MANAGEMENT OF HYPERTENSION AND DYSLIPIDEMIA IN PATIENTS WITH DIABETES

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International Diabetes Center; Adjunct Assistant Professor, University of Minnesota Department of Family Practice

Outline

- CVD Trends in Patients with Diabetes
- Management of Dyslipidemia
- Management of Hypertension
People with diabetes die younger…
….and cardiovascular disease is the main killer

Addressing Multiple Risk Factors

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The Emerging Risk Factors Collaboration, NEJM 2011

Gaede et al, NEJM, 2008
Addressing Multiple Risk Factors

Priorities of Care for Adults with Diabetes

**Diagnosis–Prevention**

Dx = A1C ≥6.5%, fasting ≥126 mg/dL (7.0 mmol/L), or random ≥200 mg/dL (11.1 mmol/L) + symptoms

**Self-Management Knowledge and Skill**

- Monitoring
- Medication
- Risk reduction
- Living & coping
- Problem solving
- Physical activity
- Food plan & nutrition

**Glucose**

- Hemoglobin A1C
  - Target < 7.0%
- SMBG
  - Pre 70-130 mg/dL (3.9-7.2 mmol/L)
  - Post <180 mg/dL (<10 mmol/L)

**Lipids**

- Annual Lipid Profile

**Hypertension**

- Blood Pressure
  - (every visit)
  - Dx and Rx < 140/90

**Macrovascular Complications**

- ASA, tobacco, ACEI/ARB, statin

**Microvascular complications**

**Other essentials of care**

- Hospital care
- Foot care
- Dental care
- Immunizations

**Annual Screening**

- Nephropathy
  - Microalbumin screening
  - Calculated GFR
  - Dilated retinal exam
  - Neuropathy
  - Neuro and foot exam
  - Sexual health

**Statin?**

© 2015 International Diabetes Center.
Relative Risk Reductions: Lipids

Effects on MAJOR VASCULAR EVENTS, per mmol/L reduction in LDL cholesterol, among participants with diabetes

<table>
<thead>
<tr>
<th>Major vascular event and prior diabetes</th>
<th>Events (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>775 (5.3)</td>
<td>0.78 (0.69 - 0.87)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2561 (7.2)</td>
<td>0.77 (0.73 - 0.81)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7.4)</td>
<td>0.77 (0.74 - 0.80)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>491 (5.2)</td>
<td>0.75 (0.64 - 0.88)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2122 (6.0)</td>
<td>0.70 (0.62 - 0.79)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2620 (5.6)</td>
<td>0.76 (0.73 - 0.80)</td>
</tr>
</tbody>
</table>

1 mmol/L [39 mg/dL] LDL reduction = 20% relative reduction in major vascular events

American Diabetes Association LDL Cholesterol Targets 2014 vs. 2015

- **LDL-C Goal Diabetes**
  - 2014: LDL-C <100 mg/dL (<2.6 mmol/L)
  - 2015: No target

- **LDL-C Goal Diabetes + CVD**
  - 2014: LDL-C <70 mg/dL (<1.8 mmol/L)
  - 2015: No target

ADA Clinical Practice Recommendations, Diabetes Care 2014; 37 Suppl 1; ADA Standards of Medical Care, Diab Care 2015; 38 Suppl 1
Rationale

- Statin therapy benefits most diabetes patients
- No LDL targets, consistent with 2013 AHA/ACC recommendations

Diabetes Care

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association

Diabetes Care Publish Ahead of Print, published online August 5, 2015
**ADA/AHA 2015 Scientific Statement on Prevention of CVD in Type 2 DM: Cholesterol**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Specific recommendation and Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>Patients with diabetes mellitus between 40 and 75 years of age with LDL-C between 70 and 189 mg/dl should be treated with a moderate-intensity statin*† (ACC/AHA Class I; Level of Evidence A) (ADA Level of Evidence A). Statin therapy of high intensity† should be given to individuals with diabetes mellitus between 40 and 75 years of age with a ≥7.5% estimated risk of ASCVD (ACC/AHA Class IIa; Level of Evidence B). Among individuals with diabetes mellitus who are &lt;40 or ≥75 years of age, practitioners should evaluate the benefit of statin treatment (ACC/AHA Class IIa; Level of Evidence C). Evaluate and treat patients with fasting triglycerides &gt;500 mg/dl.</td>
</tr>
</tbody>
</table>

