CVD risk management in diabetes

Anthony L. McCall MD, PhD, FACP
James M. Moss Professor of Diabetes University of Virginia Health System
Vice President for Clinical Science
Endocrine Society

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Disclosure to Participants

• Consultant to Novo Nordisk on cardiovascular risk and diabetes medications
• VP Clinical Science - Endocrine Society—the opinions expressed are my own not that of the Society
• NIH funding on 4 grants

Learning Objectives

After completion of the presentation, the participant will be able to:
1. Discuss appropriate BP targets for people with diabetes and their rationale
2. Indicate controversies about lipid and dyslipidemia management in diabetes
3. Relate new information how diabetes medications may affect cardiovascular risk

Patient case

• 49 y/o AA woman with type 2 DM x 9 years. HTN (HCTZ, lisinopril), dyslipidemia, suboptimal DM control (on 2 g metformin), no known CAD and no symptoms.
• Exam shows BMI 33.5, BP 138/85, some neuropathy and NPDR, - optometry exam.
• LAB: A1c 7.9%, TC 196 HDL 36 TG 198, LDL 121. ACR = 79 (normal < 30)
• What is your approach to CAD risk reduction in this person?
Incidence of Fatal or Nonfatal MI During a 7-Year Follow-up: East-West Study

<table>
<thead>
<tr>
<th>Incidence During Follow-up (%)</th>
<th>Non-DM with prior MI</th>
<th>Non-DM with no prior MI</th>
<th>DM with prior MI</th>
<th>DM with no prior MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.8</td>
<td>3.0</td>
<td>0.5</td>
<td>7.8</td>
<td>3.2</td>
</tr>
</tbody>
</table>


Events per 100 person-yr: P <0.001

Diabetes is a Cardiovascular Disease Equivalent

Cumulative Incidence of All-cause Mortality

Cumulative Incidence of CVD Mortality

Unadjusted Mortality According to Glucose Metabolism: Data from AusDiab

Diabetes is a Cardiovascular Disease Equivalent

Cardiovascular Disease

- CVD is the leading cause of morbidity & mortality for those with diabetes.
- Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for ASCVD.
- Diabetes itself confers independent risk
- Control individual cardiovascular risk factors to prevent/slow CVD in people with diabetes.
- Systematically assess all patients with diabetes for cardiovascular risk factors.

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75 - S87

Cardiovascular disease men vs. women

- Overall more heart disease in women than men although earlier onset for men (hint: women live longer) and highest rates are in the elderly
- Relative risk of CAD and stroke higher in women than men “DM as equalizer”
- Mortality is worse in women
- Prevention treatment of heart disease is less used in women than men
- Alarming women 35 to 44 years of age show CHD mortality rates increased 1.3% annually between 1997 and 2002

Hypertension

- Common DM comorbidity
- Prevalence depends on diabetes type, age, BMI, ethnicity
- Major risk factor for ASCVD & microvascular complications
- In T1DM, HTN often results from underlying kidney disease.
- In T2DM, HTN coexists with other cardiometabolic risk factors.

Blood Pressure Control & T2DM

Action to Control Cardiovascular Risk in Diabetes (ACCORD):
- Does SBP <120 provide better cardiovascular protection than SBP 130-140? No.

ADVANCE-BP:
- Significant risk reduction

Advance BP trial

- 28% in renal events, 24% in cardiovascular death and 18% in all-cause mortality. Fixed dose of perindopril (4mg), indapamide 1.25 mg, and any CCB.
- > 11,000 subjects from 20 countries.
- Reduction in SBP by 7.1 mm Hg, in DBP by 2.9 mm Hg and in A1c by 0.61% points in the combined routine BP lowering and intensive blood glucose-control group.
- Results after average 4.3 years of follow-up resulted in a relative risk reduction as noted above and next slide:

Chalmers et al. (Hypertension. 2014;63:259-264.)

Advance results

- Figure 2. Effects of the combination of perindopril (ACEI) and indapamide (diuretic) [randomized study drugs] with calcium channel blockers (CCBs) at any visit (nonstudy drug) on major cardiovascular (CV) events and death compared with participants on placebo who never received CCBs.
Recommendations: Hypertension/ Blood Pressure Control

Screening and Diagnosis:
• Blood pressure should be measured at every routine visit. B
• Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. B

Systolic Targets:
• People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. A
• Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. C

Diastolic Targets:
• Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. A
• Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. C

Diastolic Targets (3)
• Patients with BP >120/80 should be advised on lifestyle changes to reduce BP. B
• Patients with confirmed BP >140/90 should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. A

Diastolic Targets (4)
• Treatment for hypertension should include A
  – ACE inhibitor
  – Angiotensin II receptor blocker (ARB)
  – Thiazide-like diuretic
  – Dihydropyridine calcium channel blockers
• Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.

