

Controversy, the JNC-8 Hypertension Guidelines

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Year 3 UT Cardiology Fellow, for substantial contribution on
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JNC 7 published in 2003.

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Aram V. Chobanian, George L. Bakris, Henry R. Black, William C.ushman, Lee A. Green, Joseph L. Izzo, Jr, Daniel W. Jones, Barry J. Materson, Suzanne Oparil, Jackson T. Wright, Jr, Edward J. Roccella and the National High Blood Pressure Education Program Coordinating Committee

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

National Heart, Lung, and Blood Institute (NHLBI) formed JNC 8 in March 2008.

Panel members selected from >400 nominees:

- hypertension (14)
- geriatrics (2)
- nephrology (3)
- pharmacology (2)
- evidence-based medicine (3)
- informatics (4)
- primary care (6)
- cardiology (2)
- nursing (1)
- clinical trials (6)
- epidemiology (1)
- clinical guidelines (4).

The Process of JNC 8

- In January 2013, JNC 8 submitted for external peer review by NHLBI to 20 reviewers and 16 federal agencies.
- 16 individual reviewers and 5 federal agencies responded.
- Comments reviewed and discussed from March through June 2013 and incorporated into a revised document.

The Process of JNC 8

- In June 2013, NHLBI announced it would discontinue developing clinical guidelines including those in process.
- The JNC-8 writing group declined partnership with AHA/ACC and pursued publication independently to bring recommendations to the public.
- JNC 8 report was published in JAMA in December 2013.

Evidence Review

- Literature search were January 1, 1966, through December 31, 2009 and then Dec 2009 to August 2013.
- Evidence limited to randomized controlled trials, systematic reviews and meta-analyses not included.

QUESTIONS GUIDING THE EVIDENCE REVIEW

1. **Threshold**: Does initiating antihypertensive treatment at specific BP thresholds improve health?
2. **Goal**: Does treatment with antihypertensive treatment to a BP goal improve health?
3. **Choice**: Do specific drugs or drug classes differ in benefits and harms on specific health outcomes?

The Evidence Review

Studies were included if they reported:

- Overall mortality, cardiovascular disease (CVD)–related mortality, CKD-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke.
- Coronary and peripheral revascularization.
- End-stage renal disease (ESRD), doubling of creatinine, halving of glomerular filtration rate (GFR).

The Inclusion Criteria

1. Major study in hypertension
2. At least 2000 participants
3. Multi-centered
4. Met all inclusion/exclusion criteria

Evidence Quality Rating

Table 2. Evidence Quality Rating

| Type of Evidence | Quality Rating ^a |
|---|-----------------------------|
| Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect | High |
| RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed non-randomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses of such studies Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate | Moderate |
| RCTs with major limitations Non-randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate. | Low |

Abbreviations: RCT, randomized controlled trial

^aThe evidence quality rating system used in this guideline was developed by the National Heart, Lung, and Blood Institute's (NHLBI's) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline

panels and work groups during this project. As a result, it includes the evidence quality rating for many types of studies, including studies that were not used in this guideline. Additional details regarding the evidence quality rating system are available in the online Supplement.

Strength of Recommendation

Table 3. Strength of Recommendation

| Grade | Strength of Recommendation |
|-------|--|
| A | Strong Recommendation There is high certainty based on evidence that the net benefit ^a is substantial. |
| B | Moderate Recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate. |
| C | Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit. |
| D | Recommendation against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits. |
| E | Expert Opinion (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area. |
| N | No Recommendation for or against (“There is insufficient evidence or evidence is unclear or conflicting.”) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area. |

The strength of recommendation grading system used in this guideline was developed by the National Heart, Lung, and Blood Institute’s (NHLBI’s) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline panels and work groups during this project. Additional details regarding the strength of recommendation grading system are available in the online Supplement.

^aNet benefit is defined as benefits minus the risks/harms of the service/intervention.

From JNC 7 to JNC 8: What's Changed

- JNC uses randomized trials, and is explicit when a recommendation reflects only expert opinion.
- JNC 8 raises the systolic threshold to 150 mmHg at age 60.
- JNC 8 uses 140/90 for patients with diabetes or chronic kidney disease.
- In JNC 8, the initial drug choice is broadened to four classes for nonblack patients and two classes for black patients. β -blockers are no longer recommended for initial therapy because of less stroke protection.

RECOMMENDATIONS

- Recommendations 1 -5 address questions 1 & 2 concerning thresholds and goals for BP treatment.
- Recommendations 6, 7, 8 address question concerning selection of antihypertensive drugs.
- Recommendation 9 is a summary of strategies based on expert opinion for starting and adding antihypertensive drugs

Thresholds and Goals

Recommendations 1 -5

Recommendation 1

- General population aged 60 years or older

Initiate Treatment at:

**SBP \geq 150 mmHg
Or
DBP \geq 90mmHg**

Goal of Treatment:

**SBP $<$ 150 mmHg
OR
DBP of $<$ 90mmHg.**

- Strong Recommendation – Grade A

Recommendation 1: BP goal of 150 mmHg at age 60

- Acknowledged lack of unanimity in the recommendation for the 150 mmHg threshold in people ≥ 60 .
- “...the 140/90 mm Hg definition from JNC 7 remains reasonable.”
- If treatment results in SBP < 140 mm Hg and is well tolerated and without adverse effects treatment does not need to be adjusted. (Expert Opinion – Grade E)

Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

Jackson T. Wright Jr., MD, PhD; Lawrence J. Fine, MD, DrPH; Daniel T. Lackland, DrPH; Gbenga Ogedegbe, MD, MPH, MS; and Cheryl R. Dennison Himmelfarb, PhD, RN, ANP

