Management of Diabetes Mellitus

Arom Jedsadayanmata
Pharm.D., Ph.D., BCPS.
Department of Pharmacy Practice
Naresuan University

Classification of Diabetes

- Type 1 (beta-cell ถูกทำลาย)
- Type 2 (การหลั่ง insulin ลดลง โดยพบภาวะ insulin resistance ร่วมด้วย)
- Other specific types eg. Genetic defects in insulin action, genetic defects in beta-cell function
- Gestational diabetes mellitus

Diagnosis of Diabetes

- Fasting plasma glucose (FPG)
  - Preferred method for diagnosis
  - FPG ≥126 mg/dL
- Casual plasma glucose + symptoms of hyperglycemia
  - Casual plasma glucose ≥200 mg/dL
  - Symptoms: polyuria, polydipsia, unexplained weight loss

Oral glucose tolerance test (OGTT)

- 2-h plasma glucose ≥200 mg/dL following load of 75 anhydrous glucose in water
- Not recommended for routine clinical use
- Useful in further evaluation of pt strongly suspected for diabetes, but having normal FPG or impaired fasting glucose (plasma glucose 100-125 mg/dL)
Diagnosis of Diabetes

- Hemoglobin A1C
  - Not recommended for routine diagnosis
  - Lack of evidence for prognostic significance and threshold level for diagnosis

Pre-diabetes

- Impaired fasting glucose (IFG)
  - Fasting glucose 100-125 mg/dL
- Impaired glucose tolerance (IGT)
  - 2-h plasma glucose 140-199 mg/dL

Criteria in Testing for Pre-diabetes & DM

- Testing in all overweight adults (BMI ≥ 23 kg/m²) with additional risk factors
  - Physical inactivity
  - First-degree relative with diabetes
  - Members of a high-risk populations eg. Asians
  - Women who deliver a baby weighing >9 lb or were diagnosed with gestational diabetes
  - Hypertension (BP ≥ 140/90 mm Hg) or on Rx

Criteria in Testing for Pre-diabetes & DM

- Testing in all overweight adults (BMI ≥ 23 kg/m²) with additional risk factors
  - HDL-C <35 mg/dL and/or TG >250 mg/dL
  - Women with polycystic ovarian syndrome
  - IGT or IFG on previous testing
  - Conditions associated with insulin resistance eg. Severe obesity, acanthosis nigricans
  - History of cardiovascular disease
Criteria in Testing for Pre-diabetes & DM

- In the absence of aforementioned risk factors, testing should begin at age 45 years
- If results are normal, testing should be repeated at 3-year intervals
- May test more often, depending on risk factor and initial results

Goals in Management of Type 2 DM

- To prevent diabetes-related death and complications
- Macrovascular complications
  - Coronary heart disease (CHD)
  - Cerebrovascular disease
  - Peripheral arterial disease
- Microvascular complications
  - Nephropathy
  - Retinopathy
  - Neuropathy

Multiple Risk Factors Intervention in Diabetes

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Thrombosis
- Smoking

Glycemic Control in Type 2 DM
Current Guideline on Management of Hyperglycemia in Type 2 DM

- Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy
- Consensus statement from ADA and the European Association for the Study of Diabetes
- Diabetes care 2008; 31: 1-11

Glycemic Goals of Therapy: ADA 2008

- A1C < 7.0%
- Preprandial capillary PG 70-130 mg/dL
- Peak postprandial capillary PG < 180 mg/dL

AACE 2007

- A1C < 6.5%
- FPG < 110 mg/dL
- 2-h postprandial glucose < 140 mg/dL

Benefits of Glycemic Control in Type 2 DM

- Reduction in microvascular complications (retinopathy, nephropathy, neuropathy)
- Potential reduction in macrovascular complications (coronary artery disease, cerebrovascular disease, peripheral arterial disease)

Diabetes and Risk of CHD

- 65% of death in DM type 2 related to heart disease or stroke
- Higher risk for CHD mortality than non-diabetic patients
- Diabetes regarded by many as CHD-risk equivalence
Diabetes as CHD Risk Equivalence

- Cohort study
- Non-diabetics = 1373
  - 69 with prior MI
  - 1304 without prior MI
- Diabetics = 1059
  - 169 with prior MI
  - 890 without prior MI