*ADA/AHA Diab Care 2015; Online August 5*

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*Circulation. published online November 12, 2013;*
Overview of ACC/AHA Cholesterol Treatment Guidelines

- 4 Statin Benefit Groups Identified
- No specific LDL-C or Non-HDL-C Targets
- Primary Prevention for Individuals without Diabetes and LDL-C 70-189 mg/dL (1.8-4.9 mmol/L) based on Pooled Cohort Equation 10-Year ASCVD Risk ≥7.5%
- Concept of Low, Moderate and High-Intensity Statin Therapy

4 Statin Benefit Groups

1. Individuals with clinical ASCVD (ACS, MI, angina, revascularization, stroke, TIA, PAD)
2. Individuals with LDL-C ≥190 mg/dL (4.9 mmol/L)
3. Individuals 40-75 years of age with diabetes and LDL-C 70-189 mg/dL (1.8-4.9 mmol/L)
4. Individuals w/o clinical ASCVD or diabetes who are 40-75 years of age and LDL-C 70-189 mg/dL (1.8-4.9 mmol/L) and 10 year ASCVD risk ≥ 7.5%

Stone et al., Circulation. 2013; Nov Online.
### Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40)–80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td><strong>Pravastatin 10–20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20–40 mg</strong></td>
<td><strong>Lovastatin 20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td><strong>Fluvastatin 20–40 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lovastatin 40 mg</strong></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin 40 mg bid</strong></td>
<td><strong>Fluvastatin 40 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pitavastatin 2–4 mg</strong></td>
<td><strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

Statins associated with modest increased risk for diabetes (10-25%), yet CV benefit outweighs risk of diabetes

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### Intravascular Ultrasonography (IVUS)

- IVUS allows the quantification of plaque volume and objective measures of plaque progression or regression.
  - PAV: Percentage Change in Atheroma volume
  - TAV: Change in mm³ of total atheroma volume
  - Color IVUS may help identify vulnerable plaques.

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Can statins reverse atherosclerosis?

Answer: Yes in some patients and stops progression in others.

Results of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study: (2004): ACS pts with IVUS at baseline and 18 months. No progression on atorvastatin 80 mg vs. progression on pravastatin 40 mg.

Case Study: Miguel

Miguel is a 43 year old with type 2 diabetes for 2 years; family history type 2 diabetes; works as real estate broker; non-smoker

Problem List: Type 2 DM, HTN and dyslipidemia

Current Labs/BP/Weight:
A1C 7.2% (55 mmol/mol), Total –C 168 mg/dL (4.3 mmol/L), LDL 91 mg/dL (2.3 mmol/L), HDL 32 mg/dL (0.83 mmol/L), triglycerides 225 mg/dL (2.5 mmol/L)
BP: 126/75 mmHg; 185 lb (84 kg); BMI 29

Current Therapy:
Metformin 1000 mg bid; irbesartan/hydrochlorothiazide (Avalide) 150/12.5 mg; atorvastatin 20 mg; aspirin 81 mg

Do you increase his statin dose?
ASCVD Risk for Miguel

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Miguel Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M or F</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>43</td>
</tr>
<tr>
<td>Race</td>
<td>AA or WH (others)</td>
<td>WH</td>
</tr>
<tr>
<td>Total-Chol.</td>
<td>mg/dL</td>
<td>168</td>
</tr>
<tr>
<td>HDL-C</td>
<td>mg/dL</td>
<td>32</td>
</tr>
<tr>
<td>SBP</td>
<td>mmHg</td>
<td>126</td>
</tr>
<tr>
<td>HTN Treatment</td>
<td>Y or N</td>
<td>Y</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y or N</td>
<td>Y</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y or N</td>
<td>N</td>
</tr>
</tbody>
</table>

