Integrative Therapies to Control Hypertension

Shaista Malik, MD, PhD, MPH

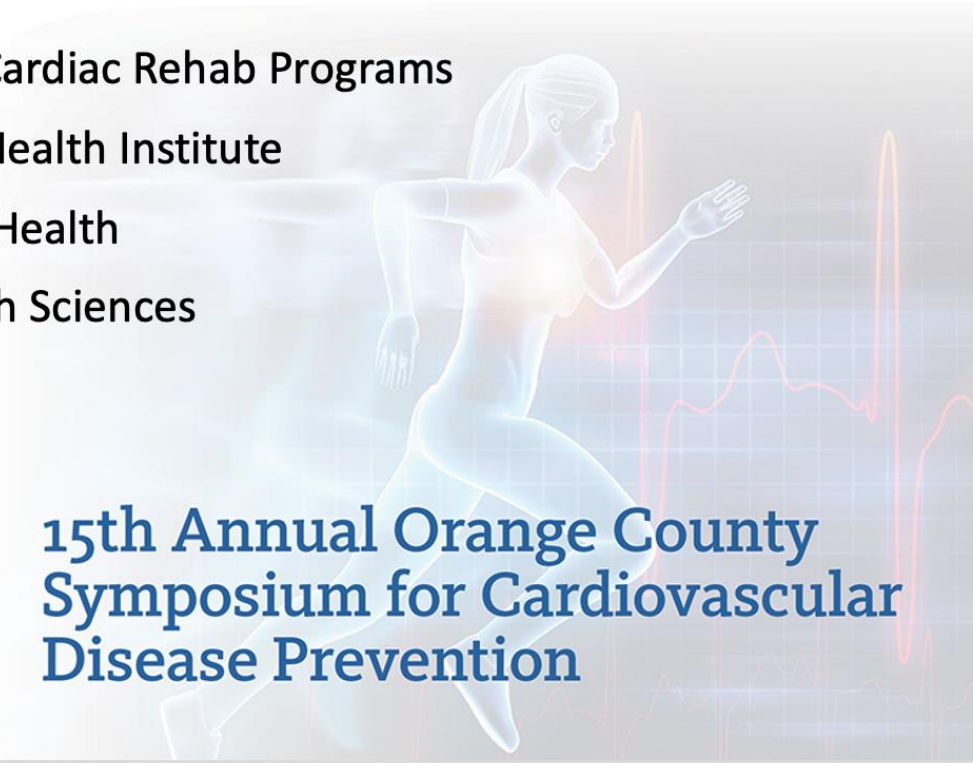
Medical Director, Integrative & Preventive Cardiology, Cardiac Rehab Programs

Executive Director, Susan Samueli Integrative Health Institute

Associate Vice Chancellor, Integrative Health

Susan and Henry Samueli College of Health Sciences

October 23, 2022



15th Annual Orange County Symposium for Cardiovascular Disease Prevention

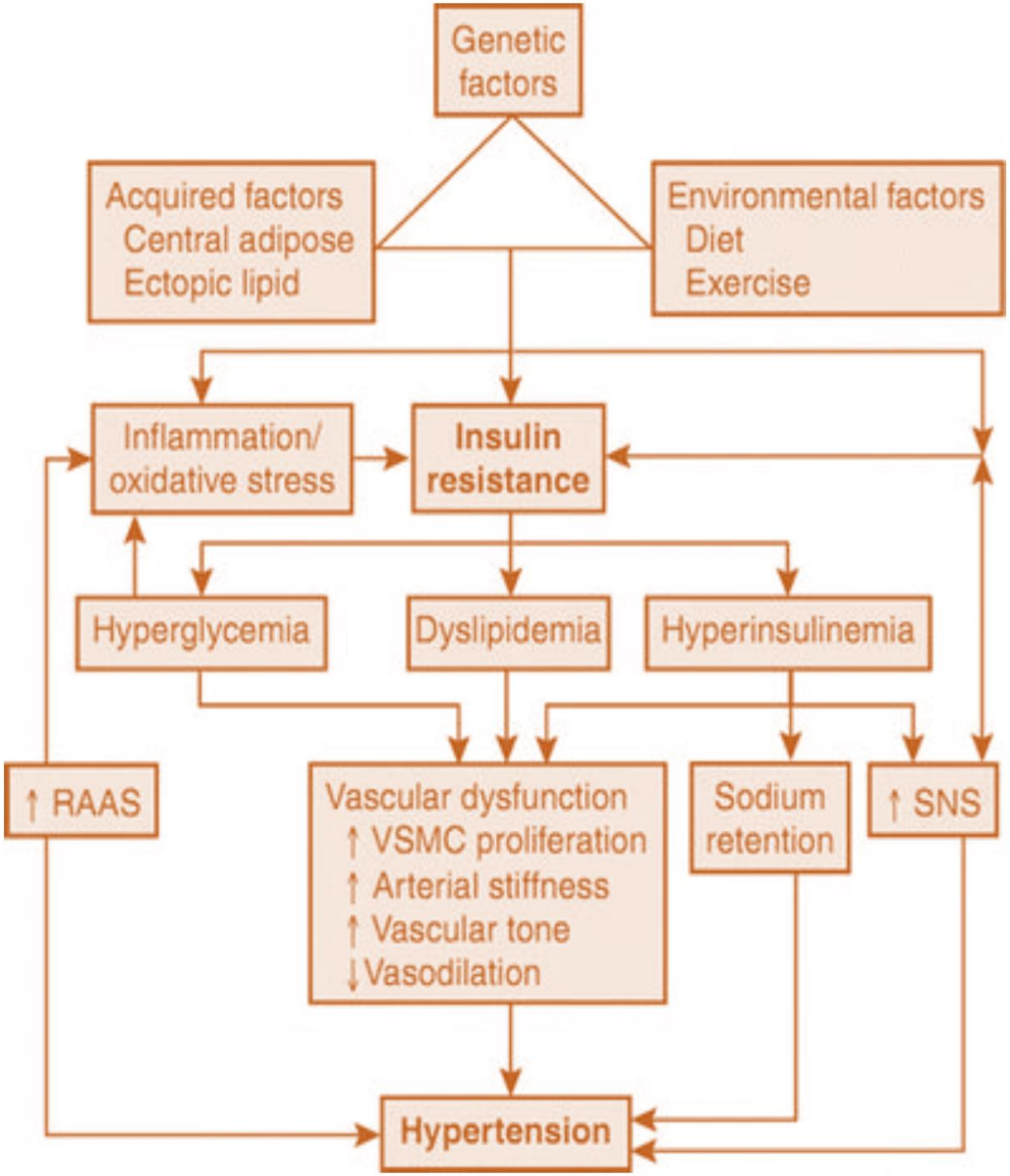
Disclosures

- NIH/NCCIH R01 AT011306-MPI
- NIH/NHLBI R01HL128801-PI
- NIH/NCCIH R01AT009247-MPI
- Adolph Coors Foundation-PI
- FluxWear: Board

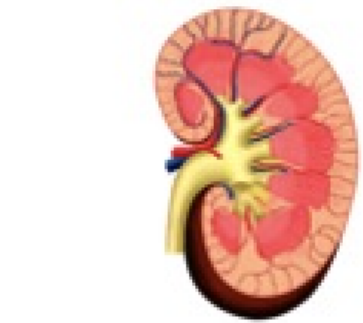
Overview

- 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

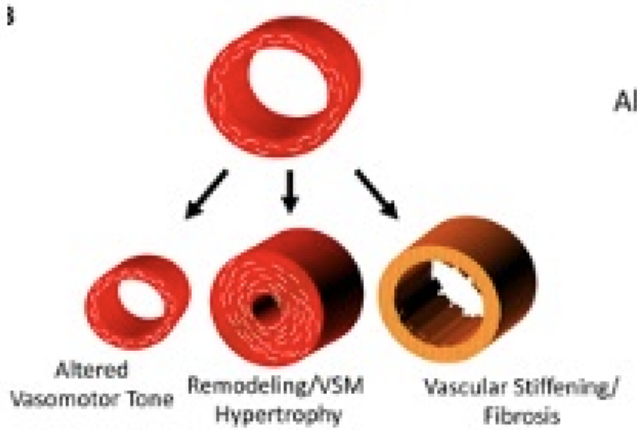


Enhanced sympathetic outflow
Vasoconstriction
Increased sodium retention
Increased Renin release from JG cells
Immune activation
Altered vagal activity and defective immune reflex