Haffner SM et al. *NEJM*. 1998; 339:229-34

Diabetes and Mortality from CHD

- Non-diabetics = 3,202,671
  - 73,155 with prior MI
  - 3,129,516 without prior MI
- Diabetics = 71,801
  - 6419 with prior MI
  - 65,382 without prior MI

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley, Carole A Gall, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study Group

*BMJ* 2000;321:405–12

- Cohort study
- N = 3642 type 2 DM
- To study association between
  - Average A1C
  - Macrovascular & Microvascular events

**Graph 1:**

- **All cause mortality**
  - Hazard ratio
  - P < 0.0001
  - 14% decrease per 1% reduction in HbA1c

**Graph 2:**

- **Fatal and non-fatal myocardial infarction**
  - Hazard ratio
  - P < 0.0001
  - 14% decrease per 1% reduction in HbA1c
UKPDS 35

- Randomized, active-controlled trial
- N = 3867 DM type 2
- Comparison
  - Intensive glucose control (A1C 7%)
  - Conventional control (A1C 7.9%)
- Outcomes
  - Macro- and Microvascular complications

UKPDS 33

- Randomized, active-controlled trial
- N = 3867 DM type 2
- Comparison
  - Intensive glucose control (A1C 7%)
  - Conventional control (A1C 7.9%)
- Outcomes
  - Macro- and Microvascular complications

UKPDS 34

- Randomized, active-controlled trial
- N = 4075 DM type 2
- Comparison
  - Intensive glucose control with metformin (A1C 7.4%)
  - Conventional control (A1C 8.0%)
- Outcomes
  - Macro- and Microvascular complications

<table>
<thead>
<tr>
<th>UKPDS 33</th>
<th>Endpoints</th>
<th>Events/1000 patient-years: Intensive</th>
<th>Events/1000 patient-years: Conventional</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related death</td>
<td>10.4</td>
<td>11.9</td>
<td>0.90 (0.73-1.11)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>14.7</td>
<td>17.4</td>
<td>0.84 (0.71-1.00)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5.6</td>
<td>5.0</td>
<td>1.11 (0.81-1.91)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Microvascular</td>
<td>8.6</td>
<td>11.4</td>
<td>0.75 (0.60-0.93)</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>
UKPDS 34

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Events/1000 patient-years: Metformin</th>
<th>Events/1000 patient-years: Conventional</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related death</td>
<td>7.5</td>
<td>12.7</td>
<td>0.58 (0.37-0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>MI</td>
<td>11.0</td>
<td>18.0</td>
<td>0.61 (0.41-0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.3</td>
<td>5.5</td>
<td>0.59 (0.29-1.18)</td>
<td>0.43</td>
</tr>
<tr>
<td>Microvascular</td>
<td>6.7</td>
<td>9.2</td>
<td>0.71 (0.43-1.15)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

ACCORD Study

- Randomized, controlled trial
- N = 10251 type 2 DM with A1C 8.1%
- Interventions
  - Intensive therapy (target A1C <6%)
  - Standard therapy (target A1C 7.0-7.9%)
- Outcomes: MI, stroke, Death from CVD
- Plan f/u 5.6 yrs (discontinued after 3.5 yrs)
ACCORD Study: Conclusion

- Intensive therapy aimed at reducing A1C to less than 6 increases death from all causes among type 2 DM.

ADVANCE Study

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group

ADVANCE Study

- Randomized, controlled trial
- N = 11140 type 2 DM
- Intervention
  - Intensive: gliclazide MR + others to achieve A1C 6.5%
  - Standard: other SUs + others to achieve A1C ~7%
- Outcomes
  - Macro- & Microvascular events
ADVANCE Study: Conclusion

- Intensive glycemic control to lower A1C to <6.5% decrease combined macro- and microvascular endpoints, but no effects on macrovascular endpoints or death among type 2 DM

