Hypertension in 2014: Advances in Treatment

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# FACULTY DISCLOSURE

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
<th>Unlabeled Product Usage</th>
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<tbody>
<tr>
<td>BOSCH Health Care Systems</td>
<td>Advisory Board</td>
<td>NONE</td>
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<td>Boehringer Ingelheim</td>
<td>Speakers Bureau</td>
<td>NONE</td>
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<td>Lilly</td>
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<td>Janssen (J&amp;J)</td>
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<td>Forest</td>
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<td>Novartis</td>
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US Adult Population at Risk

Prehypertensive
(120-139/80-89 mm Hg)

Hypertensive
(>139/89 mm Hg)

Normal
(<120/80 mm Hg)

72 M

45 M

98 M

Hypertension in USA

- 33% US Population > age 20
- 50% > age 60
- 75% > age 75
- 90% > age 90

Awareness of Hypertension 81%
On Therapy 75%
At Goal (< 140 / 90 ) 53%
CDC (2014) 64%* at Goal!

Go AS. et al 2013 AHA Update, Circulation 127: 143-52
* Morbidity and Mortality Weekly Report, 2/14/2014
Awareness, Treatment & Control of Hypertension*

* Survey participants were adults aged 18 years and older. Awareness of hypertension defined as patients with hypertension who had been told by a doctor or other healthcare professional that they had hypertension or high blood pressure. Treatment defined as currently taking prescription medication. Control defined as SBP <140 mm Hg and DBP <90 mm Hg.

NCHS=National Center for Health Statistics; NHANES=National Health and Nutrition Examination Survey.

More than 50% have ≥2 CV risk factors

>80% of Hypertensive Patients Have CV-Risk Factors = Complicated Hypertension

Men
- One 26%
- Two 25%
- Three 22%
- ≥ Four 8%

Women
- One 27%
- Two 24%
- Three 20%
- ≥ Four 12%

• Obesity (50%) • Glucose intolerance • Hyperinsulinemia • Diabetes (20%) • Reduced HDL-C • Elevated LDL-C • Elevated TG • LVH • CKD • Albuminuria

CV=cardiovascular; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LVH=left ventricular hypertrophy; TG=triglycerides.

## Failure to Deliver Recommended Care: Lives/Costs That Could be Saved Annually

<table>
<thead>
<tr>
<th>Measure</th>
<th>Avoidable Deaths/Year*</th>
<th>Avoidable Costs/Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlling high BP</td>
<td>28,300</td>
<td>$1,242,836,580</td>
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<tr>
<td>Diabetes care/ HbA$_1^C$ control</td>
<td>13,600</td>
<td>$178,464,900</td>
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<tr>
<td>Cholesterol management</td>
<td>6,500</td>
<td>$94,249,482</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>2,700</td>
<td>$97,690,642</td>
</tr>
<tr>
<td>β-blocker treatment</td>
<td>1,700</td>
<td>$11,076,204</td>
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* US Population.
How to Obtain a Correct Blood Pressure

- Sitting with back support, both legs on floor
- Rest for at least 3 min
- Ascertain correct cuff size
- Obtain 3 readings about 2 min apart
- Discard 1st reading and average 2nd and 3rd
- Obtain HOME BP readings, if possible

JNC 7, JAMA 2003
Office BP Details

How many BP readings are ideal?

AHA and JNC 7: minimum of 2 sitting BP and average out both

NHANES 1999-2008

Using 3 Readings and discarding # 1 and Averaging # 2 and # 3

RECLASSIFIES ~ 1/3 (35%) of Stage I Hypertension as being NORMOTENSIVE = NO THERAPY Needed

Handler J.et.al J.Clinical Hypertension, 2012;11: 751-759
HOME BP FACTS

1) 2 : 1 better Correlation of CV events HOME vs. OFFICE BP

2) Diagnoses MASKED Hypertension

3) Home BP taken x 2 / week for 48 weeks leads to

   4 x More Likely Reaching BP GOAL

   ( Kim J.et.al. JCH. 2010; 12: 253-260 )

