Integrative Therapies to Control Hypertension

Shaista Malik, MD, PhD, MPH
Medical Director, Integrative & Preventive Cardiology, Cardiac Rehab Programs
Executive Director, Susan Samueli Integrative Health Institute
Associate Vice Chancellor, Integrative Health
Susan and Henry Samueli College of Health Sciences
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• Adolph Coors Foundation-PI
• FluxWear: Board
Overview

- Hypertension Risk Factors
- Integrative or Whole Health Approach
- Evidence-Based Integrative Therapies for HTN
- Research on Adjunctive Role of Integrative Therapies
Factors leading to HTN
Enhanced sympathetic outflow
Vasoconstriction
Increased sodium retention
Increased Renin release from JG cells
Immune activation
Altered vagal activity and defective immune reflex

Enhanced vasoconstrictor activity due to altered GPCR activation
Reduced NO bioavailability
Loss of myoendothelial junctions
Increased stretch/endothelial activation leading to immune activation and pro-thrombosis

Increased sodium retention/
Altered pressure natriuresis
Increased renin release
ROS induced ADMA production
Enhanced renal afferent nerve traffic
Immune activation
Integrative or Whole Health Approach: Pathogenesis

Healthy → Less Healthy → Disease

- Vascular Function
- Renin Angiotensin Aldosterone System
- Oxidation/Inflammation
- Autonomic Nervous System
Integrative or Whole Health Approach: Pathogenesis

Healthy → Less Healthy → Disease

Vascular Function
RAAS
Oxidation/Inflammation
Autonomic Nervous System

Psychological stress
Poor diet
Sedentary lifestyle
Integrative or Whole Health Approach: Salutogenesis

Healthy → Less Healthy → Disease

Optimal Medical Management
Self care
Psychological Nutritional Physical
Multicomponent interventions

Psychological stress
Poor diet
Sedentary lifestyle
Hypertension: Integrative Assessment Framework
Comprehensive history (Current)
Advanced Biomarkers (Future)
Blood pressure categories in the new guideline are:

- **Normal**: Less than 120/80 mm Hg;
- **Elevated**: Systolic between 120-129 and diastolic less than 80;
- **Stage 1**: Systolic between 130-139 or diastolic between 80-89;
- **Stage 2**: Systolic at least 140 or diastolic at least 90 mm Hg;
- **Hypertensive crisis**: Systolic over 180 and/or diastolic over 120, with patients needing prompt changes in medication if there are no other indications of problems, or immediate hospitalization if there are signs of organ damage.
NEW 2021 GUIDANCE ON STAGE 1 HYPERTENSION MANAGEMENT IN LOW-RISK ADULTS.

**Table 1: AHA/ACC**

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Pressure Ranges</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BP</td>
<td>&lt;120/80 mmHg</td>
<td>Promote healthy lifestyle; reassess BP annually.</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>120-129/80 mmHg</td>
<td>Start with nonpharmacologic therapy; reassess BP in 3-6 months.</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>130-139/80-89 mmHg</td>
<td>ASCVD² or 10-year CVD² risk ≥10%: Start with both nonpharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3-6 months. If not at goal, assess for adherence and consider intensification of therapy.</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥140/90 mmHg</td>
<td>Start with both nonpharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3-6 months. If not at goal, assess for adherence and consider intensification of therapy.</td>
</tr>
</tbody>
</table>

*ACC/AHA Guidelines: Role of Nonpharmacological Therapies*

Blood pressure patterns/phenotypes and underlying mechanism

- Essential HTN
- Secondary HTN
- White Coat HTN
- Masked HTN
- Nocturnal HTN

24 HOUR AMBULATORY BP MONITOR (ABPM)

- Vascular remodeling
- Vascular inflammation
- Vascular Calcification
- Endothelial Dysfunction

CENTRAL BP ASSESSMENT (PWV)
Biomarkers
CAC
ENDOTHELIAL FUNCTION TESTING
Interpretation of ABPM

2017 ACC/AHA Guidelines

Meeting one or more of these criteria for ABPM qualifies as hypertension:

- 24 hour mean BP: 125/75 OR above
- Mean daytime BP: 130/80 OR above
- Mean nighttime BP: 110/65 OR above
Integrative Therapeutic Approach to Management of HTN

- Optimal Medical Management
- Nutrition and Lifestyle
- Nutraceuticals
- Mind-Body Interventions
  - Mindfulness/Meditation
  - Biofeedback
  - Yoga
  - Social Connection
- Adjunctive and Novel Approaches: Neuromodulation of ANS, Electroacupuncture
AHA Scientific Statement