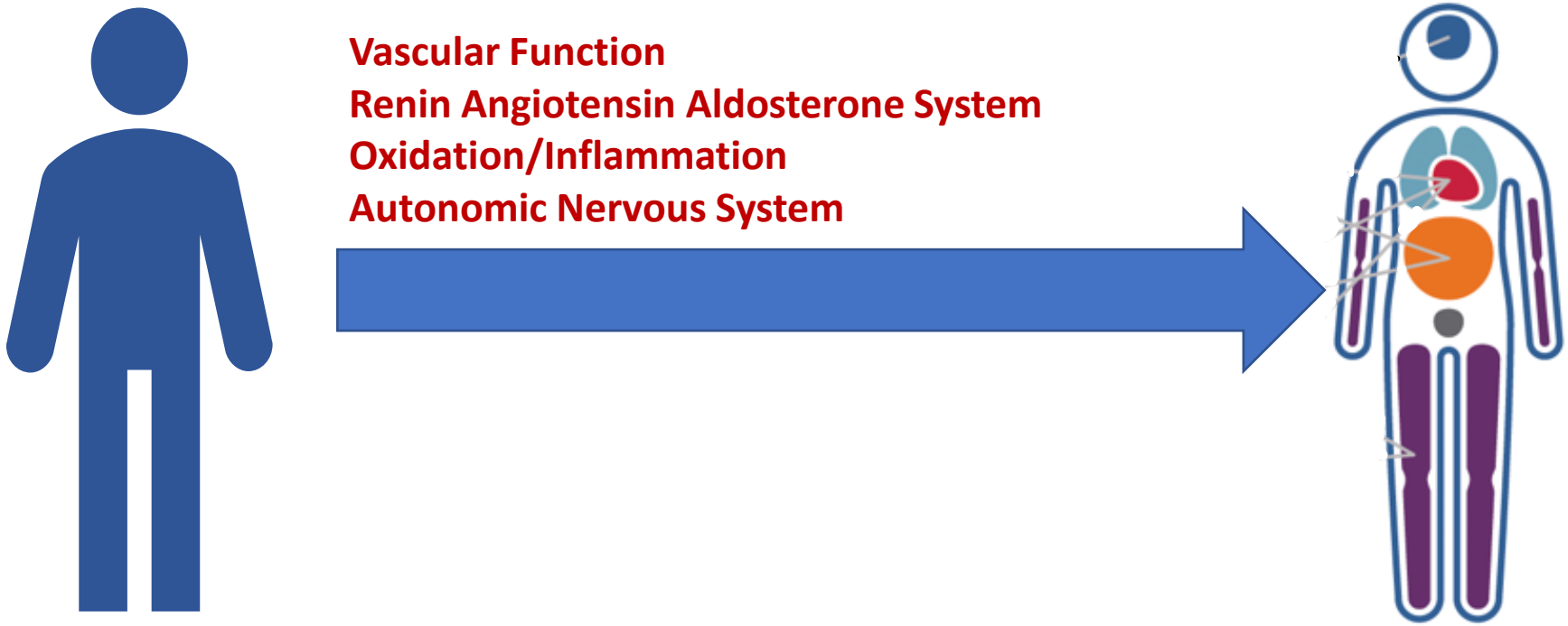
Increased sodium retention/
Altered pressure natriuresis
Increased renin release
ROS induced ADMA production
Enhanced renal afferent nerve traffic
Immune activation

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

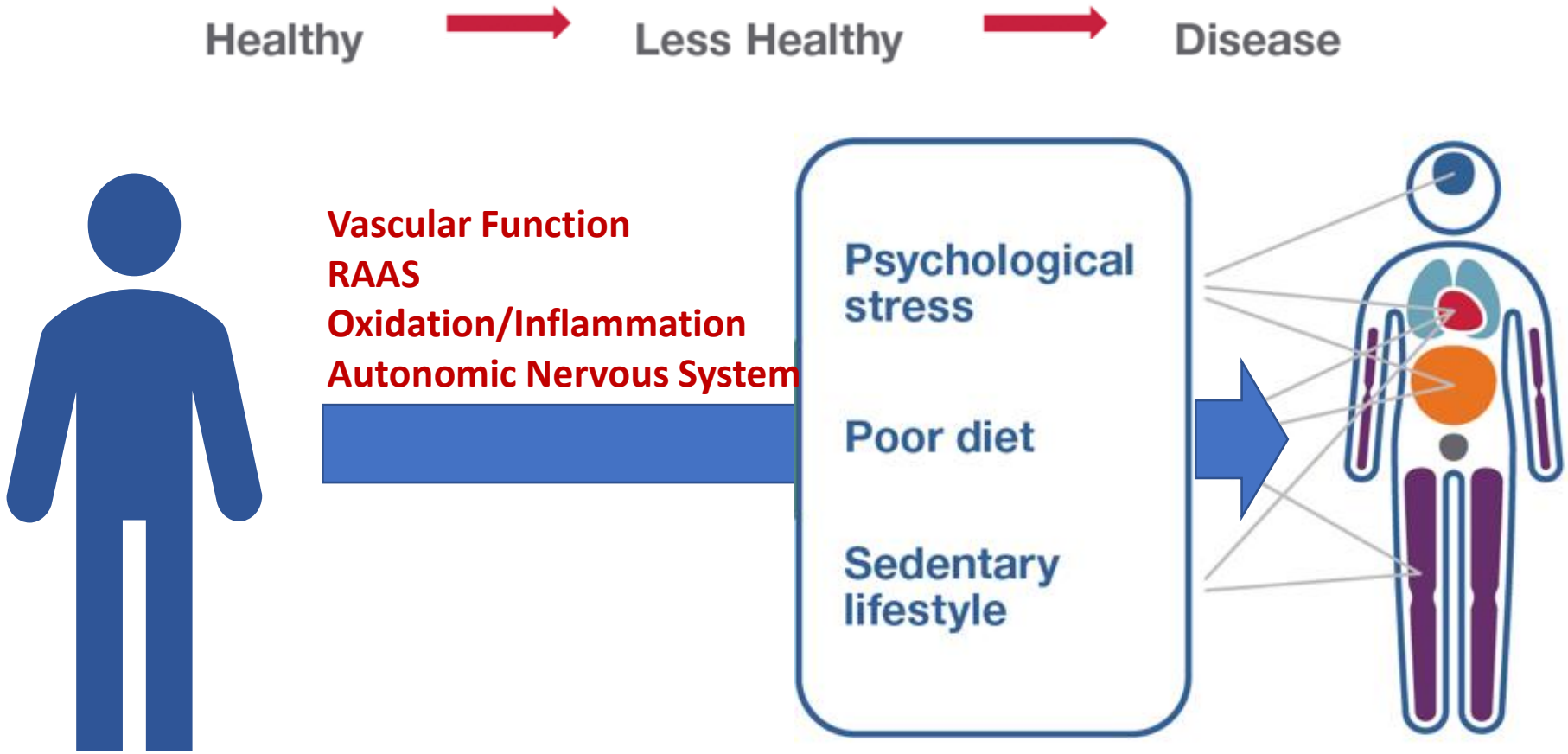


Integrative or Whole Health Approach: Pathogenesis

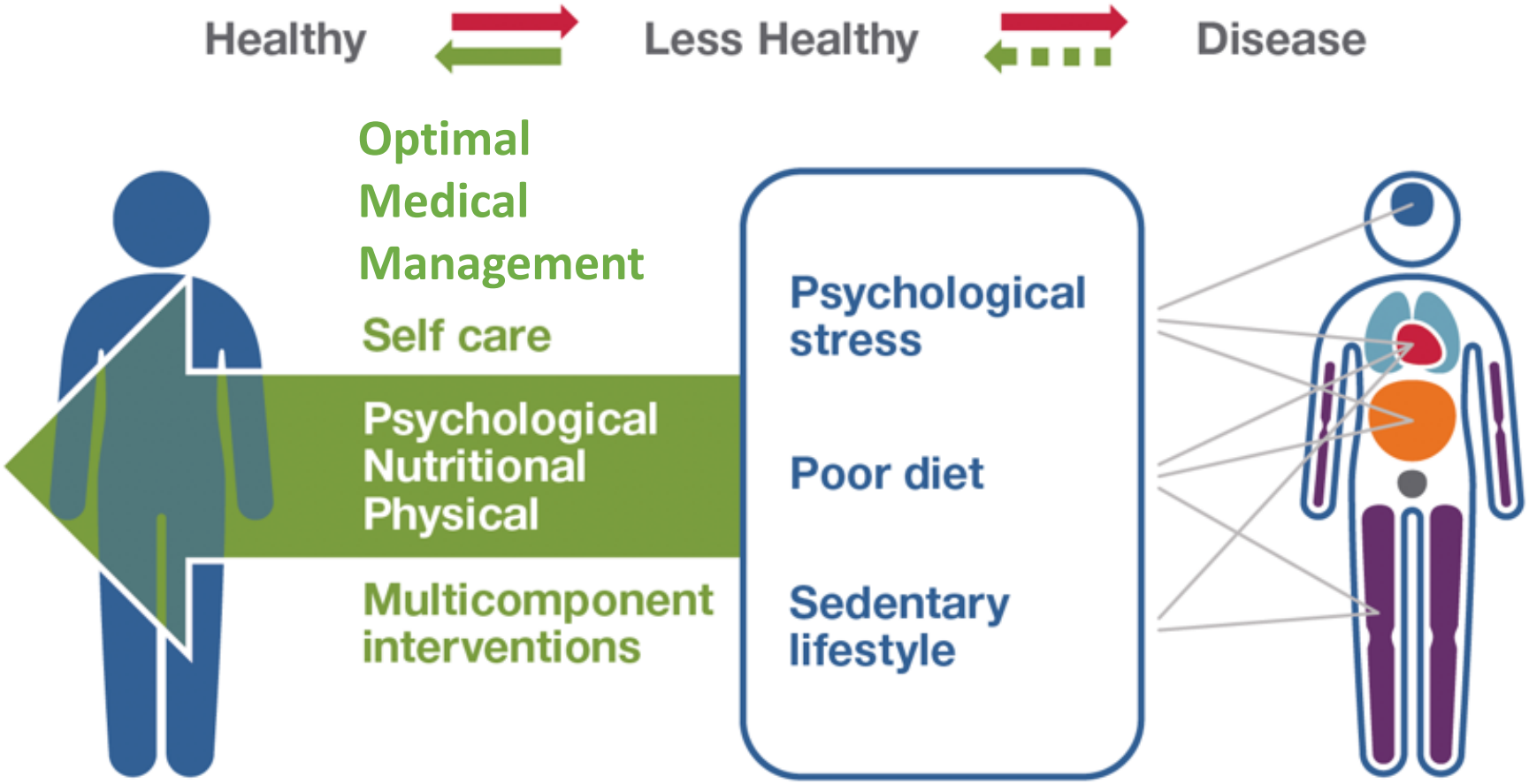
Healthy → Less Healthy → Disease



Integrative or Whole Health Approach: Pathogenesis



Integrative or Whole Health Approach: Salutogenesis



Hypertension: Integrative Assessment Framework

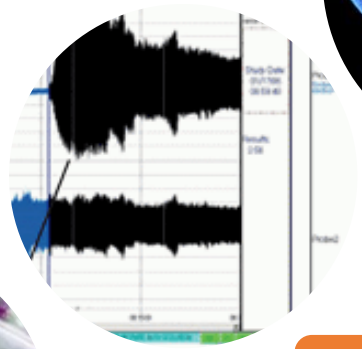
Comprehensive history (Current)
Advanced Biomarkers (Future)

Comprehensive History and Physical

Lifestyle: Nutrition and Exercise

Mind/Body: Stress & Relationships

Novel/Advanced Biomarkers



Vascular Function

Hypertension Genomics

AHA/ACC Hypertension Guidelines: 2017

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.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.*Hypertension*. 2018;72(3).