4) Diagnoses WHITE COAT Hypertension
Number Needed to Treat - NNT

Lowering Systolic BP by 12 mmHg in Stage Hypertension (140-159) for 10 years:

1 Death prevented in 11 patients
(1 in 9 with known CV disease)

Reaching Goal (<140/90) for 5 years

NNT (to prevent ONE CV event)
- CVA: 63
- MI: 86
- CVA or MI: 36

Kaiser Permanente Study 11/2013 Hypertension:1-24
IDEAL Blood Pressure?
( > 40,000 Hypertensives )

1) PROVE – IT- TIMI 4,162 patients

2) INVEST 6,400 patients with DM + CAD

3) ON TARGET 15,981 w/o and 9,603 with Diabetes

4) ACCORD 4,733 with Diabetes

LOWEST EVENT RATE ~ 135 / 85 mmHg
ASH Hypertension Guidelines 2013

BP Goals:

- Age 80 and older: < 150 / 90 mmHg
- Age 60 - 79: < 140 / 90 mmHg
- Age 50 and younger: < 140 / 90 mmHg
  - < 130 / 80 (if tolerated)

CKD or DIABETES:

- w/o Proteinuria: < 140 / 90 mmHg
- with Proteinuria: < 130 / 80 mmHg (no consensus)

ASH Guidelines for Hypertension: J.Clinical Hypertension 12, 2013
("JNC 8") Committee Guideline 2013

BP Goals

> Age 60 < 150 / 90 mmHg*
  * if BP < 140 / 90 on drug w/o AE's - no change needed

< Age 60 < 140 / 80

Chronic Kidney Disease (CKD) or DIABETES < 140 / 90 mmHg

Initial Drug Therapy

Black Patients (including with Diabetes): THIAZIDES or CCB,s

CKD: ACEI or ARB

General Population (including Diabetes):

THIAZIDE, CCB,s, ACEI or ARB,s

JAMA 2013, December 13 (online)
ACC/AHA Consensus on Hypertension in Elderly (5/2011)

New Systolic BP Goals:

Age $\geq 65$ - 79  Systolic BP  <  140  mmHg
Age $\geq 80$  Systolic BP  =  140 to 145  mmHg

Keep diastolic > 70 mmHg  after age 70

Included in Goal:

Routine standing BP readings
Start with lowest dose
ADA Blood Pressure Guidelines (2014)

GOAL < 140 / 80 mmHg

- Lower target: < 130 / 80 for young patients (if no side effects)

- ACE inhibitor or ARB: included in Therapy and ONE or more BP drugs at Bedtime

- Lifestyle:
  - DASH style diet
  - Weight Loss
  - Salt < 6 gm (2300 mg Na)
  - Increase Potassium (Fruit, Vegetables)
  - 150 min exercise / week

Executive Summary: Standards of Medical Care in Diabetes – 2014 Diabetes Care
vol.37, Suppl.1, Jan. 14
Bedtime Dosing in Diabetes or CKD
(at least 1 BP drug at HS)

**DIABETES**

ABPM 48hrs: HTN present, if BP > 135 / 85 or Nocturnal BP > 120 / 70

448 patients on 3 drugs: using ONE Drug HS

F/U 5.4 years

Each 5 mmHg Nocturnal SBP Decline = 12 % Decline of CV Events
(CVA, MI, CV death)

**CKD**

695 patients with eGFR < 60, 7 years F/U (ABPM 48hrs as above)

Each 5 mmHg Nocturnal SBP Decline = 14 % Decline of CV events

Hermida, RC, et.al. Diabetes Care 2011; 134: 1270-1276

CKD Blood Pressure Guidelines

(With or Without DIABETES - KDIGO 2013)

NO Albuminuria  BP < 140 / 90 mmHg

Albuminuria  > 30 mg / d*
  BP < 130 / 80 mmHg
  *(“Micro”-albuminuria term is deleted!)

