JNC VIII – Worth the Wait?

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MSHP/ICHP 2013 Spring Meeting
April 12, 2013 – Breakout 2: Clinical Session

Conflicts of Interest

- None to disclose

Objectives

- Recognize significant studies in hypertension management that have emerged since the publication of the JNC VII guidelines
- State specific areas where the JNC VIII guidelines might make changes or provide clearer guidance in the clinical practice of blood pressure management compared to the previous JNC VII publication

What's the hold-up?

- JNC-VII Express: 2003[1]
- Why delays in JNC-VIII?
  - Additional personnel involved in writing[2]
  - Greater emphasis on evidence-based recommendations
  - 2001 IOM Report[3]
  - ACC/AHA Guidelines 1984-2008[3]
    - Level C – 48% of recommendations

1. Bakris GL, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) Express. National Heart, Lung, and Blood Institute. *JAMA*. 2003;289:2560–2571.
2. Medscape Cardiology. Where Is JNC 8? Plus: The Conundrums of Clinical Trials. Available at: http://www.medscape.com/viewarticle/761508. Accessed March 8, 2013.
3. Family Practice News. Cardiovascular Disease. Critics dub JNC-8 as 'JNC-Late'. Available at: http://www.familypracticenews.com/news/cardiovascular-disease/single-article/critics-dub-jnc-8-as-jnc-late/6460d38db3c8a786e6131c89eee2081a.html. Accessed March 8, 2013.

More Evidence, Please

- Significant Publications and Clinical Trials for Hypertension (HTN)
  - Reappraisal of European HTN Guidelines
  - ACCORD
  - ACCOMPLISH
  - VALUE
  - ASCOT

Reappraisal of European HTN Guidelines

- Evidence lacking for starting treatment for >140/90 mmHg
- Recommendation may have included patients with BP higher than Stage 1
- Lack of evidence for recommendations in elderly
  - No trials with SBP <160 mmHg

Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens.* 2009;27:2121-2158.

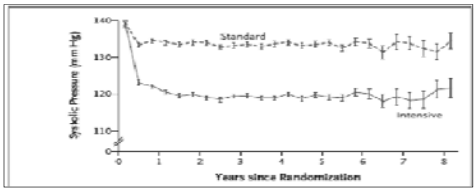
ACCORD

- Design: RCT
- Patients: 4733 with Type 2 Diabetes Mellitus (T2DM)
- Mean follow-up: 4.7 years
- Intervention: Target SBP < 120 mmHg versus Target SBP <140 mmHg
- Primary Outcome: Composite
  - nonfatal MI, nonfatal stroke, or death from CV causes

Cushman WC, Evan GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2010;362:1575-85.

ACCORD

- Results: Blood Pressure Achieved



- Mean SBP after 1 year
  - Intensive (Target <120 mmHg): 119.3 mmHg
  - Standard (Target <140 mmHg): 133.5 mmHg

Cushman WC, Evan GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2010;362:1575-85.

ACCORD

- Results – Adverse Effects

Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N = 2362)	Standard Therapy (N = 2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	13 (0.6)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
Elevation in serum creatinine			
>1.3 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m²	99 (4.2)	52 (2.2)	<0.001

Cushman WC, Evan GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2010;362:1575-85.

ACCORD

- Results – Primary and Secondary Outcomes

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N = 2362)		Standard Therapy (N = 2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	no. of events	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.61 (0.41–0.90)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

Cushman WC, Evan GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2010;362:1575-85.

ACCORD

- Implications
  - New goal BP for patients with diabetes?
  - ADA 2013 Standards of Care
    - BP Goal <**140**/80 mmHg

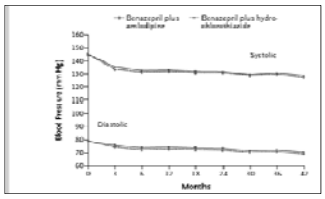
ACCOMPLISH

- Design: RCT
- Patients: 11,506 with HTN and high CV risk
- Mean follow-up: 3 years
- Intervention: ACE + CCB (DHP) versus ACE + thiazide
- Primary Outcome: Composite
  - MI, stroke, or death from CV causes, hospitalization for angina, resuscitation, coronary revascularization

Jamerson K, Weber MA, Bakris GL, Bahlof B, Pitt B, Shi V, Hester A, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med.* 2008;359:2417-2428.