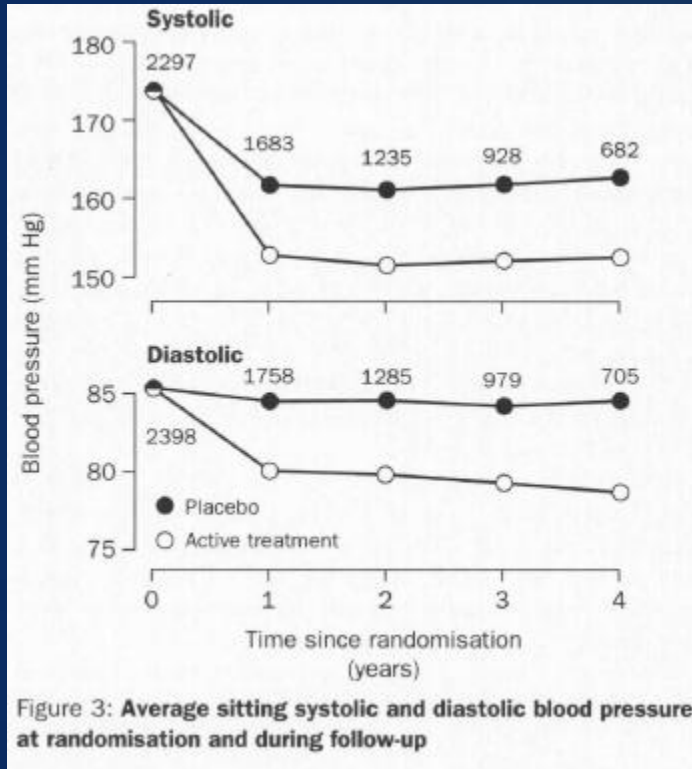
- Five of 14 members of the JNC 8 writing team released a “minority report,” protesting 150 mmHg BP goal.
- “...insufficient to increase the systolic BP goal from <140 mm Hg because of concern that increasing the goal may cause harm by increasing the risk for cardiovascular disease and partially undoing the remarkable progress ...”

Systolic Hypertension in the Elderly Program (SHEP)

- 4736 persons, aged ≥ 60
- SBP 160-219 mm Hg and DBP < 90 mm Hg.
- Chlorthalidone 12.5-25 mg, or atenolol, 25 mg.
- 5-year mean BP 155/72 mm Hg in placebo and 143/68 mm Hg in treatment.
- Reduced strokes by 36%, with 5-year absolute benefit of 3 events per 100 and cardiovascular events by 5.5 events per 100.

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group.
JAMA. 1991;265(24):3255-3264.

Syst-Eur Trial



- 4965 patients >60 years
- Nitrendipine 10-40 mg, or enalapril 5-20 mg and hydrochlorothiazide 12.5-25.0 mg daily.
- Stroke ↓42%, p=0.003
- Sudden death ↓26%, p=0.03
- Non-fatal cardiac ↓33%, p=0.03
- Fatal + non-fatal CV events ↓31%, p < 0.001

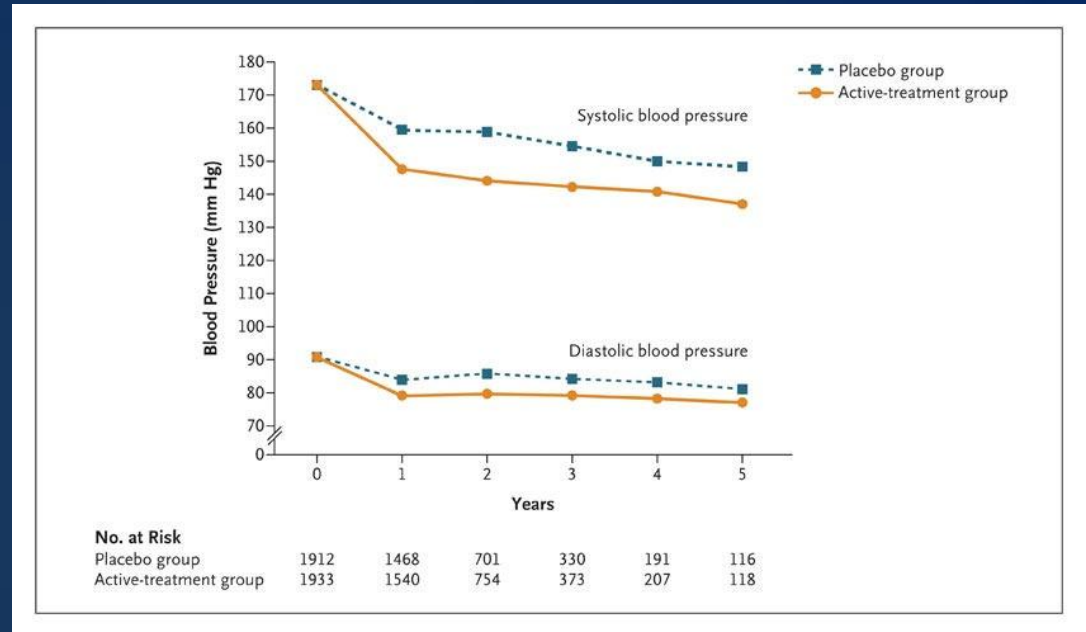
Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension

Jan A Staessen, Robert Fagard, Lutgarde Thijs, Hilde Celis, Guramy G Arabidze, Willem H Birkenhäger, Christopher J Bulpitt, Peter W de Leeuw, Colin T Dollery, Astrid E Fletcher, Françoise Forette, Gastone Leonetti, Choudomir Nachev, Eoin T O'Brien, Joseph Rosenfeld, José L Rodicio, Jaakko Tuomilehto, Alberto Zanchetti, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators*

Lancet 1997; 350: 757-64

HYVET Trial

- 3845 patients \geq 80 years
- SBP $>$ 160 mmHg
- Indapamide sustained release 1.5 mg and perindopril 2-4 mg or placebo.