Beyond Medications and Diet: Alternative Approaches to Lowering Blood Pressure

A Scientific Statement From the American Heart Association

Robert D. Brook, MD, Chair; Lawrence J. Appel, MD, MPH, FAHA, Co-Chair; Melvyn Rubenfire, MD, FAHA; Gbenga Ogedegbe, MD, MPH; John D. Bisognano, MD, PhD; William J. Elliott, MD, PhD, FAHA; Flavio D. Fuchs, MD, PhD; Joel W. Hughes, PhD; Daniel T. Lackland, DrPH, MSPH, FAHA; Beth A. Staffileno, PhD, FAHA; Raymond R. Townsend, MD, FAHA; Sanjay Rajagopalan, MD; on behalf of the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity and Metabolism
1. PRE-HTN
   - Diet + lifestyle inadequate or not adopted
   - CAN START ALTERNATIVE APPROACH AS ADJUVANT TO DIET*
     - Trial(s) for up to 1 year

2. UNTREATED HTN
   - Stage I
     - No target organ disease
     - No JNC drug indication
     - Desire to avoid medications & clinically appropriate
     - CAN START ALTERNATIVE APPROACH* Trial(s) for 6-12 months depending on CV risk status (see text)†

   - Stage II or Stage I
     - With target organ disease or a JNC drug indication
     - CAN ADD ALTERNATIVE APPROACH TO DRUGS AS AN ADJUVANT IF BP < 20/10 ABOVE GOAL*
     - Trial durations depending on CV risk status and scenario (see text)†

   - BP < 140/90
     - Yes: Continue
     - No: Start drugs or go to step 2

3. TREATED HTN
   - Controlled BP
     - On medication(s)
     - Desire to step-down or stop medications
     - CAN ADD TO THERAPY AS AN ADJUVANT ALTERNATIVE APPROACHES*

   - "Refractory HTN"
     - BP not at goal on ≥ 3 medications
     - Multiple drug SEs
     - Elevated BP - any level
     - Optimize medical & dietary therapies
     - Optimize medical & dietary therapies

   - BP at goal ‡
     - Yes: Continue
     - No: Drug therapy or go to step 3 if pertinent

   - Reduce drugs as BP response allows

   - Optimize drugs + alternative methods to achieve best BP levels achievable
Lifestyle and Blood Pressure

- **DASH diet**: whole foods, low in sugar, high in fiber, high phytonutrients – can lower SBP by 5-6 points.

- **Lowered sodium**: by cutting back by 1100 mg per day you can lower SBP by 3-4 points.

- **Lose excessive weight**: for every 5% loss of excess weight you can lower SBP by 3 points

- **Exercise**: by adding in at least 40 minutes of exercise 3-4 times per week can lower SBP by 2-5 points


DASH Diet vs. Mediterranean Diet

**Dash Diet**
- 27% of calories from fat, 6% sat fat
- Can be adapted for vegetarians

**Mediterranean Diet**
- ~35% calories from fat, ≤ 10% sat fat
- No emphasis on sodium restriction
- Emphasis on extra virgin olive oil use for cooking and dressings
- Greater emphasis on regular consumption of oily fish and α-linolenic acid

**USDA Food Patterns**
- 20-35% of calories from fat recommended, < 10% sat fat
- Includes vegetarian variations

- Increased vegetables, fruits, whole grains, nuts, legumes, unsaturated oils, low fat dairy, and lean protein (including seafood)
- Decreased trans fat, saturated fat, refined grains, and added sugars
- Moderate or no alcohol consumption

- No emphasis on oily fish
- Emphasis on reduced sodium
Nutraceuticals in Management of HTN

Consensus Document

Nutraceuticals and blood pressure control: a European Society of Hypertension position document