ACCOMPLISH

- Results – Blood Pressure Achieved



- Mean BP
  - ACE + CCB: 131.6/73.3 mmHg
  - ACE + Thiazide: 132.5/74.4 mmHg
    - *P<0.001*

Jamerson K, Weber MA, Bakris GL, Bahlof B, Pitt B, Shi V, Hester A, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med.* 2008;359:2417-2428.

ACCOMPLISH

- Results – Adverse Events

Table 3. Results of Prespecified Safety Analysis.*

Adverse Event	Any		Serious		Drug-Related Serious	
	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)
	number (percent)					
Dizziness	1189 (20.7)	1451 (25.4)	18 (0.3)	31 (0.5)	2 (<0.1)	5 (0.1)
Peripheral edema	1792 (31.2)	772 (13.4)	10 (0.2)	8 (0.1)	4 (0.1)	2 (<0.1)
Dry cough	1177 (20.5)	1220 (21.2)	7 (0.1)	7 (0.1)	1 (0.1)	1 (0.1)
Angioedema	53 (0.9)	34 (0.6)	7 (0.1)	13 (0.2)	2 (<0.1)	5 (0.1)
Hyperkalemia	34 (0.6)	33 (0.6)	10 (0.2)	11 (0.2)	6 (0.1)	6 (0.1)
Hypokalemia	5 (0.1)	17 (0.3)	2 (<0.1)	12 (0.2)	1 (<0.1)	6
Hypotension	142 (2.5)	208 (3.6)	22 (0.4)	30 (0.5)	6 (0.1)	9 (0.2)

Jamerson K, Weber MA, Bakris GL, Bahlof B, Pitt B, Shi V, Hester A, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med.* 2008;359:2417-2428.

ACCOMPLISH

- Results – Primary and Secondary Outcomes

Table 2. Hazard Ratios for Primary, Secondary, and Other Prespecified End Points, and Results of the Subgroup Analysis.

End Point	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)	Hazard Ratio (95% CI)*	P Value†
Primary				
Composite of cardiovascular events and death from cardiovascular causes — no. (%)	552 (9.6)	679 (11.8)	0.80 (0.72–0.90)	<0.001
Individual component — no. (%)				
Death from cardiovascular causes	107 (1.9)	134 (2.3)	0.80 (0.62–1.03)	0.08
Fatal and nonfatal myocardial infarction	125 (2.2)	150 (2.6)	0.78 (0.62–0.99)	0.04
Fatal and nonfatal stroke	110 (1.9)	131 (2.3)	0.84 (0.65–1.08)	0.17
Hospitalization for unstable angina	44 (0.8)	59 (1.0)	0.75 (0.50–1.10)	0.14
Coronary revascularization procedure	334 (5.8)	386 (6.7)	0.86 (0.74–1.00)	0.04
Resuscitation after sudden cardiac arrest	14 (0.2)	8 (0.1)	1.73 (0.73–4.17)	0.20
Hospitalization for congestive heart failure — no. (%)	100 (1.7)	96 (1.7)	1.04 (0.79–1.38)	0.77

Jamerson K, Weber MA, Bakris GL, Bahlof B, Pitt B, Shi V, Hester A, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med.* 2008;359:2417-2428.

ACCOMPLISH

- Implications
  - Will specific combinations be recommended for HTN and high CV risk?

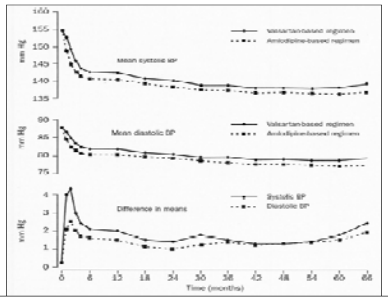
VALUE

- Design: RCT
- Patients: 15,245 with HTN and high CV risk
- Mean follow-up: 4.2 years
- Intervention: ARB versus CCB (DHP) as base agent
- Primary Outcome: Time to first cardiac event (Composite)
  - Sudden cardiac death, MI, death d/t PCI or CABG, death d/t HF, HF hospitalization, or emergency procedures to prevent MI

Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertension patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* 2004;363(9426):2022-2031.