ACC/AHA Guidelines: Role of Nonpharmacological Therapies

New 2021 Guidance on Stage 1 Hypertension Management in Low-Risk Adults.

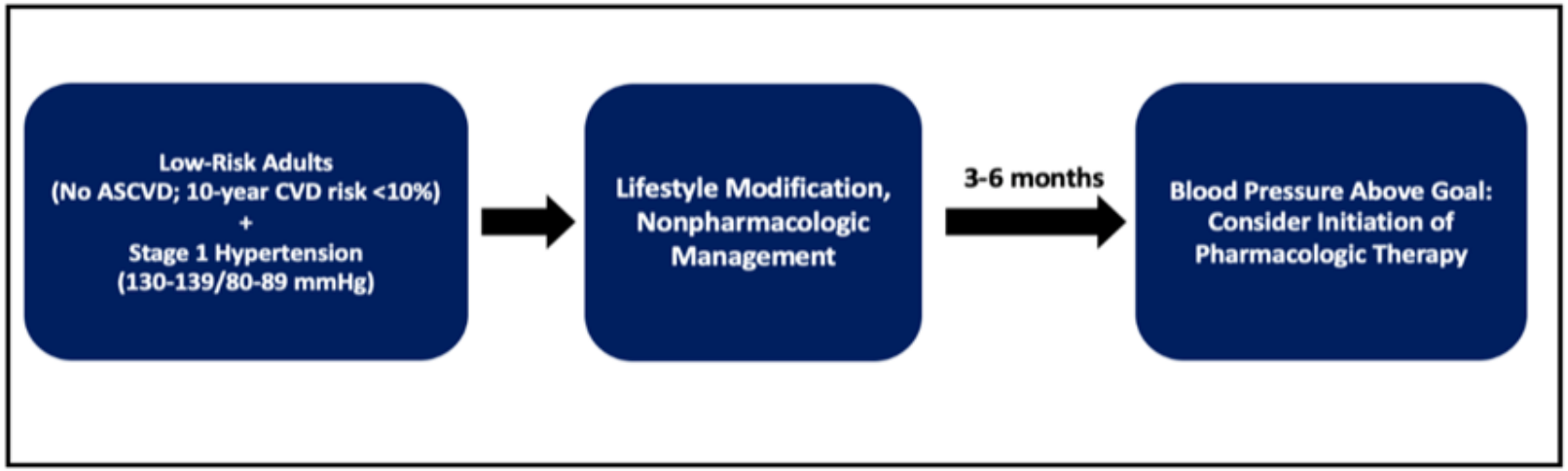


Table 1: AHA/ACC[a] Guideline Recommendations by Blood Pressure Category

BP[b] Category	Pressure Ranges	Recommendations
Normal BP	<120/<80 mmHg	Promote healthy lifestyle; reassess BP annually.
Elevated BP	120-129/<80 mmHg	Start with nonpharmacologic therapy, reassess BP in 3-6 months.
Stage1 Hypertension	130-139/80-89 mmHg	**ASCVD[c] or 10-year CVD[d] 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.
		No ASCVD and 10-year CVD risk <10%: Start with nonpharmacologic therapy, reassess BP in 3-6 months. If not at goal, consider initiation of pharmacologic therapy.
Stage 2 Hypertension	≥140/≥90 mmHg	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.

Jones DW, Whelton PK, Allen N, et al. Management of stage 1 hypertension in adults with a low 10-year risk for cardiovascular disease: filling a guidance gap: a scientific statement from the American Heart Association. *Hypertension* 2021;77:e58-e67.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127-e248.

Blood pressure patterns/phenotypes and underlying mechanism

- Essential HTN
- Secondary HTN
- White Coat HTN
- Masked HTN
- Noctural HTN

24 HOUR AMBULATORY BP MONITOR (ABPM)

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

CENTRAL BP ASSESSMENT (PWV)