10 yr CV Risk = 13%

AHA ACC Omnibus Risk Estimator [http://my.americanheart.org](http://my.americanheart.org)

Primary Prevention in Diabetes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>NHLBI Evidence Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention in Individuals With Diabetes Mellitus and LDL–C ≥70–189 mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.</td>
<td>A (Strong)</td>
<td>19, 29-34, 40</td>
</tr>
<tr>
<td>2. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk if not contraindicated.</td>
<td>E (Expert Opinion)</td>
<td>---</td>
</tr>
<tr>
<td>3. In adults with diabetes mellitus, who are &lt;40 or &gt;75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.</td>
<td>E (Expert Opinion)</td>
<td>---</td>
</tr>
</tbody>
</table>

Stone et al., Circulation, 2013; Nov Online.
Who does not endorse the new guidelines?

American Association of Clinical Endocrinologists, The European Society of Cardiology, The International Atherosclerosis Society, National Lipid Association

- Certain at-risk populations of patients will be underserved by them.
- The focus on large-scale randomized controlled trials is "highly restrictive" and leaves out much new information.
- The controversial risk calculator is “based on outmoded data and has not been validated”.
- Very-high-risk patients may need non-statin agents to achieve LDL reduction that will further reduce their coronary heart disease risk.

European Society of Cardiology Guidelines for Management of Dyslipidemia

<table>
<thead>
<tr>
<th>Dyslipidaemia in diabetes</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy is recommended in patients with T1DM and T2DM at very high-risk (i.e. if combined with documented CVD, severe CKD or with one or more CV risk factors and/or target organ damage) with an LDL-C target of &lt;1.8 mmol/L (&lt;70 mg/dL) or at least a ±50% LDL-C reduction if this target goal cannot be reached.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Statin therapy is recommended in patients with T2DM at high risk (without any other CV risk factor and free of target organ damage) with an LDL-C target of &lt;2.5 mmol/L (&lt;100 mg/dL).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Statins may be considered in T1DM patients at high risk for cardiovascular events irrespective of the basal LDL-C concentration.</td>
<td>IIB</td>
<td>C</td>
</tr>
<tr>
<td>It may be considered to have a secondary goal of non-HDL-C &lt;2.6 mmol/L (&lt;100 mg/dL) in patients with DM at very high risk and of &lt;3.3 mmol/L (&lt;130 mg/dL) in patients at high risk.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Intensification of statin therapy should be considered before the introduction of combination therapy with the addition of ezetimibe.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of drugs that increase HDL-C to prevent CVD in T2DM is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
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**Current Therapy:**
- Metformin 1000 mg bid; irbesartan/hydrochlorothiazide (Avalide) 150/12.5 mg; atorvastatin 20 mg; aspirin 81 mg

Do you start combination therapy for dyslipidemia?

**Combination Therapy for Dyslipidemia**

**Rationale**
- ACCORD trial showed the addition of fenofibrate to statin therapy did not reduce CV events compared to statin therapy alone
- AIM-High trial was stopped early due to lack of CV benefit of adding niacin to statin therapy vs. placebo
Statin & Fibrate Combo Therapy in Type 2 DM
Results of the ACCORD Lipid Study

- Addition of fibrate to statin increased HDL and decreased triglyceride modestly compared to placebo
- Trend towards benefit in patients with triglyceride ≥204 mg/dL and HDL ≤34

What about Niacin?