VALUE

- Results – Blood Pressure Achieved



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VALUE

- Results – Adverse Events

	Valsartan (n=7622)	Amlodipine (n=7576)	p
Pre-specified adverse events			
Peripheral oedema	1135 (14·9%)	2492 (32·9%)	<0·0001
Dizziness	1257 (16·5%)	1083 (14·3%)	<0·0001
Headache	1120 (14·7%)	947 (12·5%)	<0·0001
Fatigue	730 (9·7%)	674 (8·9%)	0·0750
Additional common adverse events			
Diarrhoea*	670 (8·8%)	515 (6·8%)	<0·0001
Angina pectoris*	708 (9·3%)	485 (6·4%)	<0·0001
Angina pectoris†	335 (4·4%)	284 (3·8%)	<0·0001
Oedema other*	243 (3·2%)	462 (6·1%)	<0·0001
Hypokalaemia*	266 (3·5%)	469 (6·2%)	<0·0001
Atrial fibrillation†	182 (2·4%)	151 (2·0%)	0·1197
Syncope†	129 (1·7%)	75 (1·0%)	<0·0001

*With an incidence >3% and a difference between treatment groups >1%.
†Reported as serious.

Table 5: **Adverse events**

Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertension patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363(9426):2022-2031.

VALUE

- Results – Primary and Secondary Endpoints

	Valsartan (n=7649)		Amlodipine (n=7596)		Hazard ratio (95% CI)	p
	n (%)	Per 1000 patient years	n (%)	Per 1000 patient years		
Primary composite	810 (10·6%)	25·5	789 (10·4%)	24·7	1·04 (0·94–1·15)	0·49
Cardiac mortality	304 (4·0%)	9·2	304 (4·0%)	9·2	1·01 (0·86–1·18)	0·90
Cardiac morbidity	506 (7·7%)	18·4	578 (7·6%)	18·1	1·02 (0·91–1·15)	0·71
Myocardial infarction*	309 (4·8%)	11·4	313 (4·3%)	9·6	1·19 (1·02–1·38)	0·02
Heart failure*	354 (4·8%)	11·9	400 (5·3%)	12·4	0·89 (0·77–1·03)	0·12
Stroke*	322 (4·2%)	10·0	281 (3·7%)	8·7	1·15 (0·98–1·35)	0·08
All-cause death	841 (11·0%)	26·6	815 (10·8%)	24·6	1·08 (0·94–1·24)	0·28
New onset diabetes	690 (13·1%)	32·1	845 (16·4%)	41·1	0·77 (0·69–0·86)	<0·0001

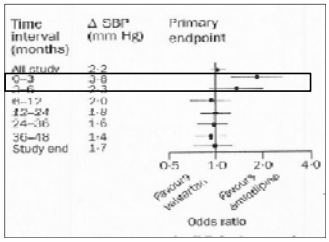
*Fatal and non fatal. †Odds ratio. Incidence rates are based on patients without diabetes at baseline.

Table 3: **Endpoints (first time occurrence in each category)**

Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertension patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363(9426):2022-2031.

VALUE

- Results – Primary and Secondary Endpoints



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VALUE

- Implications
  - Should patients ARBs or CCBs (DHP) be preferred over one another in HTN with high CV risk?
    - CCB if higher MI risk?
    - ARB if higher DM risk?
  - Is there a benefit to lowering BP more quickly?
    - 0-3 months BP reduction with CCB

ASCOT-BPLA

- Design: RCT
- Patients: 19,257 with HTN and high CV risk (3+ RFs)
- Median follow-up: 5.5 years
- Intervention: ACE + CCB (DHP) versus BB + thiazide diuretic
- Primary Outcome: nonfatal MI and fatal CHD

Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

ASCOT-BPLA

- Results – Blood Pressure Achieved

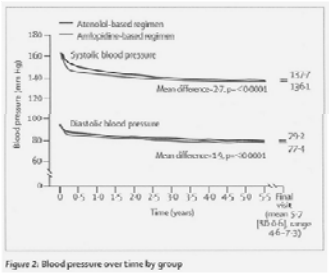
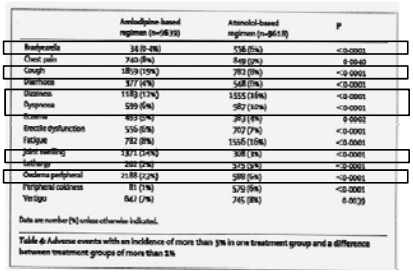