- ↓ 30% stroke, P=NS
- ↓ 39% stroke death P=0.05
- ↓ 21% all-cause mortality, P=0.02
- ↓ 23% CV death, P=0.06
- ↓ 64% heart failure, P<0.001

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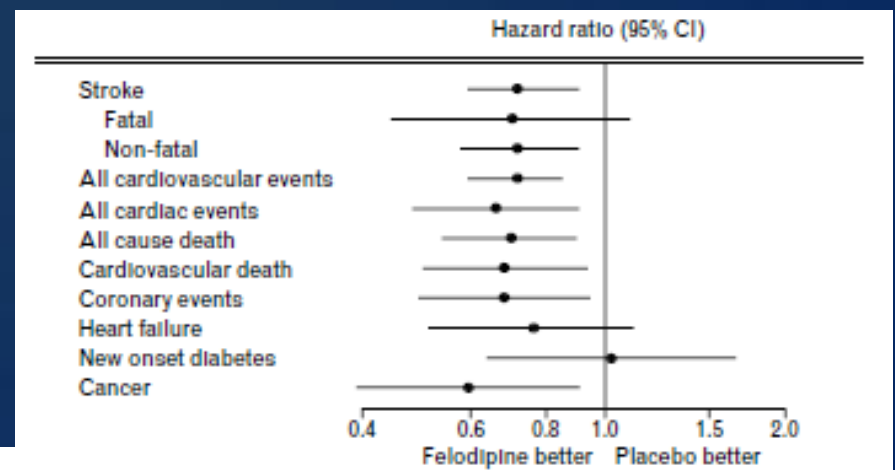
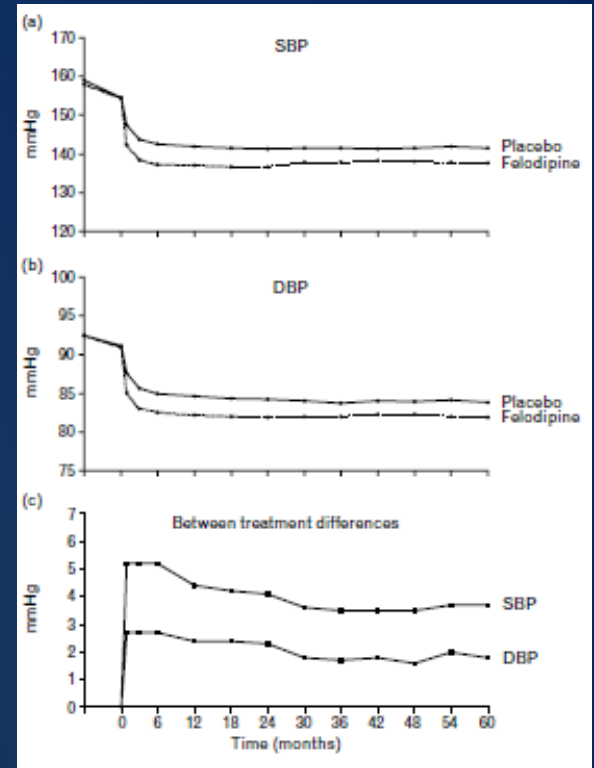
Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

FEVER Trial

- 9800 Chinese patients aged 50-79 years.
- Initial BP 140-180 systolic or 90-100 mmHg diastolic
- Felodipine decreased BP 154.2/91.0 to 137.3/82.5 mmHg
- Placebo group from 154.4/91.3 to 142.5/85.0
- Difference of 4.2/2.1 mmHg.

Journal of Hypertension 2005, 23:2157-2172

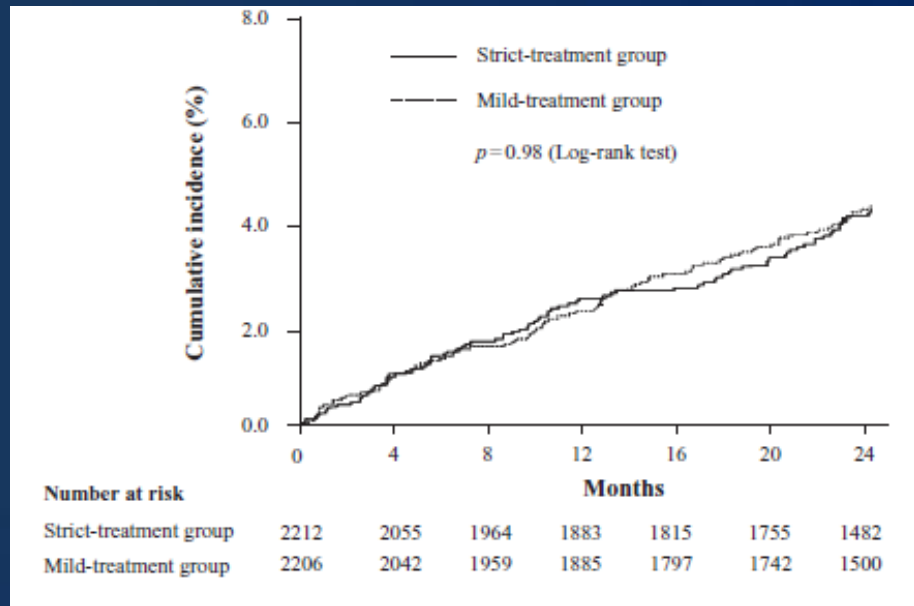
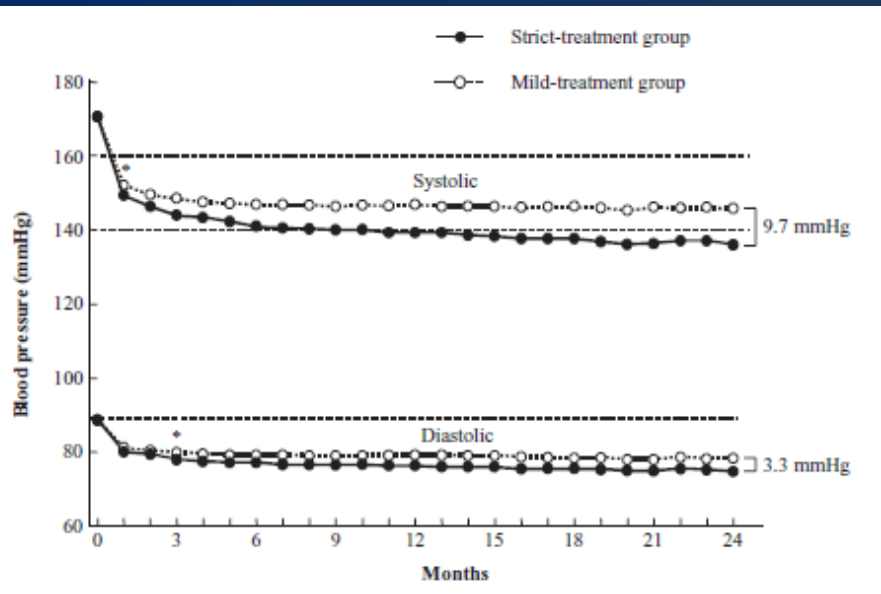