Biomarkers

CAC

ENDOTHELIAL FUNCTION TESTING

Intepretation 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

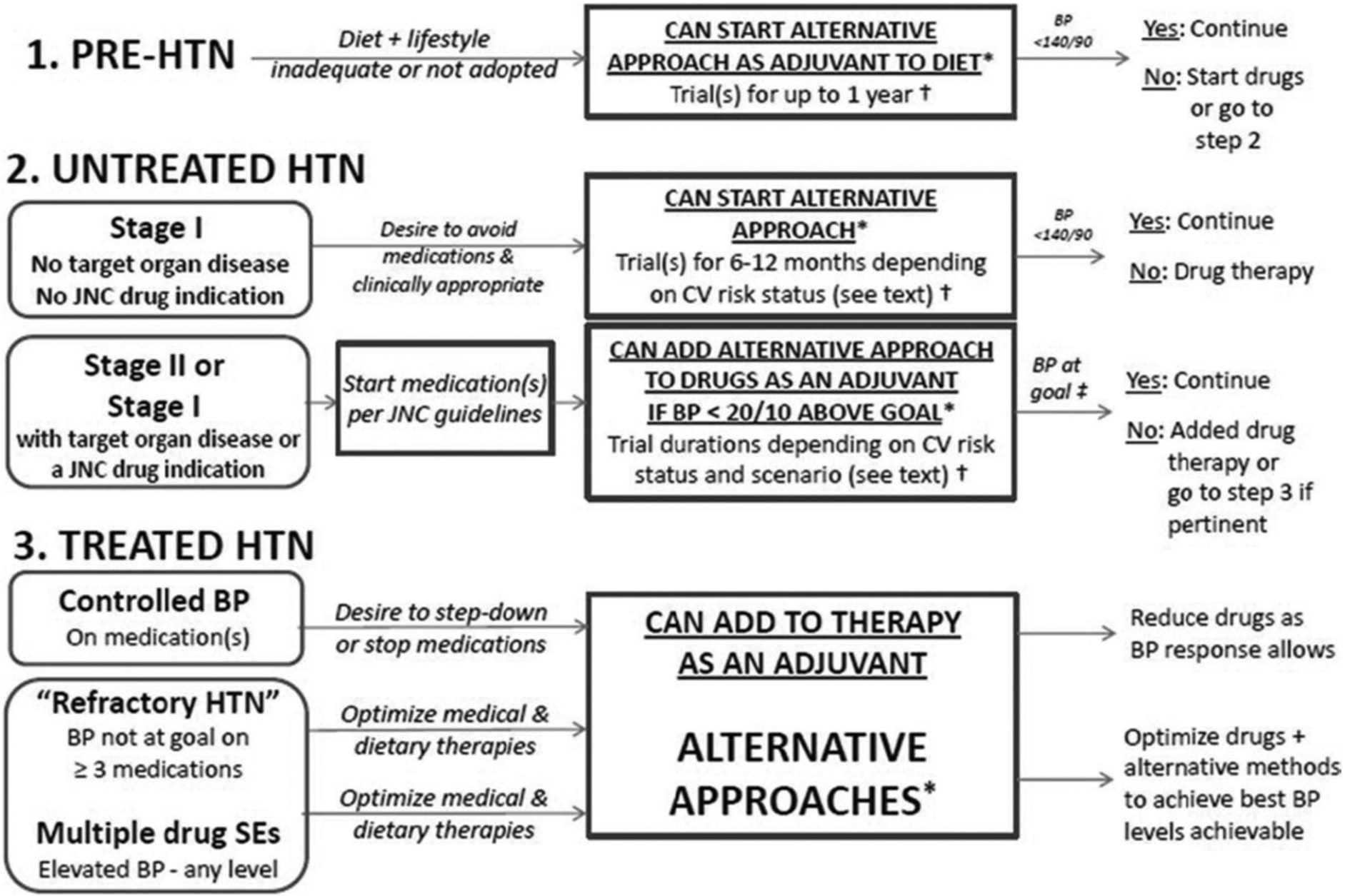
AHA Scientific Statement

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

Hypertension. 2013;61:1360–1383

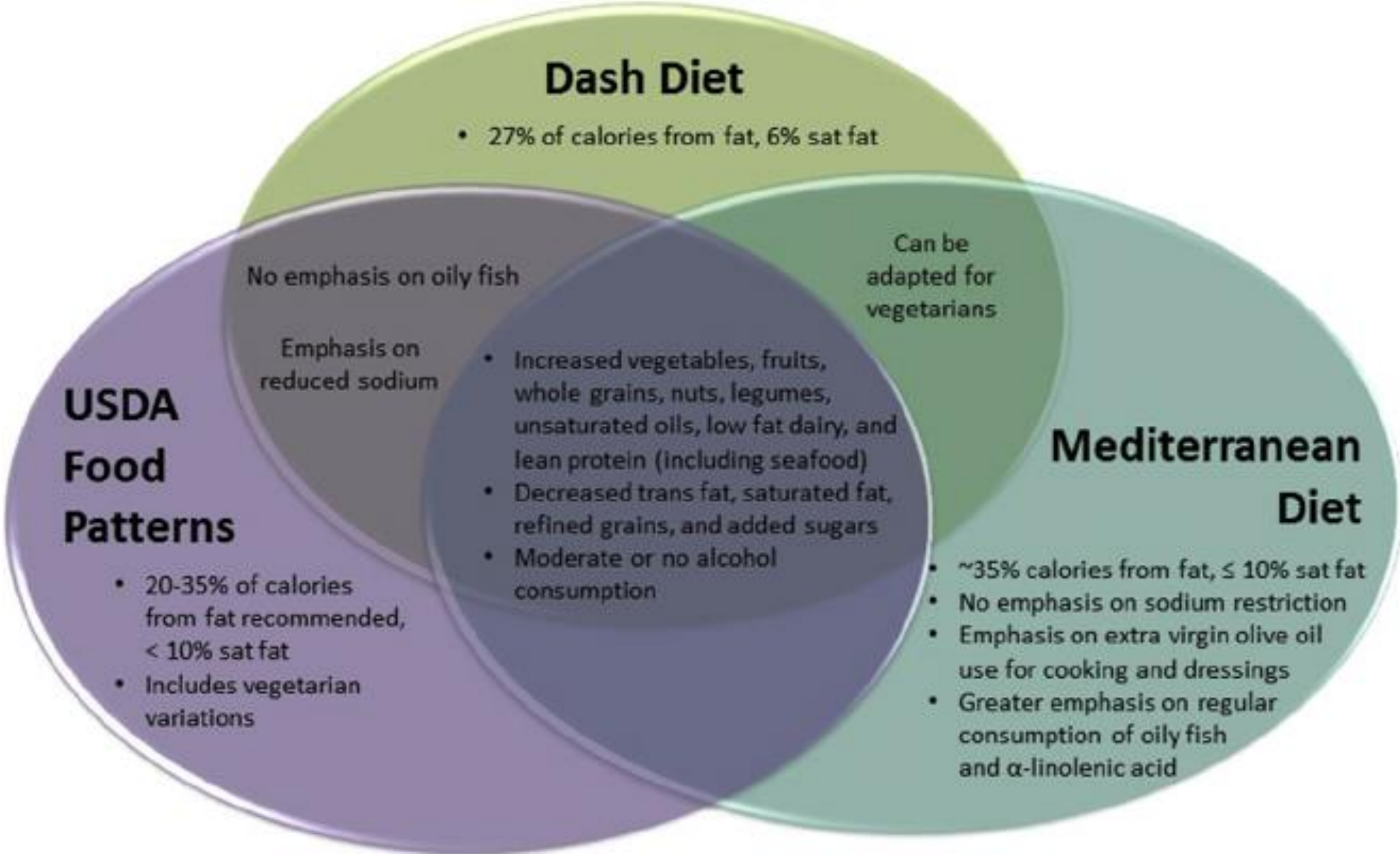

1. PRE-HTN
Diet + lifestyle inadequate or not adopted
CAN START ALTERNATIVE APPROACH AS ADJUVANT TO DIET*
Trial(s) for up to 1 year †
BP <140/90
Yes: Continue
No: Start drugs or go to step 2
2. UNTREATED HTN
Stage I
No target organ disease
No JNC drug indication
Desire to avoid medications & clinically appropriate
CAN START ALTERNATIVE APPROACH*
Trial(s) for 6-12 months depending on CV risk status (see text) †
BP <140/90
Yes: Continue
No: Drug therapy
Stage II or Stage I
with target organ disease or a JNC drug indication
Start medication(s) per JNC guidelines
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 at goal ‡
Yes: Continue
No: Added drug therapy or go to step 3 if pertinent
3. TREATED HTN
Controlled BP
On medication(s)
Desire to step-down or stop medications
"Refractory HTN"
BP not at goal on ≥ 3 medications
Optimize medical & dietary therapies
Multiple drug SEs
Elevated BP - any level
Optimize medical & dietary therapies
CAN ADD TO THERAPY AS AN ADJUVANT
ALTERNATIVE APPROACHES*
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

Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2960-2984. doi:10.1016/j.jacc.2013.11.003
2.Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102-138. doi:10.1161/01.cir.0000437739.71477.ee

DASH Diet vs. Mediterranean Diet

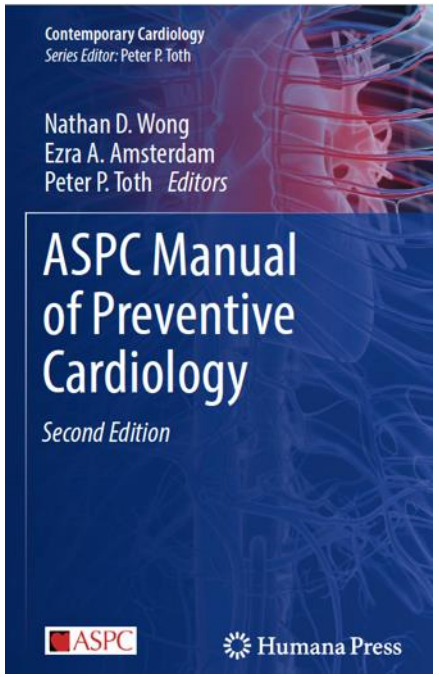


Nutraceuticals in Management of HTN

Consensus Document

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

Claudio Borghi[a], Konstantinos Tsioufis[b], Enrico Agabiti-Rosei[c], Michel Burnier[d], Arrigo F.G. Cicero[a], Denis Clement[e], Antonio Coca[f], Giovambattista Desideri[g], Guido Grassi[h], Dragan Lovic[i], Empar Lurbe[j], Thomas Kahan[k], Reinhold Kreutz[l], Bojan Jelakovic[m], Jorge Polonia[n], Josep Redon[o], Philippe Van De Borne[p], and Giuseppe Mancia[q]



Integrative Approaches for Cardiovascular Disease Prevention

Shaista Malik and Elizabeth H. Dineen

Table 1 Supplement and botanical resource

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
Acetyl-L-carnitine [21]	Ester of the amino acid, L-carnitine	Transfer long-chain fatty acids to allow the body to turn fat into energy	Diabetic neuropathy, possibly effective for diabetes	C-LD	1 gram twice daily	Gastrointestinal upset, headache Interactions: Moderate (LOE D): Acenocoumarol, warfarin Herbs/supplements: D-Carnitine
Alpha lipoic acid (ALA) [21]	Antioxidant produced naturally in the body or obtained through diet	Anti-inflammatory (reduce TNF-alpha and IL-6) and antioxidant effects	Diabetes, hyperlipidemia	C-LD	300–1800 mg daily	Gastrointestinal upset Interactions: Moderate: Alkylating agents (LOE D), anticoagulant/antiplatelet drugs (LOE D), antitumor antibiotics (LOE D), thyroid hormone (LOE D) Minor: Antidiabetes drugs (LOE B) Herbs/supplements: Those with anticoagulant/antiplatelet or hypoglycemic potential, thyroid extract
Artichoke	Perennial plant, leaves mostly used	Inhibit HMG-CoA reductase, reduce LDL oxidation [21]	Hyperlipidemia [20, 21]	B [18]	500–1920 mg daily [21]	Gastrointestinal upset [21] Interactions: Moderate (LOE D): CYP2B6 or CYP2C19 substrates
Beetroot	Flowering perennial plant	Fiber: Increases cholesterol secretion and lowers cholesterol [21] Nitrates: vasodilatory effect	HTN, hyperlipidemia [21]	C-LD [21]	500 mL juice/ day [21] ~200–350 mg/ day capsule	Pink urine, red stools [21] Interactions: None known

(continued)

Consensus Document

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

Claudio Borghi[a], Konstantinos Tsioufis[b], Enrico Agabiti-Rosei[c], Michel Burnier[d], Arrigo F.G. Cicero[a], Denis Clement[e], Antonio Coca[f], Giovambattista Desideri[g], Guido Grassi[h], Dragan Lovic[i], Empar Lurbe[j], Thomas Kahan[k], Reinhold Kreutz[l], Bojan Jelakovic[m], Jorge Polonia[n], Josep Redon[o], Philippe Van De Borne[p], and Giuseppe Mancia[q]

Journal of Hypertension 2020, 38:799–812

	Expected effect on office BP	Main mechanisms of action	Clinical evidence
Foods			
Nonroasted green coffee	−3/−2 mmHg	Antioxidant, ↑ NO bioavailability, ↓ endothelial dysfunction	Meta-analysis of 9 RCTs ($n=501$)
Pomegranate juice	−5/−2 mmHg	Antioxidant, ↓ endothelial dysfunction	Meta-analysis of 8 RCTs ($n=574$)
Tea	−2/−1 mmHg	Antioxidant	Meta-analysis of 25 RCTs ($n=1476$)
Karkadè tea	−7/−3 mmHg	Antioxidant	Meta-analysis of 5 RCTs ($n=390$)
Beetrooth juice	−4/1 mmHg	No donor	Meta-analysis of 16 RCTs ($n=254$)
Sesame	−8/−6 mmHg	Antioxidant	Meta-analysis of 8 RCTs ($n=843$)
Nutrients			
Omega−3 polyunsaturated fatty acids	−2/−1 mmHg	↓ Endothelial dysfunction	Meta-analysis of 70 RCTs ($n=2250$)
Proteins, peptides and amino-acids (L-arginine)	−3/−2 mmHg (LTPs)	ACE-inhibition	Meta-analysis of 18 RCTs ($n=904$)
	−5/−3 mmHg (L-Arg)	NO precursor	Meta-analysis of 11 RCTs ($n=400$)
Calcium	−1/−1 mmHg	Direct effect on artery wall	Mainly epidemiological data
Magnesium	−3/−3 mmHg	↑ NO synthesis, ↓ endothelial dysfunction	Meta-analysis of 34 RCTs ($n=2028$)
Potassium	−4/−3 mmHg	Balancement of negative effect of sodium on blood pressure	Meta-analysis of 33 RCTs ($n=1829$)
Vitamin C	−4/1 mmHg	NO and PGI_2 release, diuresis and natriuresis, ↓ adrenal steroid production, ↑ cyclic GMP increase, potassium channels activation, cytosolic calcium reduction	Meta-analysis of 21 RCTs ($n=1407$)
Prebiotics and soluble fibres	−3/−2 mmHg	Improvement of microbiota	Meta-analysis of 15 RCTs ($n=1302$)