<table>
<thead>
<tr>
<th>Foods</th>
<th>Expected effect on office BP</th>
<th>Main mechanisms of action</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonroasted green coffee</td>
<td>-3/-2 mmHg</td>
<td>Antioxidant, ↓ NO bioavailability, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 9 RCTs (n=501)</td>
</tr>
<tr>
<td>Pomegranate juice</td>
<td>-5/-2 mmHg</td>
<td>Antioxidant, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 8 RCTs (n=574)</td>
</tr>
<tr>
<td>Tea</td>
<td>-2/-1 mmHg</td>
<td>Antioxidant</td>
<td>Meta-analysis of 25 RCTs (n=1475)</td>
</tr>
<tr>
<td>Karkadé tea</td>
<td>-7/-3 mmHg</td>
<td>Antioxidant</td>
<td>Meta-analysis of 5 RCTs (n=590)</td>
</tr>
<tr>
<td>Beetroot juice</td>
<td>-4/-1 mmHg</td>
<td>No donor</td>
<td>Meta-analysis of 16 RCTs (n=254)</td>
</tr>
<tr>
<td>Sesame</td>
<td>-8/-6 mmHg</td>
<td>Antioxidant</td>
<td>Meta-analysis of 8 RCTs (n=843)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Expected effect on office BP</th>
<th>Main mechanisms of action</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 polyunsaturated fatty acids</td>
<td>-2/-1 mmHg</td>
<td>↓ Endothelial dysfunction</td>
<td>Meta-analysis of 70 RCTs (n=2250)</td>
</tr>
<tr>
<td>Proteins, peptides and amino-acids (L-arginine)</td>
<td>-3/-2 mmHg (LTPS)</td>
<td>ACE-inhibition</td>
<td>Meta-analysis of 18 RCTs (n=984)</td>
</tr>
<tr>
<td>Calcium</td>
<td>-1/-1 mmHg</td>
<td>Direct effect on artery wall</td>
<td>Mainly epidemiological data</td>
</tr>
<tr>
<td>Magnesium</td>
<td>-3/-3 mmHg</td>
<td>↑ NO synthesis, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 34 RCTs (n=2028)</td>
</tr>
<tr>
<td>Potassium</td>
<td>-4/-3 mmHg</td>
<td>Balancement of negative effect of sodium on blood pressure</td>
<td>Meta-analysis of 33 RCTs (n=1829)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>-4/-1 mmHg</td>
<td>NO and PGs release, diuresis and natriuresis, ↓ adrenal steroid production, ↑ cyclic GMP increase, potassium channels activation, cytosolic calcium reduction</td>
<td>Meta-analysis of 21 RCTs (n=1407)</td>
</tr>
<tr>
<td>Prebiotics and soluble fibres</td>
<td>-3/-2 mmHg</td>
<td>Improvement of microbiota</td>
<td>Meta-analysis of 15 RCTs (n=1270)</td>
</tr>
<tr>
<td>Nonnutrient nutraceuticals</td>
<td>Effect on BP</td>
<td>Effect on BP</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------</td>
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</tr>
<tr>
<td>Resveratrol and grape seed extracts</td>
<td>-9/-1 mmHg</td>
<td>Antioxidant, ↓ insulin-resistance</td>
<td>Meta-analysis of 17 RCTs (n=782)</td>
</tr>
<tr>
<td>Cocoa flavonoids</td>
<td>-2/-2 mmHg</td>
<td>Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 40 RCTs (n=1804)</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>-5/-2 mmHg</td>
<td>Antioxidant, hormone-replacement therapy like effect</td>
<td>Meta-analysis of 12 RCTs (n=1551)</td>
</tr>
<tr>
<td>Aged garlic extract</td>
<td>-9/4 mmHg</td>
<td>Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 9 RCTs (n=482)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>-5/-1 mmHg</td>
<td>Antioxidant, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 6 RCTs (n=482)</td>
</tr>
<tr>
<td>Pycnogenol</td>
<td>-3/-3 mmHg</td>
<td>Antioxidant, ↓ Endothelial dysfunction, angiotensin-converting enzyme inhibitor</td>
<td>Meta-analysis of 9 RCTs (n=549)</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>-8/-7 mmHg</td>
<td>Antioxidant</td>
<td>Meta-analysis of 7 RCTs (n=478)</td>
</tr>
<tr>
<td>Slow-release melatonin</td>
<td>-6/-3 mmHg</td>
<td>Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction</td>
<td>Meta-analysis of 7 RCTs (n=221)</td>
</tr>
<tr>
<td>Taurine</td>
<td>-7/-5 mmHg</td>
<td>GABA_A receptors activation</td>
<td>Single large RCT (n=120)</td>
</tr>
<tr>
<td>Probiotics</td>
<td>-4/-2 mmHg</td>
<td>Improvement of microbiota</td>
<td>Meta-analysis of 9 RCTs (n=543)</td>
</tr>
</tbody>
</table>
Beetroot Juice

