Hypertension & Lipid Treatment in People with Diabetes

Marc Jaffe, MD
Cardiovascular Risk Reduction Clinical Leader, Kaiser Northern California
Endocrinology Subchief, Kaiser South San Francisco Hospital
Associate Clinical Professor of Medicine, UCSF
November 30, 2010

Objectives

Control BP in individuals with diabetes

Treat Dyslipidemia in individuals with diabetes

Speaker Disclosure for Dr. Jaffe

I have no financial relationship with any medically related enterprise other than Kaiser Permanente

I am not an investigator for pharmaceutical sponsored trial

I am not on a pharmacy sponsored speakers bureau

I do not own stock in pharmaceutical companies

I bought my laser pointer at Office Depot and batteries at Radio Shack

History of Diabetes Therapy

1500 BC - Description
History of Diabetes Therapy

1850-1870
High Glucose Diets
London Homeopathic Hospital 1859

1870-1900
Starvation Diets
Affiliated Colleges of UCSF 1896

Insulin
Isolated in 1921 by Banting and Best at the University of Toronto

Bottom Line for DM Control and CAD
"...appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventing cardiovascular morbidity and mortality."

Blood Pressure Matters in Diabetes

"Tight" achieved BP 144/82 vs 154/87 in "usual" care


NNT 9-25 over 10 years

Marc Jaffe, MD, Kaiser Permanente 11/10

ACCORD Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Intensive Events (%)/yr</th>
<th>Standard Events (%)/yr</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.88 (0.73-1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>150 (1.28)</td>
<td>144 (1.19)</td>
<td>1.07 (0.85-1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>60 (0.52)</td>
<td>58 (0.49)</td>
<td>1.06 (0.74-1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>126 (1.13)</td>
<td>146 (1.28)</td>
<td>0.87 (0.68-1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>34 (0.30)</td>
<td>55 (0.47)</td>
<td>0.63 (0.41-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total Stroke</td>
<td>36 (0.32)</td>
<td>62 (0.53)</td>
<td>0.59 (0.39-0.89)</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Marc Jaffe, MD, Kaiser Permanente 11/10

ACCORD Adverse Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE</td>
<td>77 (3.3)</td>
<td>30 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>0.003</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bradycardia or Atrial</td>
<td>12 (0.5)</td>
<td>3 (0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>5 (0.2)</td>
<td>1 (0.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>eGFR ever &lt;30 mL/min/1.73m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Dialysis or ESRD</td>
<td>59 (2.5)</td>
<td>58 (2.4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Dizziness on Standing†</td>
<td>217 (44)</td>
<td>188 (40)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

† Symptom experienced over past 30 days from HRQL sample of N=969 participants assessed at 12, 36, and 48 months post-randomization

Marc Jaffe, MD, Kaiser Permanente 11/10

ACCORD: SBP < 140 v < 120 in DM

- Fewer strokes
- No change in mortality
- More adverse events

Was it underpowered?
Fewer than expected events in both groups

Marc Jaffe, MD, Kaiser Permanente 11/10
BP arm still doesn’t tell us exactly where the target BP benefit and the target BP harm curves cross. We know it is below 140/90 but we knew that before ACCORD. We still don’t know how far below 140/90. Not clear just how low to go… <140/80? < 140/90? <130/80?

Mrs. Jones is a 75 year old female with DM2 for 6 years with an A1C of 6.8 on Metformin 500 mg twice daily. Her last BP in the clinic was 158/72 three months ago and today it is 147/70.

You advise her to...
1) Work on diet and exercise for another 3 months
2) Admit to the ICU for IV labetolol
3) Start an ACE inhibitor
4) Start a thiazide diuretic
5) Start both a ACE inhibitor and thiazide diuretic

What’s the best drug for hypertension in people with diabetes?

2010 HTN Care Path

HTN Treatment Plan for people with and without DM

Management of ADULT HYPERTENSION

2010 HTN Care Path

HTN Treatment Plan for people with and without DM
Diuretics Rule!

- Diuretics recommended as first line by most authorities
- No other med has proven to be more effective
- Some have been shown to be similar in effect

Diuretics Rule! ALLHAT Trial

Diuretic, ACEI, and CCB all similar results for all cause mortality

Diuretics Rule! ALLHAT Trial

Diuretics superior to ACEI and CCB to prevent CHF

CCB  ACE Inhibitor  Diuretics

HYVET Trial (Indapamide + Perindopril)
Fixed Dose Combination Therapy

Placebo  ACE I + Diuretic
ADVANCE (Indapamide + Perindopril) Fixed Dose Combination Therapy in DM


What's the best drug for hypertension in people with diabetes?