- Improves all major lipid fractions
- The most HDL raising drug (15-35%)
- LDL ↓ 15-35%; TG ↓ 20-50%; LP(a) ↓ 25%
- Raises plasma glucose ~8-9 mg/dL (0.4-0.5 mmol/L)
- Poor side effect profile (flushing)
- Limited established prevention of CVD
  - AIM-HIGH stopped 05/11 – no CVD benefit
  - HPS2 –THRIVE stopped 12/12 - no CVD benefit
AIM-HIGH Stopped Early

- Patients with vascular disease, LDL to goal on statin and Zetia if needed, HDL <40 mg/dL (1.03), and triglycerides >160 mg/dL (1.79)
- Simvastatin 40 mg +/- niacin
  - Poor side effect profile with niacin
- Study stopped early. No difference in MI, CVA, ACS, or vascular death with niacin.
- Small excess of ischemic stroke on niacin. 9 of those patients had stopped niacin.

HPS2-Thrive: Effect of Extended Release Niacin/Laropiprant on CV Events

- Risk ratio 0.96 (95% CI 0.90 – 1.03)
- Logrank P=0.29

Update: January, 2013 EMA suspends marketing of nicotinic acid/laropiprant (Tredaptive, Trevaclyn and Pelzont) due to HSP2-Thrive results and increased risk of myopathy, skin and gastrointestinal side effects.
What about Ezetimibe (Zetia)?

- Cholesterol absorption inhibitor
- Modest LDL lowering (15-20%) alone or when added to statin
- Generally well tolerated
- ENHANCE Trial showed no benefit in carotid intima-media thickness above statin alone
- Modest reduction CVD in Improve-It

**Primary Endpoint — ITT**

*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event Rate (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>34.7%</td>
<td>50</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>32.7%</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.936 CI (0.887, 0.988)
p=0.016

2742 events, 2572 events

7-year event rates
What about Omega-3 Fatty Acids?

- Lowers TG 30-40%, LDL↑3-5% (DHA responsible – new EPA-only formulation Vascepa 01/13); HDL 0%
- Lovaza, prescription for omega 3-acid
  - Approved by FDA for triglycerides ≥500 mg/dL (5.6 mmol/L)
  - Usual dose 1000 mg capsule qid or 2 capsules bid
  - Lowers triglycerides 20-50%; may raise LDL
- Vascepa – 4000 mg/day divided as 2 capsules bid
- Limited CVD outcome data
  - ORIGIN study negative

CV Outcomes with Omega-3 Fatty Acid Supplementation in ORIGIN Trial

New Class of Lipid Medication

- Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors
  - Monoclonal antibodies to PCSK-9
  - Injectable medication (every 2 weeks to monthly)
  - Reduce LDL >60% on top of statin
  - Alirocumab (Praluent) approved by FDA and Evolocumab (Repatha) approved by EMA and likely soon to be approved by FDA
  - Expensive medications e.g. Praulent is $14,600/year (U.S. dollars)

PCSK9 Mode of Action

Dadu, R. T. & Ballantyne, C. M. (2014) Lipid lowering with PCSK9 inhibitors
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2014.84
LDL Lowering Potential of Alirocumab (Praluent)


PCSK9 Indications

**Evolocumab (Repatha)**

Primary Hypercholesterolemia and Mixed Dyslipidemia
- In combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolemia
- Adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia in combination with other lipid-lowering therapies.

**Alirocumab (Praluent)**

1. Adults with atherosclerotic cardiovascular (CV) disease for additional lowering of LDL-C when used as an adjunct to diet and maximally-tolerated statin therapy
2. Adults with heterozygous familial hypercholesterolemia for additional lowering of LDL-C, as an adjunct to diet and maximally-tolerated statin therapy
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**Diagnosis–Prevention**
- Dx = A1C ≥6.5%, fasting ≥126 mg/dL (7.0 mmol/L), or random ≥200 mg/dL (11.1 mmol/L) + symptoms

**Self-Management Knowledge and Skill**
- Monitoring
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- Hemoglobin A1C
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- Annual Lipid Profile
  - Statin?
- SMBG
  - Pre 70–130 mg/dL (3.9–7.2 mmol/L)
  - Post <180 mg/dL (<10 mmol/L)