Recommendations: Hypertension/ Blood Pressure Treatment (2)
• Patients with confirmed office-based blood pressure >160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. A
• Lifestyle intervention including:
  – Weight loss if overweight
  – DASH-style diet
  – Moderation of alcohol intake
  – Increased physical activity

Recommendations: Hypertension/ Blood Pressure Treatment (3)
• Treatment for hypertension should include A
  – ACE inhibitor
  – Angiotensin II receptor blocker (ARB)
  – Thiazide-like diuretic
  – Dihydropyridine calcium channel blockers
• Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.
Recommendations: Hypertension/Blood Pressure Treatment (4)

- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio $>300$ mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted.

**American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75–S87**

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**ACCORD BP Kaplan-Meier Analyses of Selected Outcomes**

Despite small CVA Benefit, there is NO Evidence of overall CV benefit.

Side effects were Troublesome leading To AKI, K+ problems, Syncope, etc.

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**JNCG 8 getting started**

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**JNC-8 minority report**

Substantial reductions have occurred in ASCVD rates if we raise SBP guidelines, will we see successes lessen?

Table 1. U.S. Cardiovascular Disease Death Rates for Persons Younger and Older Than 65 y

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**Minority concerns JNC-8**

“We, the panel minority, believed that evidence was insufficient to increase the SBP goal from its current level of less than 140 mm Hg because of concern that increasing the goal may cause harm by increasing the risk for CVD and partially undoing the remarkable progress in reducing cardiovascular mortality in Americans older than 60 years.”

**Recommendations for Statin Treatment in People with Diabetes**

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**Age** | **Risk Factors** | **Statin Intensity**
--- | --- | ---
>75 years | ASCVD risk factors | Moderate or high
60–74 years | ASCVD risk factors | Moderate or high
55–59 years | ASCVD risk factors | Moderate or high
50–54 years | ASCVD risk factors | Moderate or high
45–49 years | ASCVD risk factors | Moderate or high
40–44 years | ASCVD risk factors | Moderate or high
35–39 years | ASCVD risk factors | Moderate or high
30–34 years | ASCVD risk factors | Moderate or high
**American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75–S87**
**Recommendations: Lipid Management (4)**

- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). E

- Ezetimibe + moderate intensity statin therapy provides add'l CV benefit over moderate intensity statin therapy alone; consider for patients with a recent acute coronary syndrome w/ LDL ≥ 50mg/dL or in patients with a history of ASCVD who can’t tolerate high-intensity statin therapy. E

**Recommendations: Lipid Management (5)**

- Combination therapy (statin/fibrate) doesn’t improve ASCVD outcomes and is generally not recommended. A

- Combination therapy (statin/niacin) hasn’t demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended. A

- Statin therapy is contraindicated in pregnancy. B

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**High- and Moderate-Intensity Statin Therapy**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL by ≥50%</td>
<td>Lower LDL by 30% - &lt;50%</td>
</tr>
<tr>
<td>Rosuvastatin 40-80 mg</td>
<td>Rosuvastatin 10-20 mg</td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td>Pravastatin 5-10 mg</td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 20-40 mg</td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td>Pitavastatin 2-4 mg</td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

* Once-daily dosing. XL, extended release

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**Highlights of 2013 Guidelines**

- No LDL-C or non-HDL-C treatment targets
- Unavailable to find RCT data to support specific cutoffs for therapy
- Appropriate intensity of therapy (high or moderate) should be applied to risk groups
- Non-statin therapies do not provide acceptable ASCVD risk reduction compared to potential for adverse events.

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**Highlights of 2013 Cholesterol Guidelines - AHA/ACC**

- Statin therapy recommended in 4 groups:
  1. Individuals with known ASCVD*, without Class II-IV heart failure or receiving hemodialysis
  2. Individuals with LDL-C ≥190 mg/dL
  3. Individuals 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dL
  4. Individuals 40 to 75 years of age with estimated 10-year ASCVD* risk ≥7.5% and LDL-C 70-189 mg/dL

ASCVD = Atherosclerotic cardiovascular disease

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**Highlights of 2013 Guidelines**

- New Pooled Cohort Equations for atherosclerotic cardiovascular disease (ASCVD) risk assessment
  - Predict 10-year risk of stroke & myocardial infarction
    - Former guidelines focused only on myocardial infarction
    - Framingham Risk Score
    - Separate equations for nonwhite populations
      - White and black men and women
      - Importance of race/ethnicity in risk of ASCVD
  - No RCT of statins that has used global risk assessment
  - Suggests high risk groups that may not benefit
    - NYHA Class 2-4 heart failure
    - Renal disease
Treatment Threshold: 7.5%
- Lowered from former threshold of 20% risk of MI over 10 years or >10% with multiple risk factors
- Based on NHANES data:
  - Men
    - 50% of all African-American men and 30% white men in 50’s
    - Almost all men in 70’s
  - Women
    - 20% African-American women and 60% white women in 60’s
- Guidelines emphasize the importance of chronological age
  - Health age and chronological age may be very different