This is a trick question since it’s hard to select a “best drug” for the treatment of hypertension in people with diabetes due to the fact that so few individuals will have their blood pressure reach target on a single drug alone.

However, using a combination of the two “best” drugs in a single tablet (such as lisinopril + hydrochlorothiazide) is an effective strategy as an initial treatment and can be titrated as needed to achieve control in many patients.

Marc Jaffe, MD, Kaiser Permanente 11/10

Recommendations for patients with ACEI intolerance

If intolerant to ACEI (for example cough…).
ARB substitution is an acceptable alternative
ARB’s are less well studied but appear to be as effective than ACE Inhibitors

Marc Jaffe, MD, Kaiser Permanente 11/10

ONTARGET Trial
ACEI and ARB Reduce CV Events

ACE and ARB equally effective at reducing CV events. No additional benefit when combined

6,000 of the 16,000 trial participants had diabetes

Marc Jaffe, MD, Kaiser Permanente 11/10
HTN Care Path for DM

Start with combination lisinopril HCTZ 20/25 mg tabs

ACE-Inhibitor\(^2\) / Thiazide Diuretic

| Lisinopril / HCTZ | 20 / 25 mg × ½ daily
|-------------------|------------------------
| (Advance as needed) | 20 / 25 mg × 1 daily
|                   | 20 / 25 mg × 2 daily

Pregnancy Potential: Avoid ACE-Inhibitors\(^2\)

If ACEI intolerant or Pregnancy Potential

Thiazide Diuretic

Chlorthalidone 12.5 mg → 25 mg
OR
HCTZ 25 mg → 50 mg

If not at goal on ACE inhibitor + thiazide diuretic then add…

Calcium Channel Blocker

Add amlodipine 5 mg × ½ daily → 5 mg × 1 daily → 10 mg daily

What’s the 4th Drug to use for HTN?

If not at goal on ACE inhibitor + thiazide diuretic + CCB then…

Beta-Blocker OR Spironolactone

Add amlodipine 25 mg daily → 50 mg daily (Keep heart rate > 55)
OR
If on thiazide AND eGFR ≥ 60 ml/min AND K < 4.5
Add spironolactone 12.5 mg daily → 25 mg daily
Spironolactone - the 4th Drug to use for HTN


Marc Jaffe, MD, Kaiser Permanente 11/10

Simvastatin 40 mg in DM in HPS DM Reduces likelihood of CV events


Marc Jaffe, MD, Kaiser Permanente 11/10

What’s the best 2nd drug for lipid control in in people with diabetes?

Mr. Garcia is a 72 year old male with DM2 for 12 years with A1C of 6.7 on Metformin 500 mg twice daily and BP 129/74 on lisinopril 20/HCTZ 25 mg daily. His recent lipid panel had a Total Chol 188, LDL 115, HDL 38, and TG 175 while taking simvastatin 80 mg daily.

You advise him to...
1) Work on diet and exercise for another 3 months
2) Admit to the ICU for plasmaphoresis twice weekly
3) Change to a more potent statin
4) Add ezetimibe 10 mg daily
5) Add Slo-Niacin and titrate to 1000-1500 mg daily

Marc Jaffe, MD, Kaiser Permanente 11/10

LDL < 100 Evidence

Lack of Evidence for Recommended LDL Treatment Targets: A Solvable Problem

Hayward RA. Annals of Internal Medicine

Narrative Review: Lack of Evidence for Recommended Low-Density Lipoprotein Treatment Targets: A Solvable Problem

"No high-quality evidence could be found that suggests that titrating lipid therapy to recommended low-density lipoprotein (LDL) cholesterol targets is superior to empirically prescribing doses of statins used in clinical trials for all patients at high cardiovascular risk."


Marc Jaffe, MD, Kaiser Permanente 11/10
LDL < 100 Evidence

Current recommendations to manage dyslipidaemia in diabetic patients are based on observational evidence and expert judgment. It remains unclear whether the benefits of statins are mediated by lowering LDL, whether goals of treatment should be expressed as LDL, and whether a fixed dose of statin, increasing doses of statin, or multiple drugs can be used to achieve these goals with acceptable safety.