The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients

JATOS Trial

- Randomized to SBP < 140 mmHg vs. 140-160 mmHg
- Population: 4418 patients
 - 65-85 years old
 - Systolic >160 mmHg

Principal Results of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS)

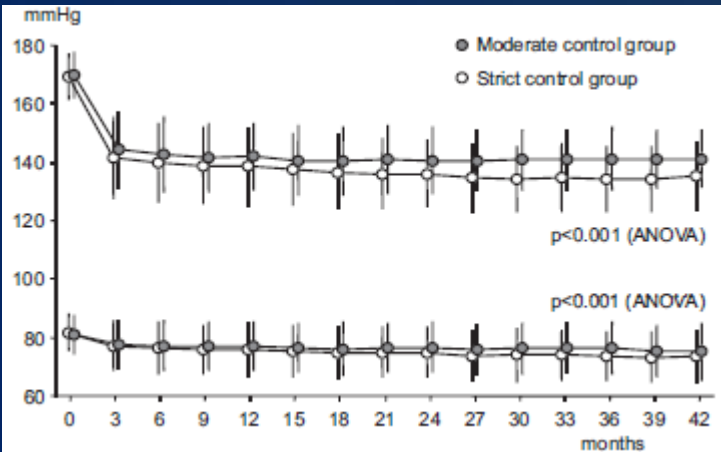


No benefit of <140 mmHg goal

Valsartan in Elderly Systolic Hypertension Study

- BP <140 vs. moderate BP 140 -150 mm Hg
- 3260 Japanese patients aged 70 to 84 years.
- Valsartan plus other class meds.

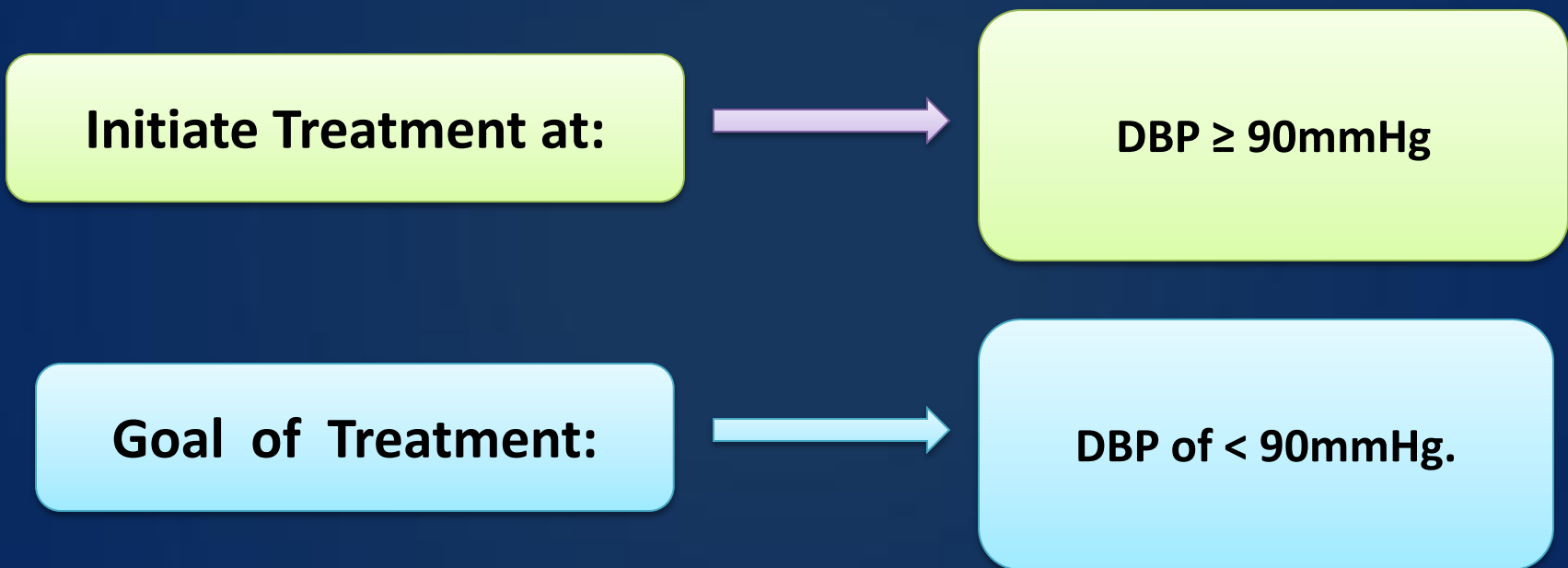
| | Strict control (N=1545) | Moderate control (N=1534) | p value | Hazard ratio (95% CI) | Strict better 0.1 | Moderate better 1 10 |
|---|-------------------------|---------------------------|---------|-----------------------|-------------------|----------------------|
| Primary endpoint | | | | | | |
| Composite endpoint ¹⁾ | 47 (3.04) | 52 (3.39) | 0.383 | 0.89 (0.60-1.31) | | |
| Secondary endpoint | | | | | | |
| Hard endpoint ²⁾ | 32 (2.07) | 37 (2.41) | 0.484 | 0.84 (0.53-1.36) | | |
| All cause death | 24 (1.55) | 30 (1.96) | 0.362 | 0.78 (0.46-1.33) | | |
| Cardiovascular death | 11 (0.71) | 11 (0.72) | 0.950 | 0.97 (0.42-2.25) | | |
| Sudden death | 6 (0.39) | 8 (0.52) | 0.564 | 0.73 (0.25-2.11) | | |
| Fatal and non-fatal stroke | 16 (1.04) | 23 (1.50) | 0.237 | 0.68 (0.36-1.29) | | |
| Fatal and non-fatal myocardial infarction | 5 (0.32) | 4 (0.26) | 0.761 | 1.23 (0.33-4.56) | | |
| Unplanned hospitalization | 12 (0.78) | 14 (0.91) | 0.656 | 0.84 (0.39-1.82) | | |
| Renal insufficiency | 5 (0.32) | 2 (0.13) | 0.267 | 2.45 (0.48-12.64) | | |