Figure 2: Blood pressure over time by group

Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

ASCOT-BPLA

- Results – Adverse Events



	Amlodipine-based regimen (n=9639)	Atenolol-based regimen (n=9618)	P
Bradycardia	34 (0·4%)	536 (5%)	<0·0001
Chest pain	740 (8%)	849 (9%)	0·0040
Cough	1859 (19%)	782 (8%)	<0·0001
Diarrhoea	377 (4%)	548 (6%)	<0·0001
Dizziness	1183 (12%)	1555 (16%)	<0·0001
Dyspnoea	599 (6%)	987 (10%)	<0·0001
Eczema	493 (5%)	383 (4%)	0·0002
Erectile dysfunction	556 (6%)	707 (7%)	<0·0001
Fatigue	782 (8%)	1346 (14%)	<0·0001
Joint swelling	1371 (14%)	308 (3%)	<0·0001
Lethargy	202 (2%)	375 (4%)	<0·0001
Oedema peripheral	2188 (23%)	588 (6%)	<0·0001
Peripheral coldness	81 (1%)	579 (6%)	<0·0001
Vertigo	647 (7%)	745 (8%)	0·0039

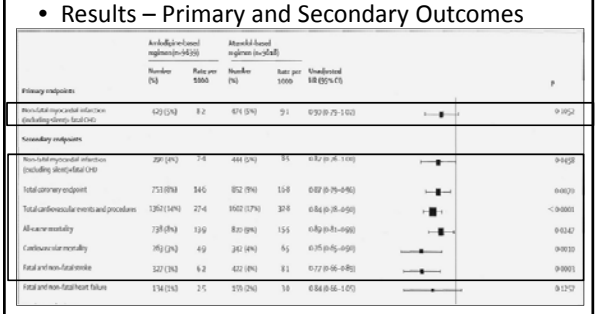
Data are number (%) unless otherwise indicated.

Table 4: Adverse events with an incidence of more than 5% in one treatment group and a difference between treatment groups of more than 1%

Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

ASCOT-BPLA

- Results – Primary and Secondary Outcomes



	Amlodipine-based regimen (n=9639) Number (%)	Rate per 1000	Atenolol-based regimen (n=9618) Number (%)	Rate per 1000	Unadjusted RR (95% CI)	P
Primary endpoints						
Non-fatal myocardial infarction (excluding silent) + fatal CHD	429 (5%)	8·2	474 (5%)	9·1	0·90 (0·79–1·02)	0·1052
Secondary endpoints						
Non-fatal myocardial infarction (excluding silent) + fatal CHD	297 (3%)	5·6	444 (5%)	8·5	0·67 (0·58–0·78)	0·0458
Total coronary endpoint	753 (8%)	14·6	852 (9%)	16·8	0·87 (0·79–0·96)	0·0030
Total cardiovascular events and procedures	1362 (14%)	27·4	1602 (17%)	32·8	0·84 (0·78–0·90)	<0·0001
All-cause mortality	738 (8%)	13·9	820 (9%)	15·5	0·89 (0·81–0·98)	0·0347
Cardiovascular mortality	265 (3%)	4·9	341 (4%)	6·5	0·78 (0·65–0·91)	0·0030
Fatal and non-fatal stroke	327 (3%)	6·2	422 (4%)	8·1	0·77 (0·66–0·89)	0·0001
Fatal and non-fatal heart failure	174 (2%)	3·5	170 (2%)	3·6	0·84 (0·68–1·05)	0·1257

Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

ASCOT-BPLA

- Implications
  - Is CCB (plus ACE) based regimen favorable to a BB (plus thiazide) based regimen in HTN with high CV risk?
  - Should a BB be considered as initial first line therapy in high CV risk?

Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

Areas for change?

- Should >140/90 mmHg still be standard for initial pharmacological treatment?
  - Reappraisal of European HTN Guidelines
- Should elderly patients have different BP goals?
  - Reappraisal of European HTN Guidelines

Areas for change?

- Goal BP for patients with DM still <130/80 mmHg?
  - ACCORD
- Are specific agents or combinations preferred in high CV risk?
  - ACCOMPLISH
  - VALUE
  - ASCOT-BPLA

Post-Test Questions

Which of the following trials may influence the JNC-VIII recommendations for the blood pressure goal for patients with diabetes?

A. ALLHAT
B. ACCOMPLISH
C. ASCOT-BPLA
D. ACCORD

Which of the following studies demonstrated the combination of an ACE and CCB may be favorable to a BB and thiazide diuretic for treatment of hypertension in patients with high risk for cardiovascular disease?

A. ALLHAT
B. ACCOMPLISH
C. ASCOT-BPLA
D. VALUE

Based on the reappraisal of the European guidelines for the management of hypertension, which recommendation did the authors note there was little evidence to support?

- a. Treating systolic blood pressure >160 mmHg in elderly patients
- b. Treating blood pressure >140/90 mmHg with pharmacologic therapy
- c. Treating blood pressure in patients with a history of myocardial infarction
- d. Treating blood pressure in patients with a history of high CV risk

Questions?