Consensus Document

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

Claudio Borghi[a], Konstantinos Tsioufis[b], Enrico Agabiti-Rosei[c], Michel Burnier[d], Arrigo F.G. Cicero[a], Denis Clement[e], Antonio Coca[f], Giovambattista Desideri[g], Guido Grassi[h], Dragan Lovic[i], Empar Lurbe[j], Thomas Kahan[k], Reinhold Kreutz[l], Bojan Jelakovic[m], Jorge Polonia[n], Josep Redon[o], Philippe Van De Borne[p], and Giuseppe Mancia[q]

Journal of Hypertension 2020, 38:799–812

Nonnutrient nutraceuticals			
Resveratrol and grape seed extracts	−9/−1 mmHg	Antioxidant, ↓ insulin-resistance	Meta-analysis of 17 RCTs ($n=782$)
Cocoa flavonoids	−2/−2 mmHg	Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction	Meta-analysis of 40 RCTs ($n=1804$)
Soy isoflavones	−5/−2 mmHg	Antioxidant, hormone-replacement therapy like effect	Meta-analysis of 12 RCTs ($n=1551$)
Aged garlic extract	−9/4 mmHg	Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction	Meta-analysis of 9 RCTs ($n=482$)
Lycopene	−5/−1 mmHg	Antioxidant, ↓ endothelial dysfunction	Meta-analysis of 6 RCTs ($n=482$)
Pycnogenol	−3/−3 mmHg	Antioxidant, ↓ Endothelial dysfunction, angiotensin-converting enzyme inhibitor	Meta-analysis of 9 RCTs ($n=549$)
Alpha lipoic acid	−8/−7 mmHg	Antioxidant	Meta-analysis of 7 RCTs ($n=478$)
Slow-release melatonin	−6/−3 mmHg	Antioxidant, ↑ NO synthesis, ↓ endothelial dysfunction	Meta-analysis of 7 RCTs ($n=221$)
Taurine	−7/−5 mmHg	$GABA_A$ receptors activation	Single large RCT ($n=120$)
Probiotics	−4/−2 mmHg	Improvement of microbiota	Meta-analysis of 9 RCTs ($n=543$)

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

Kapil V, Milsom AB, Okorie M, Maleki-Toyserkani S, Akram F, Rehman F, et al. Inorganic nitrate supplementation lowers blood pressure in humans: role for nitrite-derived NO. Hypertension 2010; 56:274–281.

Kapil V, Khambata RS, Robertson A, Caulfield MJ, Ahluwalia A. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study. Hypertension 2015; 65:320–327.

Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: a systematic review and meta-analysis. J Nutr 2013; 143:818–826.

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,

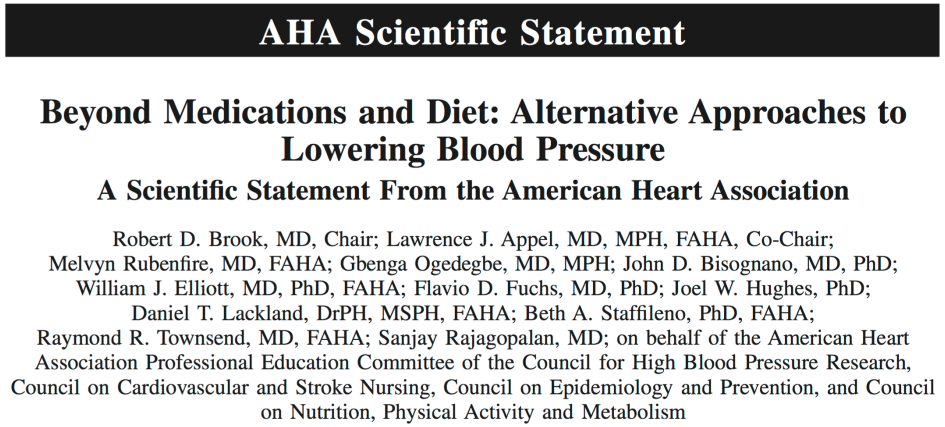
Ried K, Fakler P. Potential of garlic (Allium sativum) in lowering high blood pressure: mechanisms of action and clinical relevance. Integr Blood Press Control 2014; 7:71–82.

Rohner A, Ried K, Sobenin IA, Bucher HC, Nordmann AJ. A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension. Am J Hypertens 2015; 28:414–423.

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



AHA Scientific Statement

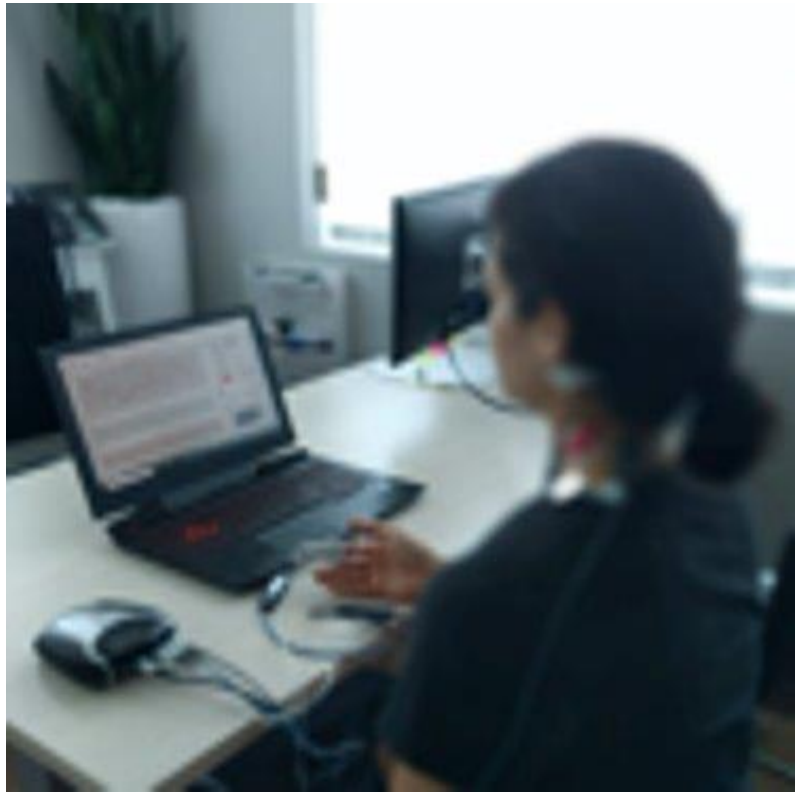
Beyond Medications and Diet: Alternative Approaches to Lowering Blood Pressure

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

Mind-Body Approaches: Biofeedback

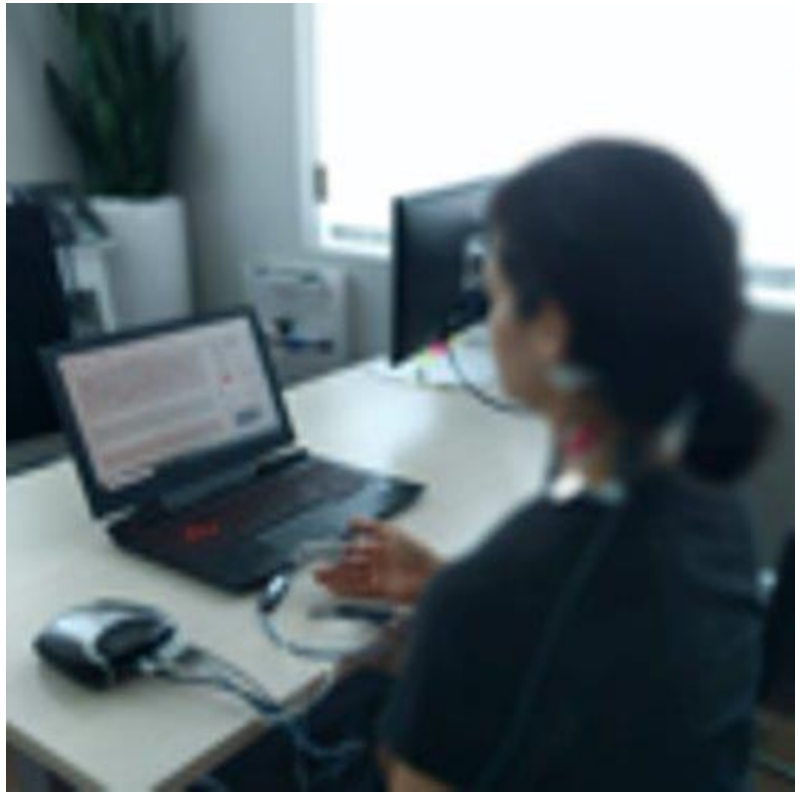
- Informational feedback about physiological response: direct-BP or indirect-HR, thermal, galvanic skin response, electromyographic activity
- RCTs using ABPM, −8/−5 mm Hg reduction
- Encourages somatic awareness (introception)
- ANS balance