**Lipids**
- Blood Pressure
  - (every visit)
  - Dx and Rx < 140/90

**Hypertension**
- Microvascular complications
- ASA, tobacco, ACEI/ARB, statin

**Macrovascular Complications**
- Annual Screening
  - Retinopathy
  - Neuropathy
  - Nephropathy
  - Microalbumin screening
  - Calculated GFR
  - Dilated retinal exam

**Other essentials of care**
- Hospital care
- Foot care
- Dental care
- Immunizations

**History of Blood Pressure Targets**

*American Diabetes Association*

- 1980-1990: Treat to “normal” BP
  - Diabetes is CVD equivalent
- 1995: <130/85 mmHg
- 2000-2012: <130/80 mmHg
  - HOT Trial
- 2013-2014: <140/80 mmHg
  - ACCORD Trial
- 2015: 140/? mmHg
New Diastolic Blood Pressure Target in 2015

- Individuals with diabetes should be treated to a diastolic blood pressure (DBP) <90 mmHg. A
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. B

Rationale

- Previous diastolic BP target <80 mmHg based on post hoc analysis of Hypertension Optimal Treatment (HOT trial)
- Consistent with JNC 8 BP targets

Role of Intensive BP Control in Diabetes

Results of the ACCORD BP Study

- Average 3.4 antihypertensive medications in intensive vs. 2.2 in standard care
- Serious adverse events occurred 3.3% intensive vs. 1.3% standard care
- What is the appropriate BP target in type 2 diabetes???
JNC 8 Guidelines are not without controversy
1. Not endorsed by any large professional association (e.g. ACC/AHA)
2. Not all panel members agreed with raising SBP >150 mmHg in individuals ≥60 years
3. May cause initiation of pharmacotherapy too early in “low risk” individuals

JNC 8 Recommendations for Individuals with Diabetes
□ In individuals ≥18 years, initiate pharmacologic treatment when BP ≥140/90 mmHg and treat to goal BP <140/90 mmHg
□ In the general nonblack population initial pharmacotherapy treatment should be:
  □ Thiazide diuretic
  □ Calcium channel blocker
  □ ACE-I or ARB
□ In the general black population initial pharmacotherapy treatment should be:
  □ Thiazide diuretic or calcium channel blocker
Age and Relationship to Systolic and Diastolic Blood Pressure

### Stratification of Total CV Risk

<table>
<thead>
<tr>
<th>Blood Pressure (mmHg)</th>
<th>Other risk factors, asymptomatic organ damage or disease</th>
<th>Grade 1 HT</th>
<th>Grade 2 HT</th>
<th>Grade 3 HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High normal SBP 130–139 or DBP 85–89</td>
<td>Low risk</td>
<td>Moderate risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Grade 1 HT SBP 140–159 or DBP 90–99</td>
<td>Moderate risk</td>
<td>Moderate to high risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Grade 2 HT SBP 160–179 or DBP 100–109</td>
<td>Moderate to high risk</td>
<td>High risk</td>
<td>High to very high risk</td>
<td></td>
</tr>
<tr>
<td>Grade 3 HT SBP ≥180 or DBP ≥110</td>
<td>High to very high risk</td>
<td>Very high risk</td>
<td>Very high risk</td>
<td></td>
</tr>
</tbody>
</table>

- **BP** = blood pressure; **CKD** = chronic kidney disease; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **HT** = hypertension; **OD** = organ damage; **RF** = risk factor; **SBP** = systolic blood pressure.