No benefit of <140 mmHg goal

Recommendation 2

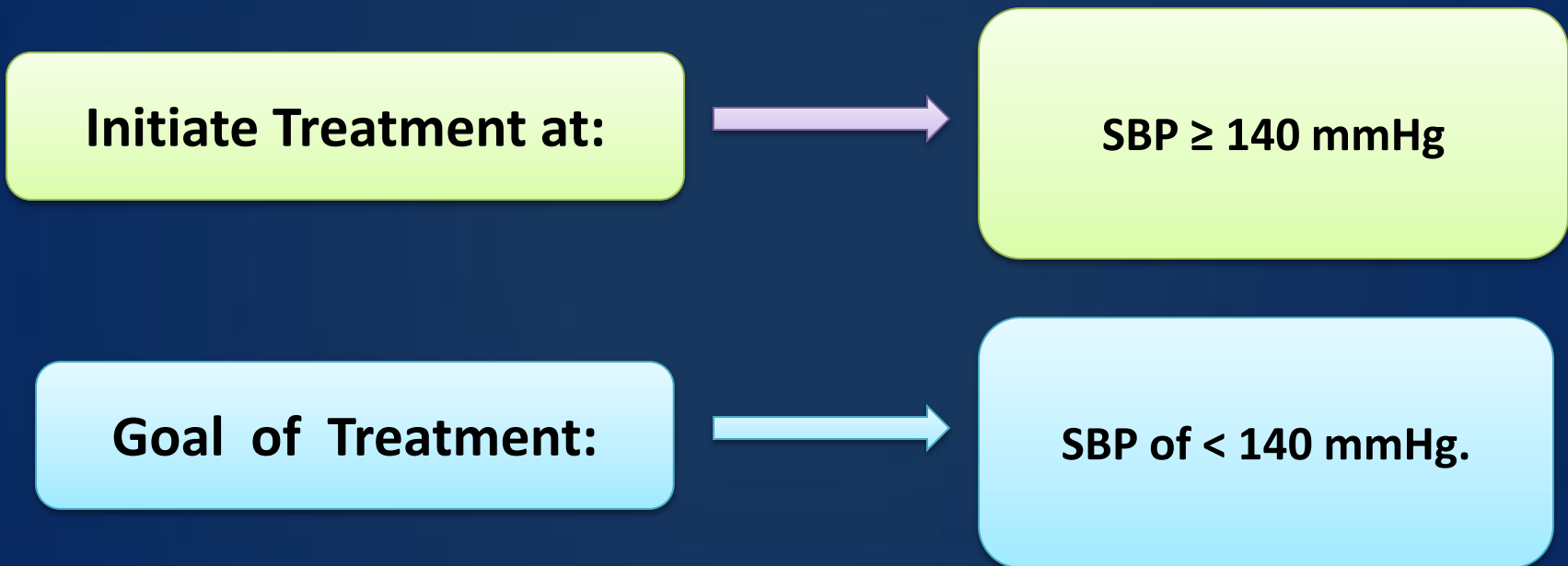
- **General population < 60 years**



- For ages 30-59 years, Strong Recommendation – Grade A
- For ages 18-29 years, Expert Opinion – Grade E

Recommendation 3

- General population < 60 years



•Expert Opinion – Grade E

Recommendation 4

- Population aged 18 years or older with CKD

Initiate Treatment at:

**SBP \geq 140 mmHg
Or
DBP \geq 90 mmHg**

Goal of Treatment:

**SBP $<$ 140 mmHg
Or
DBP $<$ 90 mmHg**

•Expert Opinion – Grade E

Recommendation 5

- Population aged 18 years or older with diabetes

Initiate Treatment at:

SBP \geq 140 mmHg
Or
DBP \geq 90 mmHg

Goal of Treatment :

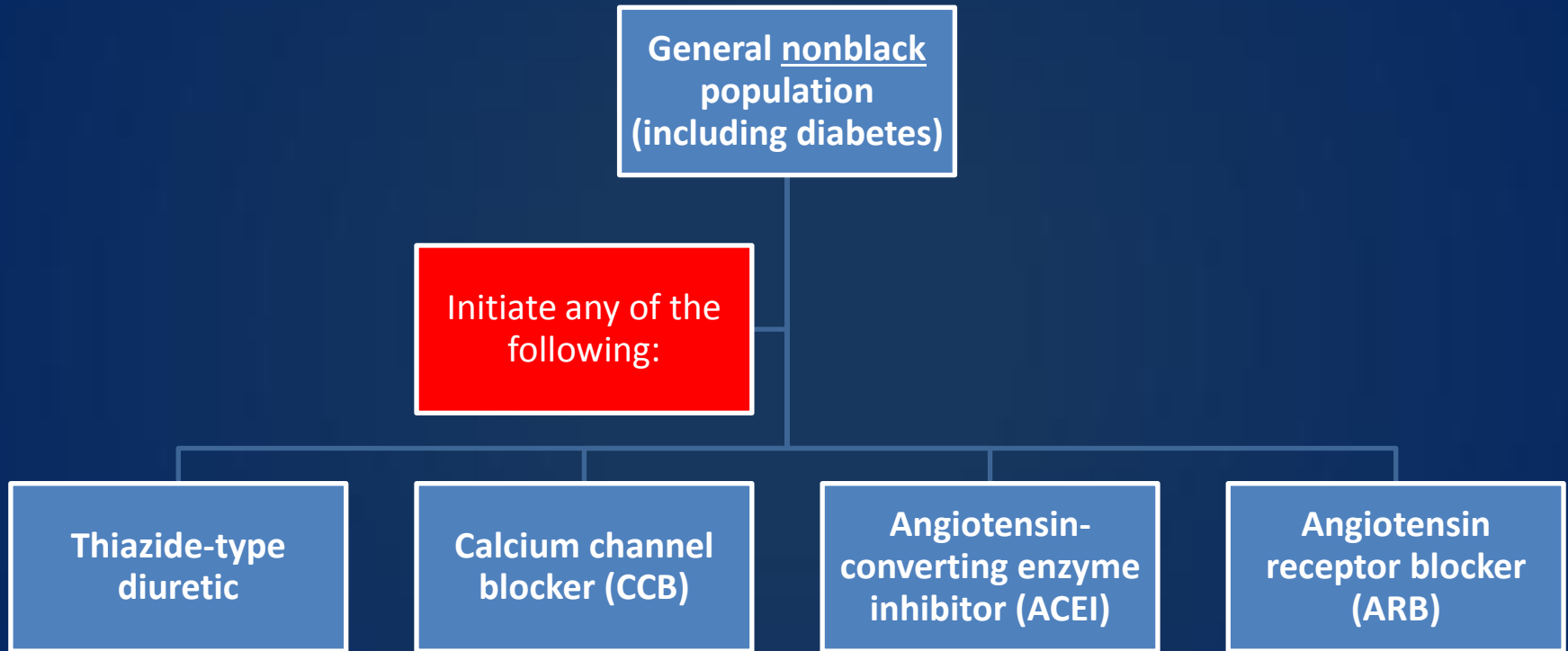
SBP $<$ 140 mmHg
Or
DBP $<$ 90 mmHg

•Expert Opinion – Grade E

Selection of Anti-hypertensive Drugs

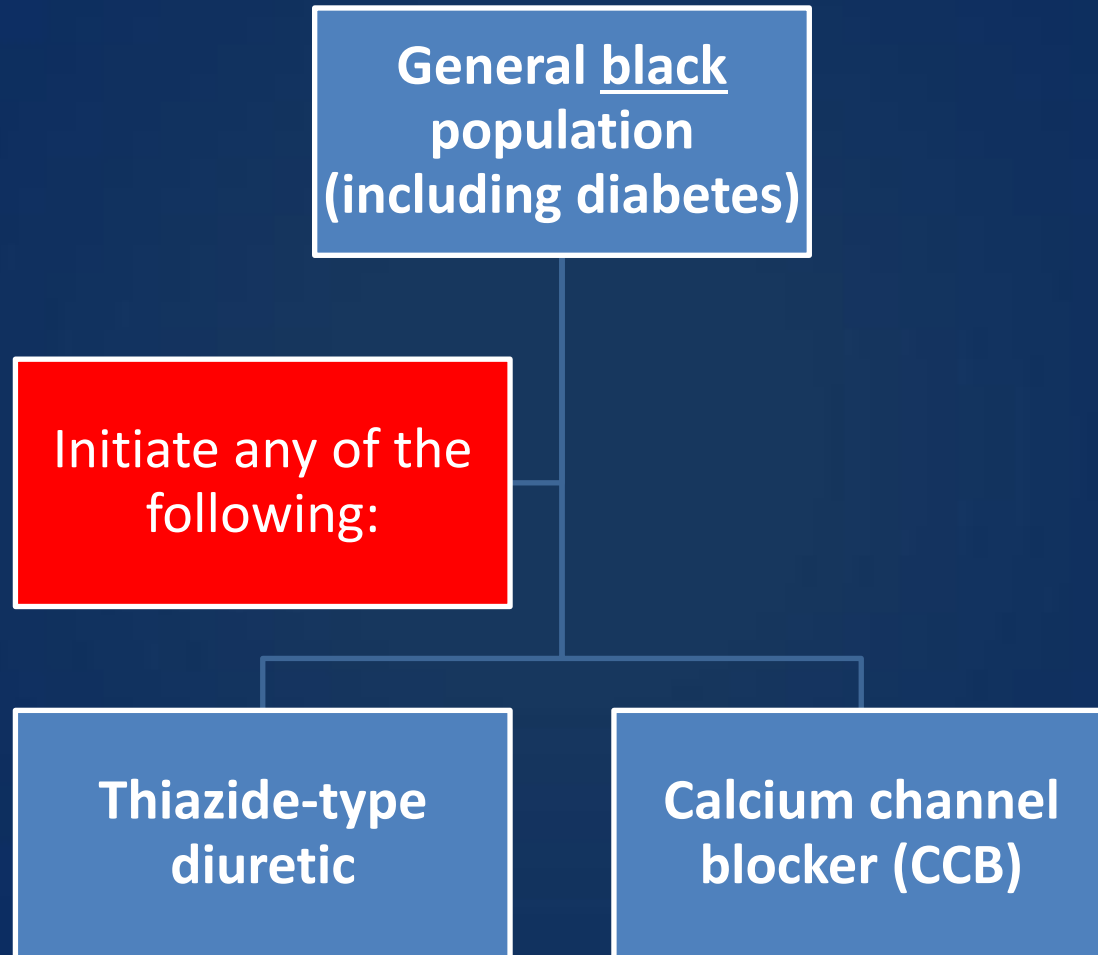
Recommendations 6-8

Recommendation 6: Initial drug choice