Glycemic Control Effect on Macrovascular Events Among Type 2 DM: Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>N (intensive/Conventional)</th>
<th>F/U duration (y)</th>
<th>Intervention in Intensive Group</th>
<th>Intervention in Conventional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA 1997</td>
<td>75/78</td>
<td>2.3</td>
<td>Insulin, SU</td>
<td>1-2 insulin/d</td>
</tr>
<tr>
<td>UKPDS33 overweight</td>
<td>1433/589</td>
<td>10.3</td>
<td>SU, Met, Insulin</td>
<td>Diet+meds</td>
</tr>
<tr>
<td>UKPDS33 nonoverweight</td>
<td>1296/549</td>
<td>9.7</td>
<td>SU, Met, Insulin</td>
<td>Diet+meds</td>
</tr>
<tr>
<td>UKPDS34</td>
<td>342/411</td>
<td>10.7</td>
<td>Met, Su, Insulin</td>
<td>Diet+meds</td>
</tr>
<tr>
<td>Kumamoto1°</td>
<td>28/27</td>
<td>8.0</td>
<td>Multiple Insulin Injections</td>
<td>1-2 insulin injections/d</td>
</tr>
<tr>
<td>Kumamoto2°</td>
<td>27/28</td>
<td>8.0</td>
<td>Multiple Insulin Injections</td>
<td>1-2 insulin injections/d</td>
</tr>
</tbody>
</table>

Glycemic Control Effect on Macrovascular Events Among Type 2 DM: Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>%A1C Intensive</th>
<th>%A1C Conventional</th>
<th>%Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA 1997</td>
<td>7.1</td>
<td>9.2</td>
<td>2.1</td>
</tr>
<tr>
<td>UKPDS33 overweight</td>
<td>7.5</td>
<td>8.3</td>
<td>0.8</td>
</tr>
<tr>
<td>UKPDS33 nonoverweight</td>
<td>8.0</td>
<td>8.3</td>
<td>0.3</td>
</tr>
<tr>
<td>UKPDS34</td>
<td>8.0</td>
<td>8.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Kumamoto1°</td>
<td>7.2</td>
<td>9.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Kumamoto2°</td>
<td>7.2</td>
<td>9.4</td>
<td>2.2</td>
</tr>
</tbody>
</table>


How Much Benefit Glycemic Control Have on Cardiovascular Outcomes Among Type 2 DM?

- Only modest benefit on macrovascular complications (relative risk reduction ~20%) as compared to microvascular complications
- Targeting macrovascular outcomes must play strong attention to other cardiovascular risk factors, i.e. hypertension, dyslipidemia, smoking

Natural History of Diabetes

Insulin Responsiveness

- Insulin Sensitive
- Insulin Resistance
  - Impaired peripheral glucose uptake
  - Impaired suppression of hepatic glucose production

Beta-cell Function

- Normal Beta-cell Function
- Compensatory Increase in Beta-cell function
- Impaired Beta-cell Function
- Progressive Beta-cell Failure

Glucose Tolerance

- Normoglycemia
- Impaired Fasting Glucose
- Diabetes Mellitus

TIME
Natural History of Diabetes

Lifestyle Intervention in Glycemic Control

- Weight reduction or maintenance
  - Improve glycemic control
  - Improve blood pressure
  - Improve atherogenic dyslipidemia

- Increase physical activity
  - At least 150 minutes per week of moderate physical activity
  - Help to maintain weight loss

- Limited long-term success of lifestyle intervention in glycemic control

Principles in Selecting Antihyperglycemic Interventions

- Effectiveness in lowering glycemia
  - A1C >8.5%: need more rapid & greater effect on glycemia or combination therapy
  - A1C <7.5%: less rapid & less potential in lowering glycemia may be considered

- Extraglycemic effects that reduce long-term complications
- Safety profiles
- Ease of use
- Expense
**Medications for Glucose-lowering Effects: Well-validated Therapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Expected decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0-2.0</td>
<td>Weight neutral</td>
<td>GI side effects, C/I in renal insufficiency</td>
</tr>
<tr>
<td><strong>Additional Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5-3.5</td>
<td>No dose limit</td>
<td>1-4 injections/day, Weight gain, Hypoglycemia</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1.0-2.0</td>
<td>Rapidly effective, Improved lipid profile</td>
<td>Weight gain, Hypoglycemia, especially long-acting eg. glibenclamide</td>
</tr>
</tbody>
</table>

**Medications for Glucose-lowering Effects: Less Well-validated Therapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Expected decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TZDs</strong></td>
<td>0.5-1.4</td>
<td>Improved lipid profile (Pioglitazone)</td>
<td>Fluid retention, CHF, Weight gain, Bone fractures, Expensive, Potential increase in MI (Rosiglitazone)</td>
</tr>
<tr>
<td>GLP-1 Agonist</td>
<td>0.5-1.0</td>
<td>Weight loss</td>
<td>2 injections/day, Frequent GI side effects, Long-term safety not known, Expensive</td>
</tr>
</tbody>
</table>