### Multi-drug Therapy Needed to Control BP

<table>
<thead>
<tr>
<th>Systolic BP</th>
<th>Number of BP Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT (135 mm Hg)</td>
<td>2</td>
</tr>
<tr>
<td>IDNT (140 mm Hg)</td>
<td>3</td>
</tr>
<tr>
<td>RENAAL (140 mm Hg)</td>
<td>3.5</td>
</tr>
<tr>
<td>UKPDS (144 mm Hg)</td>
<td>2.7</td>
</tr>
<tr>
<td>ABCD (132 mm Hg)</td>
<td>2.8</td>
</tr>
<tr>
<td>HOT (141 mm Hg)</td>
<td>3.3</td>
</tr>
<tr>
<td>AASK (134 mm Hg)</td>
<td>2.8</td>
</tr>
</tbody>
</table>

2013 ESH/ESC Guidelines

Target SBP <140 mmHg
Target DBP <85 mmHg
ACE-I or ARB preferred
Don’t combine ACE-I and ARB

Diuretics for Treatment of Hypertension

- **Thiazides** are most effective; optimal dose 6.25-25 mg
  - Good in elderly
  - Good in African Americans
  - Good for isolated systolic HTN
  - Good for CHF pts or those with edema
- Metolazone can be used if Cr CL<30
- Spironolactone works well for many who don’t tolerate thiazide
- Loop diuretics (except torsemide) usually need to be given twice a day
Chlorthalidone vs. Hydrochlorothiazide

- Chlorthalidone - much longer half-life
  - may provide better 24 hr control with once daily dosing

<table>
<thead>
<tr>
<th></th>
<th>HCTZ</th>
<th>Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half–life (hrs)</td>
<td>8-15</td>
<td>45-60</td>
</tr>
<tr>
<td>(Long-term dosing)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Concentrates within Erythrocytes
  - Extends T ½
  - Buffers concentration effect: 8X increase in dose 25 → 200 mg QD leads to a 2 X increase in serum concentration

- Chlorthalidone is more potent than HCTZ (1.5 - 2 X)

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**ALLHAT**

Combined CHD in Participants with a History of Diabetes Mellitus or FG 126+ mg/dL at Baseline

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>1.02 (0.93-1.12)</td>
<td>0.64</td>
</tr>
<tr>
<td>L/C</td>
<td>1.03 (0.94-1.13)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Cumulative Combined CHD Event Rate vs. Years to Combined CHD Event
Dihydropyridine CCBs: The Swiss Army Knife of BP Meds

- No contraindicating medical conditions (CHF, diabetes, CKD, arrhythmias etc)
- Effective in all ages and ethnicity groups
- Good dose response curve
- Can be used with any other drug class, including non-dihydropyridine CCBs

Dihydropyridine CCBs: Dosing

- **Amlodipine**: 2.5-10 mg qd
- **Felodipine**: 2.5-20 mg qd
- **Isradipine**: 2.5-10 mg bid
- **Nicardipine SR**: 30-60 mg bid
- **Nifedipine ER**: 30-120 mg qd
- **Nisoldipine**: 20-60 mg qd
The Big Three Concept

- Thiazides, ACEI and CCBs
- All appear about equally effective
- Work well together

A Modest Proposal: 3 Drug Step-Care

- Step 1: Start any of the big 3 (ex lisinopril, hydrochlorothiazide or amlodipine)
  - If SBP >20 mmHg above goal start 2
- Step 2: If close to goal increase thiazide dose to 25 mg or amloidpine dose to 10 mg
  - Otherwise add second drug
- Step 3: Add 3rd drug (CCB, ACE, diuretic)
Possible Combinations of Antihypertensive Drugs

Green dashed line: Useful w. some limitations
Black dashed line: Possible, less well tested

Green line: Preferred Combination
Red line: Not recommended

Bedtime Dosing of One BP Medication in Resistant Hypertension

MAPEC Study: Benefit of Taking BP Medications at Bedtime

- 2,156 pts with HTN randomized to group taking all BP medications in AM vs 1 or more taken at bedtime
- Reduced non-dipping (34% vs 62% p<0.001)
- Lower # CVD events 187 vs 68 p<0.001
- Less CVD mortality, MI, ischemic and hemorrhagic stroke


Questions?