hypertension increases with age, is 67% among those ≥60 years and older [Ostchega 2008]
- Based on NHANES data, patients who are normotensive at 55 years old have a 90% risk of developing hypertension during the rest of their life [IOM 2010]
- In patients ≥60 years, only 58% likely to have hypertension controlled [Ostchega 2008]
- Isolated SBP elevation is the most common form of hypertension in patients >50 years [Korc 2009]
- SBP and pulse pressure more accurate markers of CVD risk than DBP [Giles 2009]
- Hypertension is a major risk factor for vascular cognitive impairment [Oveisgharan 2010]
- Older patients who are incontinent should avoid diuretics; older patients who are prone to dizziness and falls are more sensitive to the effects of beta blockers [IOM 2010]
- Many physicians are nonadherent to JNC-7 guidelines to treat elderly hypertension; misconception that elevated SBP is necessary with hardened arteries or that elderly can't tolerate antihypertensive therapy [IOM 2010]
- Dihydropyridine CCBs (eg, nifedipine, amlodipine), which exert blood pressure–lowering effects almost entirely on the peripheral vasculature, may be well suited to treat elderly isolated systolic hypertension

- Relevant recent clinical studies
  - SHEP [Pastel 2000]; 14-year follow-up [Patel 2008]
  - HYVET [Beckett 2008]
  - Canadian Study of Health and Aging [Oveisgharan 2010]
- Clinical implications of studies outcomes
  - Treatment of elderly hypertension significantly reduced the incidence of fatal and non-fatal CVD events (hemorrhagic or ischemic stroke, MI, coronary artery disease, all-cause mortality [Perry 2000]
  - At 14-year follow-up, the treated group had a significantly lower incidence of CVD-related deaths [Patel 2008]
  - Treatment of very elderly hypertension significantly reduced the incidence of stroke, heart failure, CVD-related deaths, all-cause deaths; incidence of treatment-related serious AEs was less than in placebo group [Beckett 2008]

- Control of hypertension in the elderly may reduce by one-third progression from mild cognitive impairment to dementia [Oveisgharan 2010]

SHEP = Systolic Hypertension in Elderly Program
HYVET = Hypertension in the Very Elderly Trial

Proposed Faculty

David A. Calhoun, MD
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University of Alabama at Birmingham School of Medicine
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Area of expertise — Resistant hypertension, primary aldosteronism**;** Writing Committee Chair, American Heart Association Guidelines, Resistant Hypertension

Joseph T. Flynn, MD
Professor, Nephrology
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Area of expertise — Pediatric hypertension; President-elect, American Society of Pediatric Nephrology

William C. Cushman, MD
Professor, Preventive Medicine; Medicine
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Area of expertise — Hypertension in African Americans, the elderly, patients with diabetes; Lead Hypertension Consultant for JNC 7, JNC 8

Suzanne Oparil, MD
Professor of Medicine; Physiology; Biophysics
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Area of expertise — Novel treatments that target the fundamental mechanisms of CVD; Past-President American Heart Association; American Society of Hypertension

All faculty members will be screened for possible conflicts of interest (COI) and the program will be executed in a manner that is consistent with OIG, FDA, ACCME, and ACPE standards and guidelines.

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