**Medications for Glucose-lowering Effects: Other Therapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Expected decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, Three times/day dosing, Expensive</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5-1.5</td>
<td>Rapidly effective, Weight gain, Three times/day dosing, Hypoglycemia, Expensive</td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5-1.0</td>
<td>Weight loss</td>
<td>Three injections/day, Frequent GI side effects, Long-term safety not known, Expensive</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Long-term safety not known, Expensive</td>
</tr>
</tbody>
</table>

**Metformin**

- Initial therapy in all type 2 DM
- Inhibit hepatic glucose production and lower fasting glycemia
- No hypoglycemia, Weight loss/neutral
- May have beneficial effect on CVD outcomes (need confirmation)
- Rare lactic acidosis (1:100,000)
- Safe unless GFR <30 ml/min
ADA Guideline on Titration of Metformin

- Begin with low-dose (500 mg) taken OD or BID with meals (breakfast and/or dinner) or 850 mg OD
- After 5–7 days, if no GI side effects, advance dose to 850 or 1000 mg tablets, BID (to be taken before breakfast and/or dinner)
- If GI side effects appear, decrease to previous lower dose and try to advance the dose at a later time
- The max effective dose ~ 1,000 mg BID but often 850 mg BID
- Modestly greater effectiveness observed at 2,500 mg/day

บทบาทของ early insulin therapy

- DM เป็น progressive disease
- Glucotoxicity
  - oxidative stress
  - beta-cell apoptosis
  - acceleration of beta-cell failure
- การควบคุมระดับน้ำตาลได้แก่เน้นๆ ช่วยชะลอการเสื่อมของเบต้าเซลล์
- Insulin เป็นยาลด A1C ที่มีประสิทธิภาพที่สุด
Insulin Replacement Therapy

- Once-daily basal insulin
  - Mafik to be combined with oral antihyperglycemics
  - NPH or glargine
  - Start with 10 units or 0.1-0.2 units/kg/day
  - Aim: fasting blood glucose

Basal Insulin Dose Adjustment

<table>
<thead>
<tr>
<th>Fasting Blood Glucose (mg/dL)</th>
<th>Basal Insulin Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>Increase insulin dose by 4 units</td>
</tr>
<tr>
<td>70-130</td>
<td>Increase insulin dose by 2 units</td>
</tr>
<tr>
<td>131-179</td>
<td>No insulin dose adjustment</td>
</tr>
<tr>
<td>≥180</td>
<td>Reduce insulin dose by 2 units</td>
</tr>
</tbody>
</table>

* Do not increase insulin dose if fasting blood glucose is <70 mg/dL on any given day or if hypoglycemia is noted.

Insulin & Insulin Analogs

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Onset (h)</th>
<th>Time-to-Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>0.5-1</td>
<td>2-4</td>
<td>6-8</td>
</tr>
<tr>
<td>Lispro</td>
<td>0.1-0.5</td>
<td>0.5-2.5</td>
<td>2-4</td>
</tr>
<tr>
<td>Aspart</td>
<td>0.1-0.3</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>NPH</td>
<td>1-3</td>
<td>5-10</td>
<td>13-18</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-2</td>
<td>6-8</td>
<td>20-24</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2</td>
<td>No pronounced peak</td>
<td>20-24</td>
</tr>
</tbody>
</table>
### Barriers to Insulin Initiation: Psychological Insulin Resistance
- Perceived loss of control over one's life
- Poor self-efficacy
- Perceived personal failure
- Perceived disease severity
- Injection-related anxiety
- Perceived no benefit of insulin therapy

### Barriers to Insulin Initiation: Health Personnel
- Delayed initiation
  - ไม่อยากฝันใจผู้ป่วย
  - เกรงผลไม่พึงประสงค์
  - ใช้เวลาในการทำความเข้าใจกับผู้ป่วย
- Delayed intensification
  - กลัวการเกิด hypoglycemia