Use ACEI or ARB’S if > 30mg /d Albuminuria

Lifestyle:
  BMI > 20 – 25, Salt < 5 gm (2000 mg Na)
  Exercise 30 min 5 X / week
Mono /Combo - Therapy

1) Average MONO therapy (Placebo corrected)

9.1 / 5.5 mm Hg BP Reduction
(in Stage I Hypertension, Law BMJ, 2003)

2) NHANES (2007-2010) Combination Therapy to Goal

75% needed 2 drugs
25% needed 3 drugs
## Majority of Patients Need Multiple Medications to Help Reach Goal of \(<140/90^*\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Percent of Patients Treated With (\geq 2) Agents</th>
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<tr>
<td>ALLHAT (N=33,357)</td>
<td>62%</td>
</tr>
<tr>
<td>CONVINCE (N=16,476)</td>
<td>72% (verapamil) 74% (atenolol or HCTZ)</td>
</tr>
<tr>
<td>ASCOT-BPLA* (N=19,257)</td>
<td>78%</td>
</tr>
<tr>
<td>INVEST† (N=22,576)</td>
<td>82% (verapamil) 83% (atenolol)</td>
</tr>
<tr>
<td>LIFE‡‡ (N=9,222)</td>
<td>85% (losartan) 85% (atenolol)*</td>
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</table>

*Included a lower goal for diabetics = 130/80 mm Hg  
†Included a lower goal for diabetics = 130/85 mm Hg  
‡‡ Excluded patients off study drugs

Doubling of Mono - vs. Combination Therapy

Metanalysis of 11,000 patients in 42 trials

COMBO - THERAPY = 5 X more likely to ACHIEVE BP GOAL (in 6 month)
Maximal Achieved Goal in ANY Hypertensive Trial

= 89% at 9 months

Co-team of MD, Pharm D (Carter et. al. JCH 08)
Combos to **AVOID** in Hypertension

1) Beta Blocker + Verapamil or Diltiazem

2) Beta Blocker + Centrally acting antihypertensives
   (Clonidine)

**DUAL RAAS BLOCKADE:**

ACE Inhibitors + Angiotensin Receptor Blockers
   (ONTARGET trial)

Aliskiren + ACE inhibitors (ALTITUDE trial)

Aliskiren + ARB

(ADACTONE and ACEI or ARB excluded)
OBESITY and HYPERTENSION

68% of US adults are Overweight (BMI > 25)
33% Obesity (BMI > 30)
33 to 38% Metabolic Syndrome

~75% of Obese patients have Hypertension

1/3 of US adults (18 and older) have Hypertension

50% of all Hypertensive have BMI > 30

Linear Relationship between Weight and SBP (BMI 25-35):

10 lbs Weight Gain ~ 4.5 mmHg Systolic BP Increase
Mechanism of Hypertension in Obesity

1) Activation of RAAS (Adipocytes produce ALL components of RAAS)
2) Elevated ALDOSTERONE levels
3) Activation of the Sympathetic Nervous System
   (Leptin acting centrally)
4) Increased Renal Tubular Na - Reabsorption
   (expanded ECV and Vasoconstriction)
Therapy in Obesity - Hypertension

Options considering Mechanisms: NO NATIONAL GUIDELINES

- RAAS Blockade (ACEI or ARB)
- DIURETICS
- ALDACTONE
- VASOdilating BETA BLOCKERS

Traditional BB will cause weight gain and have negative metabolic effects: HYPERLIPIDEMIA and HYPERGLYCEMIA

- WEIGHT LOSS
  1) Diet (DASH)  2) Exercise  3) Bariatric surgery  4) Drugs (3 recent FDA approvals)

  (10 kg Weight Loss = up to 10 – 12 mm Hg Systolic BP Decline)
Resistant and Refractory Hypertension

Definitions:

**Resistant**
- Uncontrolled on 3 or more drugs incl. Diuretic and BP still > 140/90 or
- Controlled on 4 or more drugs with BP < 140/90

**Refractory**
- Uncontrolled on 5 or more classes of drugs and BP still > 140/90

Incidence:

- Resistant Hypertension: 10-15% of all treated Hypertensive Patients
- Refractory Hypertension: 10% of all Resistant Hypertension

Concern:

- High Risk for CV Events (CVA, CAD, CHF)
- Target Organ Damage (LVH, Albuminuria, CKD)
- Framingham CAD Score 2x compared with "essential Hypertension"
Issues in Resistant Hypertension

1) 1/3 controlled by ABPM and therefore NOT “Resistent” (*)

2) Adherence

   German study using urine and blood drug analysis had only 53% compliance (#)

3) Low Use Mineralocorticoid Antagonists:

   Aldactone, Eplrenone, Chlorthalidone

   NHANES 3%
   REGARDS 18%

Jung O et al. J.Hypertens 2013;31:766-774
REGARDS Study: Calhoun DA et al. Hypertension 2014;63:451
ABPM in Resistent Hypertension

8,295 Spanish patients with Resistent Hypertension - Uncontrolled by Office BP (on 3 drugs, including a Diuretic)

ABPM showed 1/3 controlled with BP < 140/90 mmHg

De la Siera et.al. Hypertension 2011;57:898-902
Stage II Hypertension (BP >160 / 100)

ASH and ISHIB Recommendations:

Initiate single pill combination therapy with **ACE inhibitor and CCB Combination** because of

20% fewer CV Events (CVA, MI) and CKD Progression compared to

ACEI / HCTZ Combination (ACCOMPLISH Trial 2008)

ASH American Society of Hypertension
ISHIB International Society of Hypertension in Blacks

Byrd JB et al, Current Hypertension Reports 2014, 16: 419
Guidelines to Resistent Hypertension

Exclude **White Coat Effect** (24 hr AMBP, Home BP)
Assure **Compliance** (MEMS or Urine screen for drugs)
Use correct 3 drug regimen
  - RAAS blocker, CCB and Diuretic (**Chlorthalidone**)
Use **Full Dosing** of above listed drugs
Evaluate for
  - ALDO excess (20% !) Aldo / Renin ratio, CKD, OSA, Pheo
Check for
  - **Excessive Salt Intake** (> 6 gm) = 24 hr Urine
  - NSAID Use (may raise BP by 10 / 5 mmHg)
  - Drug Abuse (Cocaine, Amphetamine, ETOH excess)

Add **ALDACTONE** 12.5 – 25 mg / day
USA: Primary Care Study

140 RH Patients with 24 hr ABPM and MEMS
(Medication Electronic Monitoring System)

- 22% White Coat Effect
- 29% Poor Drug Adherence
- 44% Suboptimal Therapy
- 38% Beta Blocker as 1 of 3 drugs

NO Patient on Aldactone or Chlorthalidone

Hydrochlorothiazide (HCTZ) vs. Chlorthalidone (CLD)

HCTZ  No outcome data!

CLD  Advantages over HCTZ:

- Longer duration of action
- Effective to eGFR ~ 30 ml (HCTZ above 40 ml ONLY)
- Up to 8 mmHg Lower SBP
- Lower Microalbuminuria levels

SHEP (22 year follow up) = for each month on CLD

- ONE extra day of life expectancy vs. HCTZ (= 264 days)

(AHA) Hypertension Journal and JAMA, Dec. 2011
NSAID use in Hypertension and CKD

- Lower Efficacy of ALL Antihypertensive Drugs, incl. Diuretics by 10-15% (except CCB’s)

- Cause Salt Sensitivity (> 3-4 day use)

- In CKD 3 (< 60 ml GFR)
  - Reduce GFR by 10-15%
  - Risk of Hyperkalemia, AKI and CHF
BP Variability

Definition: Visit to Visit BP levels above / below 140 / 90 mmHg (SBP +/- 10 mmHg)