- Meta-analysis of RCTs beetroot juice consumption, daily doses ranging from 321–2790 mg
- Associated with dose-dependent changes in SBP [mean reduction. 4.4mmHg (95% CI 5.9 to 2.8)

Mechanism of Action:

- Inorganic nitrate (NO$_3$) metabolizes in vivo to bioactive nitrite (NO$_2$)
- NO$_2$ conversion to functional nitrogen oxides, including NO

Aged Garlic

- Meta-analysis of nine RCTs including 482 individuals treated with aged garlic extract for 8–26 weeks,
- Reduction in SBP and DBP: 9.1mmHg (95% CI 12.7 to 5.4), 3.8mmHg (95% CI 6.7 to 1.0)
- Additive to antihypertensive therapy

- Mechanism of Action:
  - Garlic-derived polysulfides stimulate the production of the vascular hydrogen sulfide
  - Enhance the regulation of endothelial NO:
    - Smooth muscle cell relaxation
    - Vasodilation and BP reduction
  - Aged dry garlic extract also have ACE inhibitory and calcium channel blocking activity, that reduce catecholamine sensitivity,

Reid K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomized controlled trial. Maturitas 2010; 67:144–150.
Mind-Body Therapies: Transcendental Meditation and Reduced Blood Pressure (2013) and Cardiac Events (2017)

• AHA scientific statement also reported the finding that lower blood pressure through Transcendental Meditation practice is associated with substantially reduced rates of death, heart attack and stroke.

• The AHA scientific statement concludes that alternative treatments that include the Transcendental Meditation technique are recommended for consideration in treatment plans for all individuals with blood pressure greater than 120/80 mm Hg

• Mechanism: Reductions in stress and physiological arousal, producing favorable effects on autonomic nervous system balance
Mind-Body Approaches: Biofeedback

- Informational feedback about physiological response: direct-BP or indirect-HR, thermal, galvanic skin response, electromyographic activity
- RCTs using ABPM, −8/−5 mm Hg reduction
- Encourages somatic awareness (introception)
- ANS balance

Mind-Body Approaches: Acupuncture

- WHO (1996) lists acupuncture as effective for HTN
- Meta-analyses inconclusive
- Challenges of isolating therapies from Traditional Medical Systems (availability, multimodal)
- Mechanisms:
  - Acupuncture-sensory mechanoreceptor and nociceptor stimulation
  - Electroacupuncture-stimulation of peripheral nerve fibers, including vagal afferents and reduction in reflex sympathetic activity

Measuring the Mechanism and Biological Effect of Electroacupuncture for Hypertension: Neuromodulation

• Targeting Sympathetic Nervous System Activation

• Use of 4 acupoints to treat Hypertension (targeting Sympathetic Nervous System (SNS))
  - Neiguan, Jianshi (pericardial meridian, P 6 and 5 points, on the palmar side of both arms and Zusanli, Shangjuxi (stomach meridian, ST 36 and 37, on the anterolateral side of the leg)

• Once a week treatment (for 30 minutes) for 8 continuous weeks, followed by once a month treatment to maintain reduced blood pressure.¹

Electroacupuncture in Hypertensive Patients (Active vs. Sham acupoints)

- Peak SBP dropped 8 mm Hg, DBP dropped 5 mm Hg
- Norepinephrine decreased 41%, Renin decreased 67%, aldosterone 25%

30% Non-response rate: Post-menopausal Women

Electroacupuncture for Hypertension in Middle-aged Women: Cardiovascular and Endocrine Acupoints

• Can targeted acupuncture be used for different indications?

• Use of 8 acupoints to treat Hypertension (targeting SNS and Endocrine System)
  Including P 5 + LI 4, ST 36 + SP 6, CV 3+ 4, LR 3 + KI 3.

• Once a week treatment (for 30 minutes) for 8 continuous weeks, followed by once a month treatment to maintain reduced blood pressure.

Grant Funding (2016-2019): Coors Foundation (Tjen-A-Looi and Malik, Co-PIs)

Tjen-A-Looi, Xie L, Fu L, Li P, Malik S. Enhanced Blood Pressure Lowering Responsiveness with Endocrine-Sympathoinhibitory Electroacupuncture in Middle-Aged Hypertensive Women. Experimental Biology, April 2018
Electroacupuncture in Middle-Aged Hypertensive Women

Tjen-A-Looi, Xie L, Fu L, Li P, Malik S. Enhanced Blood Pressure Lowering Responsiveness with Endocrine-Sympathoinhibitory Electroacupuncture in Middle-Aged Hypertensive Women. Experimental Biology, April 2018

Peak SBP dropped 10 mm Hg
DBP dropped 5 mm Hg
Measuring the Mechanism and Biological Effect of Acupuncture using Metabolomics
Metabolomics of Targeted Electroacupuncture in Post-menopausal women

Study Objective

The goal of this study is to identify metabolomic changes associated with two types of electroacupuncture treatment in post-menopausal women.