Therapeutic Benefits of Statins
- High intensity therapy – lowering LDL cholesterol by >50%
- Moderate intensity therapy – lowering LDL cholesterol by 30-50%
- Reduces ASCVD events across the spectrum of baseline LDL-C levels >70 mg/dl
- Relative reduction in ASCVD risk is consistent for primary and secondary prevention.
- Secondary prevention – high dose statins (unless over 75 years of age – moderate intensity)
- Absolute reduction in ASCVD events is proportional to baseline absolute ASCVD risk.
- Statin therapy only for individuals at increased ASCVD risk.

Primary Prevention, LDL-C 70-189 mg/dL
- Most controversial area of guideline because of risk equations & lower cut off
- Reasonable to offer statin therapy to those with risk of 5-7.5% (conflicting evidence [IIa, B])

Primary prevention in patients with diabetes and LDL 70-189 mg/dL
- Extrapolation of data for primary prevention in high risk (≥7.5% 10 yr risk) who did not have diabetes
  - Expert opinion, some conflicting data [IIa, B]
  - Data for those with type 1 DM is lacking
- <40 or >75 yrs the decision to initiate statin therapy should be individualized
  - Expert opinion, divergent opinions [IIa, C]
Doubt raised about the AHA/ACC Omnibus calculator

Ridker & Cook
Mar. 19, 2013
Calculation of risk
By AHA new
Calculator
Vs. observed rates
Why the difference?
1. Overestimation
   Explained by statin
   Use in cohort?
2. Has this been
   Shown to explain the
   Difference?

Comparison of AHA/ACC
Calculator to other studies

75% to 150% overestimation of risk assumed
Is this data estimation adequate for estimating risk
Or is there some other method that should be used?
This will be discussed and debated for some time
One suspects that there is not a perfect answer:
Some considerations:
How many more people will be treated with statins?
How many fewer people on them will stop them?
Both seem likely to be substantial in numbers.
Studies to be the predictor—poorly represent
Observation in the field has its issues as well.

Issues and opinions
- Lack of RCT evidence for LDL targets vs. statin intensity goals
- Should the calculator be amended (includes strokes but may
  still be off)—this can be fixed.
- Concern about lowering risk threshold for primary prevention
- Question whether starting with high intensity is the right
  approach for most patients—tolerability and adherence

EMPA-REG—CV Outcomes and Death from Any Cause.

CV Events

Meta-analysis
Intensive Control DM2
CV events:
- MACE- reduced 9%
- CVA- no diff
- MI- reduced 15%
- Hosp./Fatal CHF no diff

Downs & Good, Ann Intern Med.
Published online 28 January 2014
Also importance of individualization of therapies

3-point MACE: sensitivity analyses

Patients with event/analysed
Empagliflozin Placebo HR (95% CI)
Intent to treat population 490/4687 282/2333 0.86 (0.74, 0.99)* 0.0382
On-treatment analysis** 487/4654 278/2316 0.86 (0.75, 1.00) 0.0519
Per-protocol analysis*** 490/4687 282/2333 0.86 (0.74, 0.99)* 0.0382

Cox regression analysis. MACE, Major
Adverse Cardiovascular Event; HR, hazard
ratio.

*95.02% CI.
**Excluding events >30 days after last intake of study drug
and patients who received study drug for <30 days (cumulative).
***Patients treated with ≥1 dose of study drug who did not have important protocol violations.
**LEADER trial**

Primary and Exploratory Outcomes.


Time to first endpoint better for subjects on Liraglutide:

1. Primary outcome
2. Death from CV causes
3. Death from any Cause

What are the mechanisms?

- Weight loss, insulin resistance
- Other

P=0.01

P=0.007

P=0.02

**Cardiovascular Outcomes.**


Semaglutide a once weekly GLP-1 agonist also shows substantial reduction in Time to first event, NF CVA

P=0.02

P=0.04

Effects of Canagliflozin on Glycated Hemoglobin Level, Body Weight, and Systolic and Diastolic Blood Pressure in the Integrated CANVAS Program.


Cardiovascular Outcomes in the Integrated CANVAS Program.