Multiple studies (INVEST, UK-TIA) in 50 to 75% variability

2.2 to 3.5 X greater
- Mortality
- CV events
- CVA's

Mechanisms include
- Increased vascular stiffness
- Large Pulse Pressure

Dipping vs. NON Dipping

Circadian mean nocturnal BP falls by 10-20% from daytime = DIPPING

“NON-dipping” < 10% nightly BP fall

Clinical Relevance of NON-dipping:

- Endothelial Dysfunction
- LVH
- TOD greater (i.e. Albuminuria)
- Mortality higher

Blood Tests for NON-dipping (new onset HTN only and before therapy)

- Elevated hs-cTnT and NT-pro BNP

CAYLI, M.et.al. JCH 2013,15:731
SALT Sensitivity
( no clinical test available )

- Hypertension (~ 50 %)
- CKD
- Diabetes
- Afro-Americans
- Elderly
- Obesity
- NSAID use (beyond 4-5 days)
Salt and Hypertension

BP differences of 6 vs. 9 gm SALT
(2400 vs. 3600 mg Na)

- Caucasian - 5.5 / - 2.8 mmHg
- Blacks - 6.4 / -2.4 “
- Asian - 10.2 / -2.6 “

Issues with Salt restrictions:

- 80% of salt in processed food / dining out
- No good test for salt sensitivity

Triglyceride / HDL Ratio
- \( > 3.5 \) Caucasian, \( > 3.0 \) Latino
- \( > 3.5 \) Afro American = Suggestive of Salt Sensitivity

? J-Curve for healthy people for SALT

Best (except in CHF) \( > 3 \text{ gm} \) but \( < 6 \text{ gm} \) SALT

( Negative CV outcome in general population: 2 trials, 8 year follow up (RAAS activation?)

JAMA 6/12
Potassium and BP

- Causes Renal Vasodilation and Natriuresis
- Lowers BP

50 meq. Of K → BP 4.4 / 2.5 mmHg

DASH diet: BP reduced by 11.6 / 5.3 in Hypertension
High K* blunts High Na* Intake ( Normal BP )

1,285 People, General Public collected 12 hr Urine Overnight

86 % Salt > 6 gm ( 2400 mg Na )
88 % K < 4.7 gm ( 112 mm/L )

1st Quartile Na vs 4th Quartile Na = BP up by 8 / 7 mmHg
1st Quartile K vs. 4th : K = BP down by 6 / 4 mmHg

Conclusion:

High K* Intake CANCELS High Na* Intake in Normotension

Rodrigues SL. et.al. JASH ,2014 Jan.2 ( on line )
Drug Adherence in Hypertension

Retrospective electronic monitoring of 4,783 patients using once / day drug for Hypertension:

12 month follow up = 50% STOPPED Drug

1 Day Omission = 42%
2 Consecutive Days Missed = 15%
3 Or More Consecutive Days = 42%

Drug Adherence in Hypertension and Stroke

Finnish Population study of 73,527 hypertensive patients followed from 1995 - 2007

NON - Adherent patients:

OR 3.01 (CI 2.37 - 3.83) HIGHER Odds of Stroke Death

The Poorer the Adherence the Higher the Death and Hospitalization Rate

Hypertension and Dementia

Hypertension is associated with Vascular Dementia
( Micro-Infarcts, CVA and Alzheimer’s Disease )

Systolic BP 110-139 vs. > 160 mmHg
OR (odds ratio) = 4.3 for Dementia (Honolulu Heart)

Antihypertensive Therapy Lowers Risk of Alzheimer’s Disease
Hazard Ratios: HCT 0.51, ACEI 0.5, ARB 0.31
CCB 0.62, BB 0.58
Gingko Evaluation / Memory study: 1900 pat. = 6.1 year F/U

Proteinuria (> 300 mg/d) is associated with
Cognitive Decline (even without CKD)
ASH Hypertension Guidelines 2013

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Age 60 to 79 < 140 / 90 mmHg
Age 50 and younger < 140 / 90 mmHg

< 130 / 80 (if tolerated)

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with Proteinuria < 130 / 80 mmHg (no consensus)

ASH Guidelines for Hypertension: J. Clinical Hypertension, 12 / 2013