The Evidence Supporting Statin Titration

“Current recommendations to manage dyslipidaemia in diabetic patients are based on observational evidence and expert judgment. It remains unclear whether the benefits of statins are mediated by lowering LDL, whether goals of treatment should be expressed as LDL, and whether a fixed dose of statin, increasing doses of statin, or multiple drugs can be used to achieve these goals with acceptable safety.”


Adding Meds to Statins - Evidence

“No firm trial evidence showed that combining a statin with another agent (bile-acid sequestrant, fibrate, ezetimibe, niacin, or -3 fatty acids) improved clinical outcomes (myocardial infarction, stroke, or mortality) more often than high-dose statin monotherapy.”


Lipid Med Care Path for people with DM

Step 1
Simva 40 or 80

Step 2
Slo-Niacin

Step 3
Many options
Niacin - New Role for Old Drug

Niacin + Statin combo in the news lately
2 new branded meds
Advicor (lovastatin + niacin ER)
Simcor (simvastatin + niacin ER)
Several favorable trials (HATS, OCEANS)
Lowers LDL and TG and raises HDL

Slo-Niacin - Affordable and OTC

Slo-Niacin can be added to Statins
Simva 80 + Slo-Niacin 1-1.5 g daily max
Simva 40 + Slo-Niacin 2 g daily max
Start with Slo-Niacin 250 mg BID or HS, titrate every 1-4 weeks to 500 bid or 1000 HS
Niaspan (Niacin ER) $1600/yr
Simcor (Simvastin + Niacin ER) $1500/yr
Slo-Niacin $115/yr
Prices 9/9/2010 @ drugstore.com website

Niacin and Diabetes

How much does Niacin raise glucose?
Measure | Change  | Daily Dose
---|---|---
FBS | 5% Increase | Niacin ER 2000mg
A1C | 0-0.3% | Niacin ER 1500mg


Should niacin be given to people with diabetes?

"Clinical trials with doses of niacin used clinically today appear to result in only minor deterioration of glycemic control in most patients with diabetes. The favorable effects of niacin on HDL-cholesterol, TG, lipoprotein (a), and LDL particle size, along with its lesser effect in lowering LDL-cholesterol, probably outweigh the small detriment in glycemic control in diabetes."

Adding Fibrate to Statin in people with DM

CONCLUSIONS
The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00006260.)

The ACCORD Study Group, Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. NEngl J Med 2010

Prevent Heart Attacks and Strokes Everyday  Marc Jaffe, MD, Kaiser Permanente 11/10

April 2010 Kaiser California Drug Bulletin

Marc Jaffe, MD, Kaiser Permanente 11/10

Recommendations for Lipid Control in People with Diabetes

“Statin therapy (such as simvastatin 40 mg or higher) remains the primary focus for people ages ≥ 40 with diabetes as there is compelling evidence that this reduces the likelihood of cardiovascular events. No current high quality evidence demonstrates additional cardiovascular benefit from adding fibrates (such as fenofibrate) to patients with diabetes already taking statins.”

Their proposal [fixed dose statin use] makes a lot more sense than chasing a target,” says Joe Selby, director of the Kaiser Permanente Division of Research, who was not involved in the Annals analysis. At the beginning of this year, Kaiser’s northern California doctors began tracking the percentage of high-risk patients who are prescribed statins, in addition to tracking how many patients were meeting cholesterol targets. Kaiser [NCal] says it allows its clinics and hospitals to be graded on either of these metrics.”

Tuesday, June 15, 2010 New York 90° 77°
THE WALL STREET JOURNAL BUSINESS
HEART BEAT | JUN 15, 2010
A Radical View on Giving Statins
BY ANNA WILDE MATHEWS

Prevent Heart Attacks and Strokes Everyday  Marc Jaffe, MD, Kaiser Permanente 11/10

Prevent Heart Attacks and Strokes Everyday  Marc Jaffe, MD, Kaiser Permanente 11/10

LDL Control and Med Use

Prevent Heart Attacks and Strokes Everyday  Marc Jaffe, MD, Kaiser Permanente 11/10

Prevent Heart Attacks and Strokes Everyday  Marc Jaffe, MD, Kaiser Permanente 11/10
Our Mantra!

TEST THE UNTESTED

TREAT THE UNDERTREATED AND UNTREATED

Marc Jaffe, MD, Kaiser Permanente 11/10