NS

NS

NS

P=0.02

Summary of 3 CVOTs in T2DM

<table>
<thead>
<tr>
<th>CVOT</th>
<th>EMP-REG</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>All T2D &amp; CVD</td>
<td>A1c 7-10%</td>
<td>&gt;50 yrs &amp; CVD or &gt;60 yrs &amp; &gt;1 RF</td>
</tr>
<tr>
<td>Treatment</td>
<td>Empagliflozin (SGLT2i)</td>
<td>Liraglutide (daily GLP-1 agonist)</td>
<td>Semaglutide (weekly GLP-1 agonist)</td>
</tr>
<tr>
<td>Duration</td>
<td>3.1 yrs</td>
<td>3.8 yrs</td>
<td>2.05 yrs</td>
</tr>
<tr>
<td>Baseline A1c</td>
<td>8.1%</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>↓ 14% (1% to 26%)</td>
<td>↓ 13% (3% to 22%)</td>
<td>↓ 26% (5% to 42%)</td>
</tr>
<tr>
<td>CV death</td>
<td>↓ 38% (23% to 51%)</td>
<td>↓ 22% (7% to 34%)</td>
<td>↓ 2% (–48 to 35%)</td>
</tr>
<tr>
<td>MI</td>
<td>↓ 13% (–9% to 30%)</td>
<td>↓ 12% (–3 to 25%)</td>
<td>↓ 26% (–8% to 49%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑ 24% (–8% to 67%)</td>
<td>↓ 11% (–11 to 28%)</td>
<td>↓ 39% (1% to 72%)</td>
</tr>
<tr>
<td>CHF hospitalization</td>
<td>↓ 35% (15% to 50%)</td>
<td>↓ 13% (–5 to 27%)</td>
<td>↑ 11% (–23% to 72%)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Genitourinary infections, no DKA</td>
<td>Higher retinopathy rate</td>
<td>Gallesone, other effects</td>
</tr>
</tbody>
</table>

**Likely Mechanism of benefit**

- Rapid, suggest hemodynamic or metabolic Vascular?
- Slower, suggest ASCVD, ↓ hypoglycemia
- Slower effects suggest ASCVD benefit

**CANVAS Program Primary and Secondary Outcomes**

positive Primary outcome (MACE) and CHF, renal outcomes but ↑ amputations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin (n=5795)</th>
<th>Placebo (n=4347)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (CV death, nonfatal MI, or nonfatal stroke)</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86</td>
<td>0.75–0.97</td>
<td>0.02 for superiority</td>
</tr>
<tr>
<td>All-cause death</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87</td>
<td>0.74–1.01</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87</td>
<td>0.72–1.06</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67</td>
<td>0.52–0.87</td>
<td></td>
</tr>
<tr>
<td>Albuminuria progression</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73</td>
<td>0.67–0.79</td>
<td></td>
</tr>
<tr>
<td>Renal composite (40% eGFR reduction, renal replacement therapy, or death)</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60</td>
<td>0.47–0.77</td>
<td></td>
</tr>
<tr>
<td>Amputations</td>
<td>6.3</td>
<td>3.4</td>
<td>1.97</td>
<td>1.41–2.75</td>
<td></td>
</tr>
</tbody>
</table>

What about our patient?

1. Should this patient be on statins?
ASCVD Risk Estimator shows as a non smoker with HTN not ideally controlled, dyslipidemia and DM not well controlled—her risk is 17.9% over 10 years!! And lifetime risk of 50%--Moderate to high intensity statins should be used if possible.

What should our patient's BP be?

138/85 is probably not ideally controlled.
A case can be made to aim for at least less than 130 systolic and possible addition of CCB to ACE/ARB plus diuretic (if doses are not optimal).

What should be added to metformin?

She does not precisely fit the profile of patients benefitting in the studies. (not known CVD)
Nonetheless, one may favor SGLT2 or GLP-1 drug given her very high CV risk.
They might have additional BP benefit but not likely to the degree that a CCB would have.

Conclusions

1. Statin therapy: should be a default option for most patients, for all with known CVD and for those with high risk of CVD using the AHA/ACC risk estimation equations.
2. High intensity statins: in those with active CV disease? Use of risk engines to individualize? More information is helpful especially for primary prevention. Type 1 diabetes not adequately studied.
3. Non-statin drugs: fibrate/Statin are not advised but continue to have some outcome data—long term now many go off this medication. niacin has old data suggesting benefit but with aggression LDL lowering not shown to benefit
4. BP control: needs to be individualized, ACE/ARB with Thiazide & CCB may help if tolerated. Watch out for secondary causes (e.g., OSA)
5. DM2 with CVD & CHF: consider DHFA, avoid CANA with PVD
6. GLP-1 drugs: also a strong consideration for CVD and/or high risk DM2 patients—possibly, but not clearly yet a class effect