Greenhalgh J, Dickson R, Dundar Y. Biofeedback for hypertension: a systematic review.J Hypertens. 2010; 28:644–652.
Nakao M, Yano E, Nomura S, Kuboki T. Blood pressure-lowering effects of biofeedback treatment in hypertension: a meta-analysis of randomized controlled trials.Hypertens Res. 2003; *26*:37–46

Mind-Body Approaches: Acupuncture

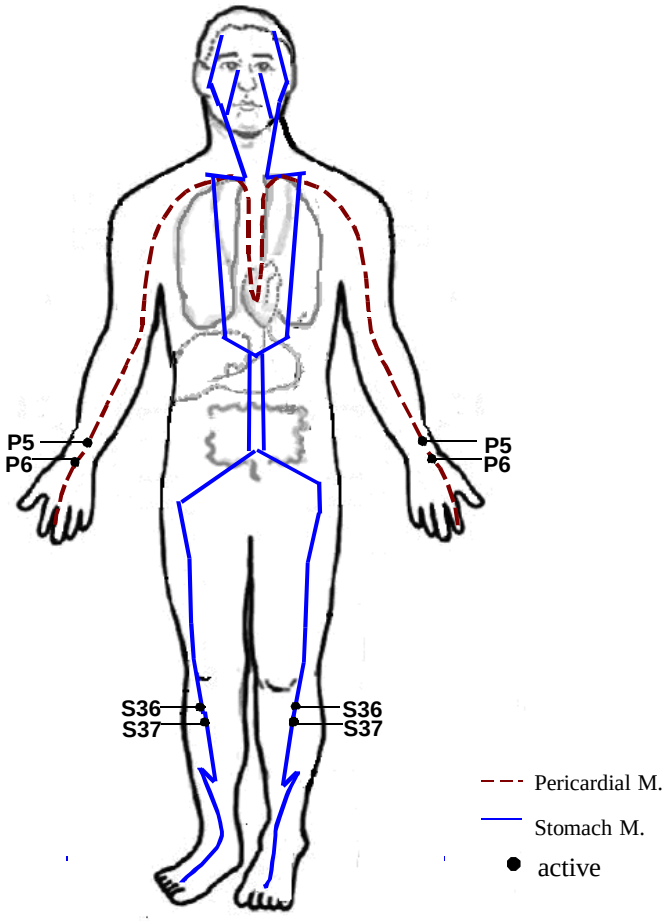
- WHO (1996) lists acupuncture as effective for HTN
- Meta-analyses inconclusive
- Challenges of isolating therapies from Traditional Medical Systems (availability, multimodal)
- Mechanisms:
  - Acupuncture-sensory mechanoreceptor and nociceptor stimulation
  - Eletroacupuncture-stimulation of peripheral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



Greenhalgh J, Dickson R, Dundar Y. Biofeedback for hypertension: a systematic review.J Hypertens. 2010; 28:644–652.
Nakao M, Yano E, Nomura S, Kuboki T. Blood pressure-lowering effects of biofeedback treatment in hypertension: a meta-analysis of randomized controlled trials.Hypertens Res. 2003; *26*:37–46

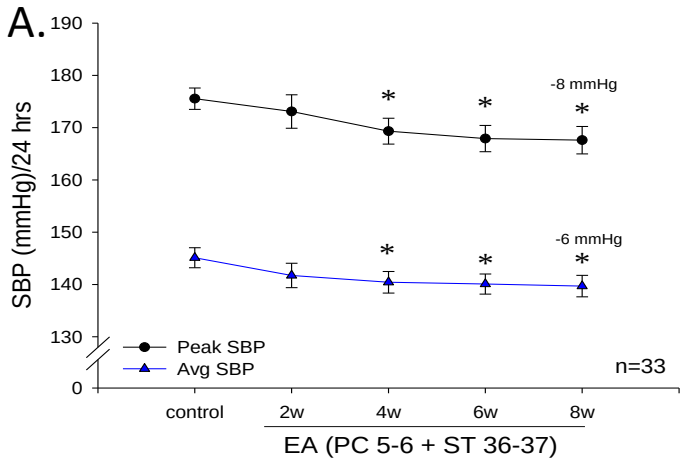
Measuring the Mechanism and Biological Effect of Electroacupuncture for Hypertension: Neuromodulation

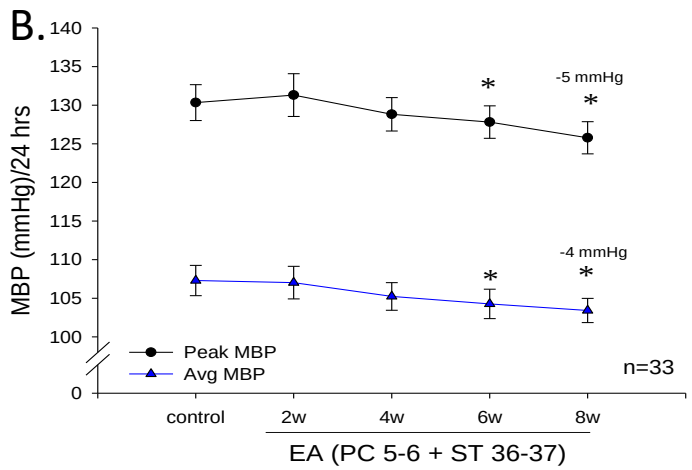
- Targeting Sympathetic Nervous System Activation
- Use of 4 acupoints to treat Hypertension (targeting Sympathetic Nervous System (SNS))
  - Neiguan, Jianshi (pericardial meridian, P 6 and 5 points, on the palmar side of both arms and Zusanli, Shangjuxi (stomach meridian, ST 36 and 37, on the anterolateral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

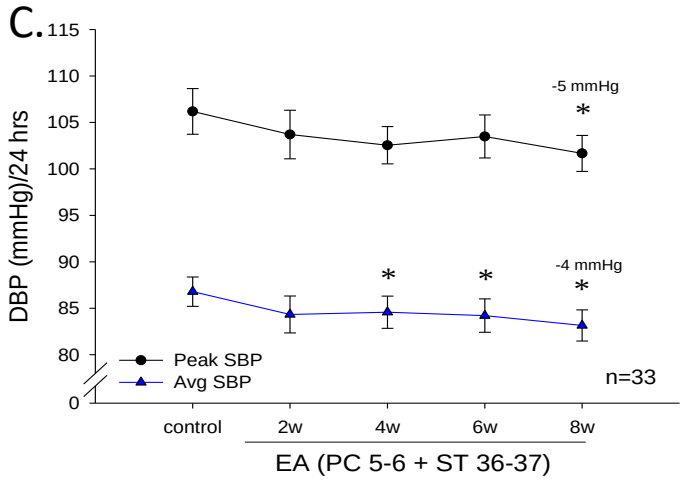


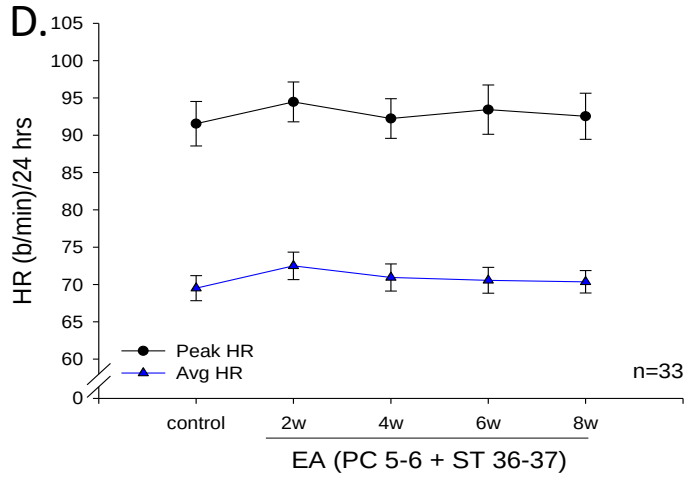
[1] Li P, Tjen-A-Looi S,...Longhurst. Long-lasting reduction of Blood Pressure by Electroacupunture in Patients with Hypertension. Medical Acupunture, 27:4:2015

Electroacupuncture in Hypertensive Patients (Active vs. Sham acupoints)









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

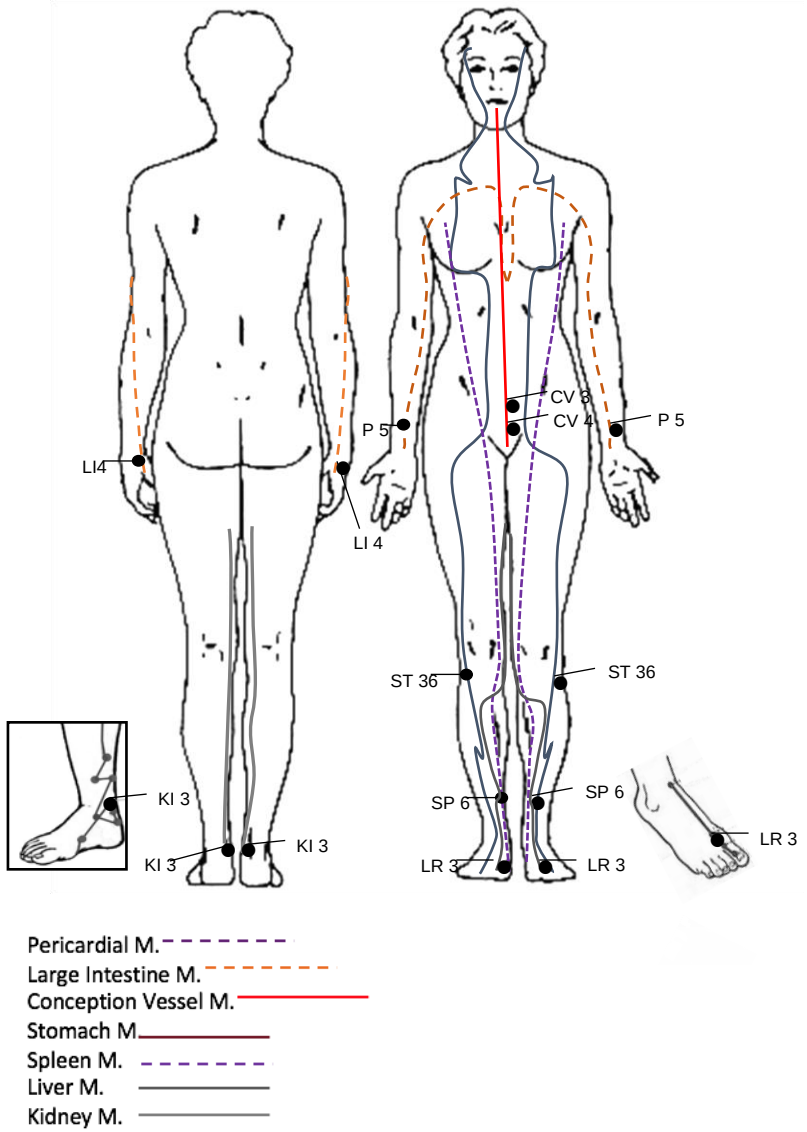
30% Non-response rate: Post-menopausal Women

Li P, Tjen-A-Looi S,...Longhurst. Long-lasting reduction of Blood Pressure by Electroacupuncture in Patients with Hypertension. Medical Acupunture, 27:4:2015

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.