Study Design

48 plasma samples sent to Metabolon. Global metabolic profiles were determined from the experimental groups outlined in the table below. 1,172 biochemicals were run.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time Point</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNS EA only</td>
<td>Treatment 1</td>
<td>N=10</td>
<td>N=10</td>
</tr>
<tr>
<td>SNS +Endocrine</td>
<td>Treatment 2</td>
<td>N=14</td>
<td>N=14</td>
</tr>
</tbody>
</table>

Funding: Coors Foundation
Subjects who has undergone treatment 2 (SNS+Endocrine) had significantly lower levels of Beta –oxidation (Short and Medium Chain Fatty Acids)

<table>
<thead>
<tr>
<th>Sub Pathway</th>
<th>Biochemical Name</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Short Chain)</td>
<td>acetylcarnitine (C2)</td>
<td>1.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Medium Chain)</td>
<td>hexanoylcarnitine (C6)</td>
<td>1.08</td>
<td>0.74</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Long Chain Saturated)</td>
<td>myristoylcarnitine (C14)</td>
<td>1.17</td>
<td>0.80</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)</td>
<td>myristoleoylcarnitine (C14:1)*</td>
<td>1.11</td>
<td>0.67</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Polyunsaturated)</td>
<td>linoleoylcarnitine (C18:2)*</td>
<td>0.98</td>
<td>0.81</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Dicarboxylate)</td>
<td>(R)-3-hydroxybutyrylcarnitine</td>
<td>1.07</td>
<td>0.85</td>
</tr>
<tr>
<td>Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)</td>
<td>deoxycarnitine</td>
<td>1.08</td>
<td>0.89</td>
</tr>
<tr>
<td>Carnitine Metabolism</td>
<td>acetoacetate</td>
<td>1.07</td>
<td>0.41</td>
</tr>
<tr>
<td>Ketone Bodies</td>
<td>3-hydroxybutyrate (BHBA)</td>
<td>0.77</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Preliminary Data
### Table 1. Examples of diseases that influence blood levels of carnitine and acylcarnitines.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Proposed Mechanism</th>
<th>Subject</th>
<th>Biospecimen</th>
<th>Disease-Induced Alterations in Carnitine/Acylcarnitine Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>Invoked metabolic flexibility pathway</td>
<td>1. Humans (T2D+complications)</td>
<td>1. Serum</td>
<td>1. 25% lower LC levels [40]</td>
</tr>
<tr>
<td></td>
<td>Impaired insulin-dependent uptake of carnitine</td>
<td>2. Humans (T2D)</td>
<td>2. Plasma</td>
<td>2. Increased C2, SCAC, MCAC in patients with higher HbA1c [41]</td>
</tr>
<tr>
<td></td>
<td>Increased production of ACs due to incomplete FAO</td>
<td>3. Humans (insulin resistant/obese)</td>
<td>3. Serum</td>
<td>3. Increased C3, C5, C6, C8:1 [42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Humans (T2D)</td>
<td>4. Plasma</td>
<td>4. Increased SCAC, MCAC, LCAC in T2D patients [22]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Humans (T2D)</td>
<td>5. Plasma</td>
<td>5. LCAC most associated with developing T2D [43]</td>
</tr>
</tbody>
</table>
Testing Neuromodulation with EA

- Sympathoinhibition
- Parasympathoexcitation
- Combined Effects on Vascular Inflammation, Endothelial function and Autonomic Tone

NIH/NCCIH R01 AT011306-Malik (PI), Tjen-A-Looi (MPI)

- Adjunctive Use of EA with Anti-hypertensive Medications

Coors Foundation Study- Malik (PI)
Conclusions

• Whole Health approach emphasizes lifestyle as well as mind/body related factors

• Paucity of well-designed, high-quality CVD outcome trials for integrative therapies in those with HTN

• Most integrative therapies offer modest BP lowering (<10 mmHg/5 mm Hg)

• More rigorous research showing changes in intermediate outcomes (LVH) and cardiovascular event reduction needed

• Research on adjunct approaches needed
Questions