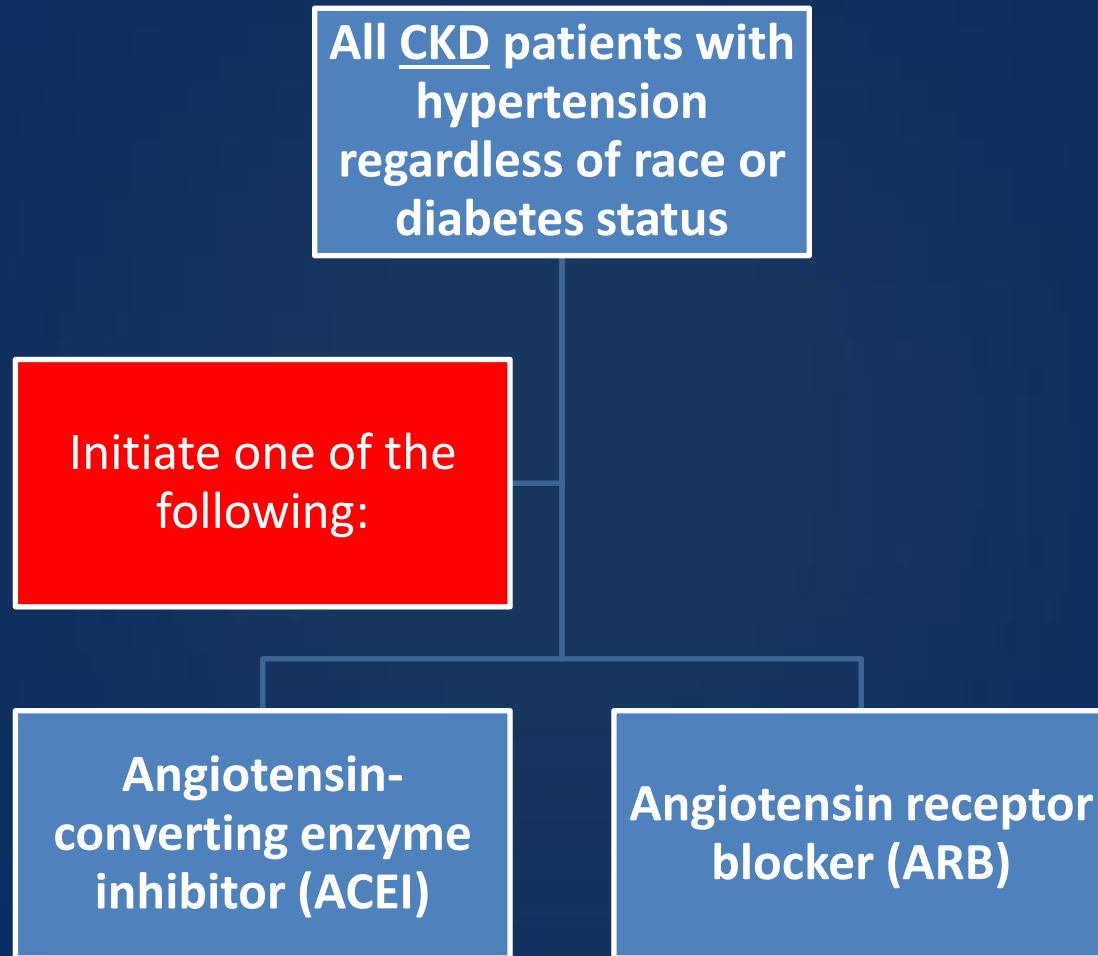
•Moderate Recommendation – Grade B

Recommendation 7: Initial drugs in blacks



- For general black population: Moderate Recommendation – Grade B
- For black patients with diabetes: Weak Recommendation – Grade C

Recommendation 8: initial drugs and CKD



- For general black population: Moderate Recommendation – Grade B
- for black patients with diabetes: Weak Recommendation – Grade C