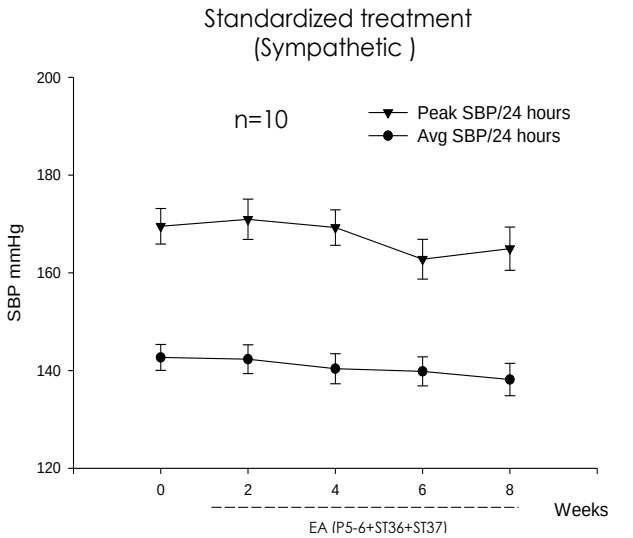


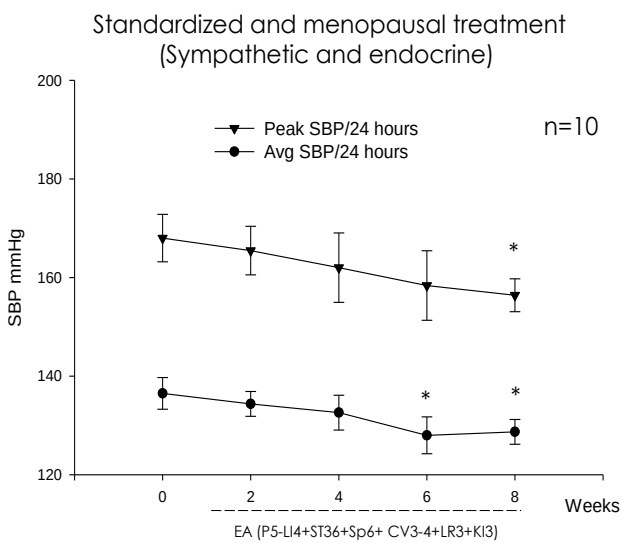
Grant Funding (2016-2019): Coors Foundation
(Tjen-A-Looi and Malik, Co-PIs)

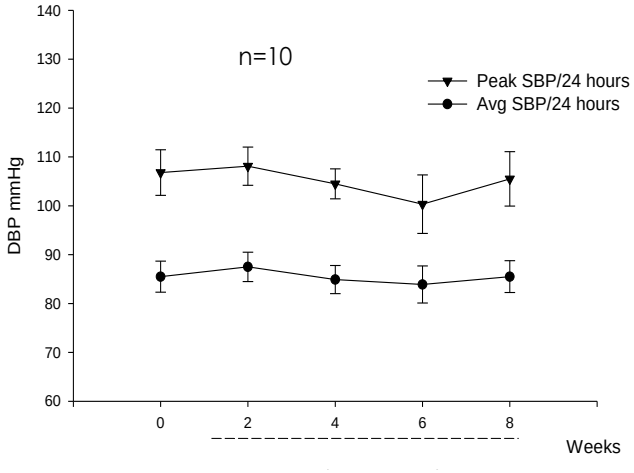
Tjen-A-Looi, Xie L, Fu L, Li P, Malik S. Enhanced Blood Pressure Lowering Responsiveness with Endocrine-Sympathoinhibitory Electroacupuncture in Middle-Aged Hypertensive Women. Experimental Biology, April 2018

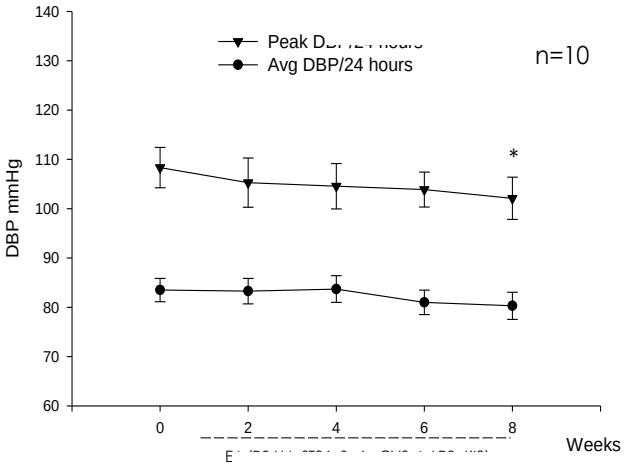
Electroacupuncture in Middle-Aged Hypertensive Women

Peak SBP dropped 10 mm Hg
DBP dropped 5 mm Hg



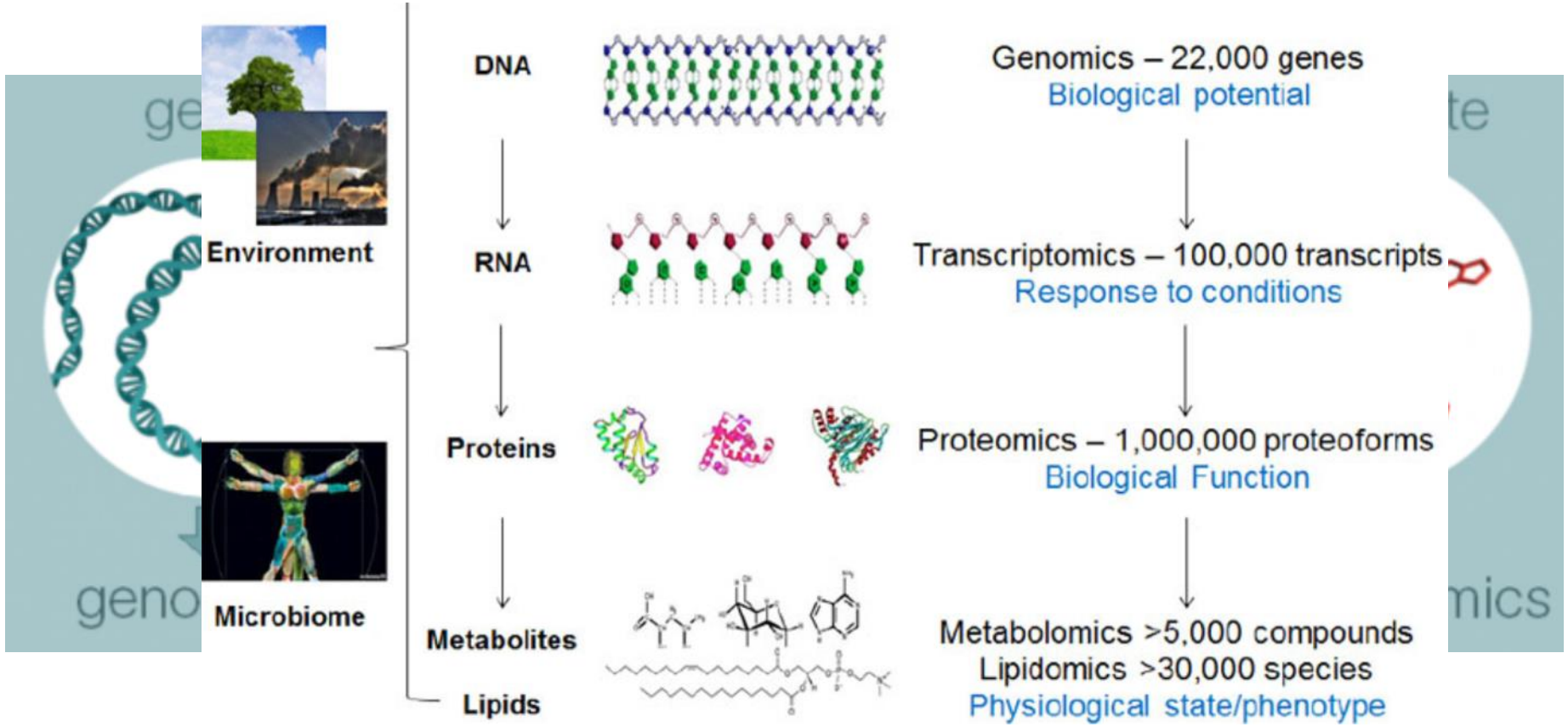






Tjen-A-Looi, Xie L, Fu L, Li P, Malik S. Enhanced Blood Pressure Lowering Responsiveness with Endocrine-Sympathoinhibitory Electroacupuncture in Middle-Aged Hypertensive Women. Experimental Biology, April 2018

Measuring the Mechanism and Biological Effect of Acupuncture using Metabolomics



Metabolomics of Targeted Electroacupuncture in Post-menopausal women

Study Objective

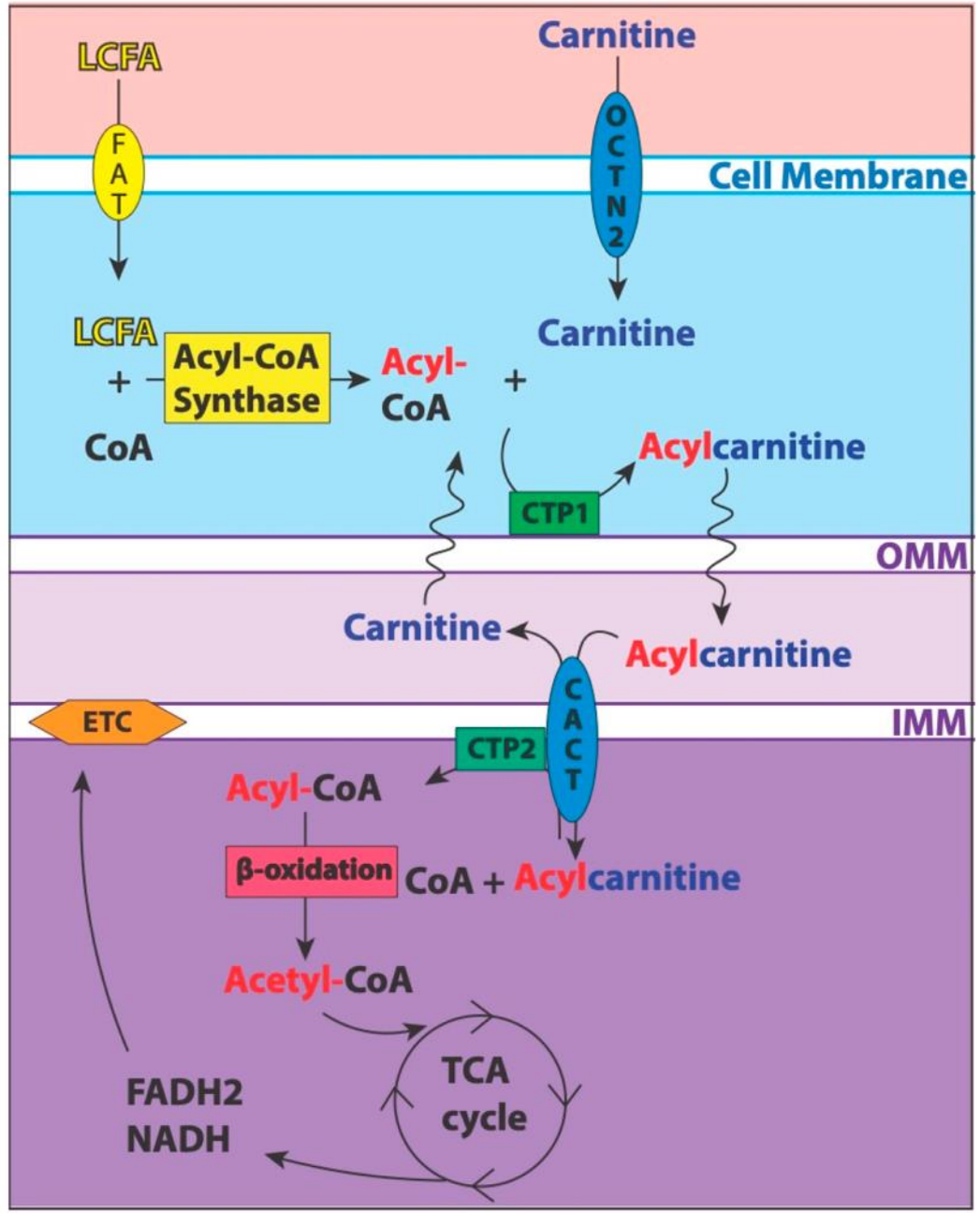
The goal of this study is to identify metabolomic changes associated with two types of electroacupuncture treatment in post-menopausal women.

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.

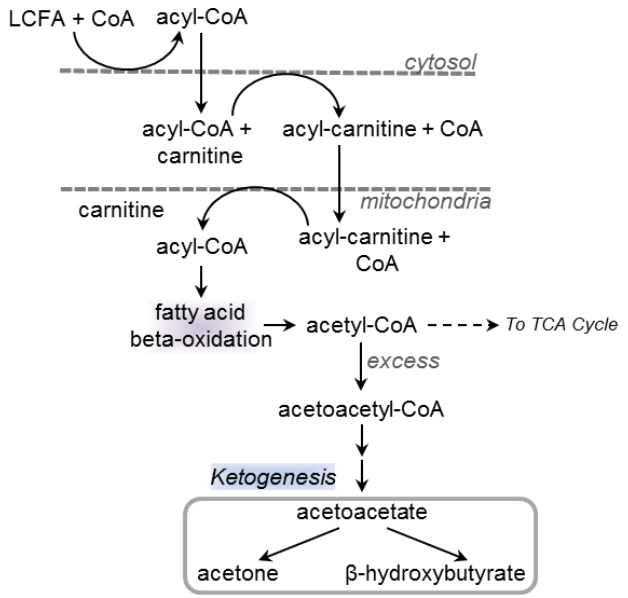
	Treatment	Time Point	
		Pre	Post
SNS EA only	Treatment 1	N=10	N=10
SNS +Endocrine	Treatment 2	N=14	N=14

Funding: Coors Foundation


LCFA
FAT
Carnitine
OCTN2
Cell Membrane
LCFA
+
CoA
Acyl-CoA Synthase
Acyl-CoA
+
Carnitine
Acylcarnitine
CTP1
OMM
Carnitine
Acylcarnitine
CACT
ETC
IMM
CTP2
Acyl-CoA
β-oxidation
CoA + Acylcarnitine
Acetyl-CoA
TCA cycle
FADH2
NADH

		ANOVA Contrasts	
		Post / Pre	
Sub Pathway	Biochemical Name	Treatment 1	Treatment 2
Fatty Acid Metabolism (Acyl Carnitine, Short Chain)	acetylcarnitine (C2)	1.01	0.79
Fatty Acid Metabolism (Acyl Carnitine, Medium Chain)	hexanoylcarnitine (C6)	1.08	0.74
	octanoylcarnitine (C8)	1.16	0.75
	nonanoylcarnitine (C9)	1.14	0.72
	decanoylcarnitine (C10)	1.15	0.67
	laurylcarnitine (C12)	1.31	0.71
Fatty Acid Metabolism (Acyl Carnitine, Long Chain Saturated)	myristoylcarnitine (C14)	1.17	0.80
	palmitoylcarnitine (C16)	1.01	0.82
	stearoylcarnitine (C18)	0.85	0.74
	arachidoylcarnitine (C20)*	0.71	0.78
	behenoylcarnitine (C22)*	0.53	0.70
Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)	cis-4-decenoylcarnitine (C10:1)	1.11	0.79
	5-dodecenoylcarnitine (C12:1)	1.13	0.62
	myristoleoylcarnitine (C14:1)*	1.11	0.67
	palmitoleoylcarnitine (C16:1)*	1.05	0.79
	oleoylcarnitine (C18:1)	0.98	0.79
	eicosenoylcarnitine (C20:1)*	1.11	0.84
Fatty Acid Metabolism (Acyl Carnitine, Polyunsaturated)	linoleoylcarnitine (C18:2)*	0.98	0.81
	linolenoylcarnitine (C18:3)*	1.00	0.64
	dihomo-linoleoylcarnitine (C20:2)*	0.90	0.84
Fatty Acid Metabolism (Acyl Carnitine, Dicarboxylate)	pimeloylcarnitine/3-methyladipoylcar	1.65	0.73
	octadecanedioylcarnitine (C18-DC)*	0.96	0.78
	octadecenedioylcarnitine (C18:1-DC)	0.94	0.71
Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	(R)-3-hydroxybutyrylcarnitine	1.07	0.85
	3-hydroxydecanoylcarnitine	1.23	0.74
	3-hydroxyoleoylcarnitine	1.05	0.72
Carnitine Metabolism	deoxycarnitine	1.08	0.89
	carnitine	1.02	0.91
Ketone Bodies	acetoacetate	1.07	0.41
	3-hydroxybutyrate (BHBA)	0.77	0.37

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



Preliminary Data

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

Disease	Proposed Mechanism	Subject	Biospecimen	Disease-Induced Alterations in Carnitine/Acylcarnitine Levels
Diabetes Mellitus	• Invoked metabolic flexibility pathway • Impaired insulin-dependent uptake of carnitine • Increased production of ACs due to incomplete FAO	1. Humans (T2D+complications)	1. Serum	1. 25% lower LC levels [40]
		2. Humans (T2D)	2. Plasma	2. Increased C2, SCAC, MCAC in patients with higher HbA1c [41]
		3. Humans (insulin resistant/obese)	3. Serum	3. Increased C3, C5, C6, C8:1 [42]
		4. Humans (T2D)	4. Plasma	4. Increased SCAC, MCAC, LCAC in T2D patients [22]
		5. Humans (T2D)	5. Plasma	5. LCAC most associated with developing T2D [43]
		6. Humans (gestational and T2D)	6. Serum	6. Strongest association with MCAC [44]

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