Evidence-Based Dosing

Table 4. Evidence-Based Dosing for Antihypertensive Drugs

| Antihypertensive Medication | Initial Daily Dose, mg | Target Dose in RCTs Reviewed, mg | No. of Doses per Day |
|-------------------------------|------------------------|----------------------------------|----------------------|
| ACE inhibitors | | | |
| Captopril | 50 | 150-200 | 2 |
| Enalapril | 5 | 20 | 1-2 |
| Lisinopril | 10 | 40 | 1 |
| Angiotensin receptor blockers | | | |
| Eprosartan | 400 | 600-800 | 1-2 |
| Candesartan | 4 | 12-32 | 1 |
| Losartan | 50 | 100 | 1-2 |
| Valsartan | 40-80 | 160-320 | 1 |
| Irbesartan | 75 | 300 | 1 |
| β-Blockers | | | |
| Atenolol | 25-50 | 100 | 1 |
| Metoprolol | 50 | 100-200 | 1-2 |
| Calcium channel blockers | | | |
| Amlodipine | 2.5 | 10 | 1 |
| Diltiazem extended release | 120-180 | 360 | 1 |
| Nitrendipine | 10 | 20 | 1-2 |
| Thiazide-type diuretics | | | |
| Bendroflumethiazide | 5 | 10 | 1 |
| Chlorthalidone | 12.5 | 12.5-25 | 1 |
| Hydrochlorothiazide | 12.5-25 | 25-100 ^a | 1-2 |
| Indapamide | 1.25 | 1.25-2.5 | 1 |

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

^aCurrent recommended evidence-based dose that balances efficacy and safety is 25-50 mg daily.

Opinion for Starting & Adding Drugs

Recommendation 9

Recommendation 9: adding drugs

- If goal BP is not reached within a month of treatment:
 - increase the dose of the initial drug **OR**
 - Add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB).
- Assess BP and adjust the treatment until goal is reached.

Recommendation 9: adding drugs

- If goal BP cannot be reached with 2 drugs:
 - Add and titrate a third drug.
- Do not use an ACEI and an ARB together in the same patient.
- If goal BP cannot be achieved combinations of ACE/ARB, thiazide, or CCB, then drugs from other classes can be used.

From JNC 7 to JNC 8: What's Changed

- JNC uses randomized trial evidence, and is explicit when a recommendation reflects only expert opinion.
- JNC 8 raises the systolic threshold to 150 mmHg at age 60.
- JNC 8 uses 140/90 for patients with diabetes or chronic kidney disease.
- In JNC 8, the initial drug choice is broadened to four classes for nonblack patients and two classes for black patients. β -blockers are no longer recommended for initial therapy because of less stroke protection.

Comparison of Hypertension Guidelines, 2011-2014

| Blood Pressure (mm Hg) | NICE 2011 | ESH/ESC 2013 | AHA/ACC/CDC 2013 | ASH/ISH 2014 | JNC 8 2014 | ACC/AHA/ASH IHD 2014 |
|---|---|---|---|---|---|---|
| Definition of hypertension | ≥140/90 and daytime ABPM or home BP ≥135/85 | ≥140/90 | ≥140/90 | ≥140/90 | Not addressed | Not addressed |
| Drug therapy | ≥160/100 or daytime ABPM ≥150/95 | ≥140/90 | ≥140/90 | ≥140/90 | <60 yr ≥140/90 ≥60 yr ≥150/90 | ≥140/90 |
| β-Blockers as first-line drug | No (Step 4) | Yes | No (Step 3) | No (Step 4) | No | No Yes if CAD |
| Diuretic | Chlorthalidone Indapamide | Thiazides, Chlorthalidone, Indapamide | Thiazides | Thiazides, Chlorthalidone, Indapamide | Thiazides, Chlorthalidone, Indapamide | Thiazides, Chlorthalidone, Indapamide |
| Initiate therapy with two drugs | Not mentioned | In patients with markedly elevated BP | ≥160/100 | ≥160/100 | ≥160/100 | ≥160/100 |
| BP targets | <140/90 ≥80 yr <150/90 | <140/90 elderly <80 yr; SBP 140-150; SBP <140 in fit patients; Elderly ≥80 yr; SBP 140-150 | <140/90 Lower targets may be appropriate in some patients, including the elderly | <140/90 ≥80 yr <150/90 | <60 yr <140/90 ≥60 yr <150/90 | <140/90 <130/80 if CAD, CAD risk equivalent, stroke, TIA, Framingham risk score ≥20% |
| BP target in patients with diabetes mellitus | Not addressed | <140/85 | <140/90 Lower targets may be considered | <140/90 | <140/90 | <140/90 Lower targets may be considered |

Comparison of Hypertension Guidelines 2011-2014

- Treat if BP $\geq 140/90$ mm Hg except in NICE and JNC 8.
- Beta-blocker is not a first-line for patients without coronary artery disease except ESH.
- Several emphasize superiority of chlorthalidone or indapamide over thiazide diuretics, and loop diuretics reserved for heart failure or chronic kidney disease.
- Most agree with initial two drugs treatment if BP is $\geq 160/100$ mm Hg.

Cont'd Comparison of Hypertension Guidelines 2011-2014

- BP target of <140/90 mm Hg, but **four** guidelines propose higher targets for the elderly.
- Definitions of the elderly vary. In NICE and ASH/ISH guidelines, age ≥ 80 years and in JNC 8, age ≥ 60 years, both with target of <150/90 mm Hg.

My Conclusion (opinion)

- JNC 8 has changed treatment, a little bit
- It provides clinicians more flexibility:
 - Now there are four first line drugs
 - For patients over 60, treatment at 140 or 150 mmHg
 - Goal for diabetes and chronic kidney disease now 140/90

I am especially appreciative of those who helped with this talk, especially Kevin Kun Xiang, M.D., Ph.D.