### Patient Education
- ไม่สร้างทัศนคติที่ไม่ต่อกการฉีดยาอินซูลิน
- ค้นหาสาเหตุแท้จริงของการไม่ยอมรับยาฉีดอินซูลิน
- แนะนำให้ลองใช้สิ่งนี้
- เสริม self-efficacy: แสดงวิธีฉีด ให้ลองฉีดเอง
- Insulin pen
- แจ้งประโยชน์ ข้อดีของยาฉีดอินซูลิน
- คลายกังวลเรื่องผลไม่พึงประสงค์ esp. hypoglycemia
- ให้ผู้ป่วยเข้ามามีส่วนร่วม, เพิ่ม self-management skill
- Needle phobia ปรึกษาผู้เชี่ยวชาญด้านจิตวิทยา

### Summary on Insulin Therapy
- โรคเบาหวานเป็น progressive disease ความต้องการอินซูลินจากภายนอกจึงมักจำเป็น และเป็นวิธีการลดระดับน้ำตาลในเลือดที่ดีสุด
- อุปสรรคในการเริ่มฉีดอินซูลินเกิดขึ้นแท้จริงจากปัจจัยผู้ป่วยและบุคลากรทางการแพทย์ ทำให้การใช้ยาฉีดอินซูลินไปถึงไม่ก็ผลิตผลต่อผู้ป่วย ทั้งการเลือกแบบยาฉีดที่ใช้กัน และภาวะแทรกซ้อน
Summary on Insulin Therapy

- Pharmacist should have a role in informing patients about insulin therapy, not just administering, to help patients comply with their dietary and medication routines.

- Initiation of insulin therapy may begin with basal insulin therapy, which can make it easier for patients to accept insulin injections.

Thiazolidinediones (TZDs)

- Act as insulin sensitizer by modulating peroxisome proliferator-activated receptor γ
- Increase sensitivity of muscle, adipose tissue, and liver to insulin
- Lower A1C by 0.5–1.4%
- Beneficial effect on lipid profile (Pio) or neutral effect (Rosi)
- Controversial issues on CVD outcomes
  - Pioglitazone: significant secondary endpoint of death, MI, stroke (PROACTIVE trial)
  - Rosiglitazone: risk of MI

Thiazolidinediones (TZDs) ADRs

- Weight gain
- Fluid retention with peripheral edema
- Increased risk of CHF
- Increased bone fractures

TZDs Reduce Intimal Medial Thickness

McGuire et al. Circulation 2008;117;440-449
Rosiglitazone and CHF

- Objective: investigate effects of rosiglitazone on LVEF in subjects with T2DM and pre-existing CHF NYHA class I to II
  - N = 224
- Intervention (f/u 52 weeks, target FBS<126 mg/dL)
  - Rosiglitazone 4-8 mg/day (n=110)
  - Placebo (n=114)
- Outcomes
  - LVEF
  - HF-related signs & symptoms

---

Rosiglitazone in CHF

<table>
<thead>
<tr>
<th>Adjudicated End Point</th>
<th>PLB, n = 114</th>
<th>RSG, n = 110</th>
<th>Hazard Ratio* (95% CI), p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or worsening CHF</td>
<td>8 (7.5)</td>
<td>11 (10.6)</td>
<td>1.283 (0.513-3.209), 0.59</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5 (4.8)</td>
<td>8 (7.7)</td>
<td>1.495 (0.487-4.593), 0.48</td>
</tr>
<tr>
<td>CV death</td>
<td>4 (3.8)</td>
<td>5 (4.8)</td>
<td>1.134 (0.303-4.254), 0.85</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Adjudicated End Point</th>
<th>PLB, n = 114</th>
<th>RSG, n = 110</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular hospitalization</td>
<td>15 (13.2)</td>
<td>21 (19.1)</td>
<td>0.465</td>
</tr>
<tr>
<td>Definite worsening CHF</td>
<td>4 (3.5)</td>
<td>5 (4.5)</td>
<td>0.858</td>
</tr>
<tr>
<td>Possible worsening CHF</td>
<td>0</td>
<td>2 (1.8)</td>
<td>*</td>
</tr>
<tr>
<td>New or worsening edema</td>
<td>10 (8.8)</td>
<td>28 (25.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>New or worsening dyspnea</td>
<td>19 (16.7)</td>
<td>29 (26.4)</td>
<td>0.197</td>
</tr>
<tr>
<td>Increase in CHF medication</td>
<td>20 (17.5)</td>
<td>36 (32.7)</td>
<td>0.037</td>
</tr>
</tbody>
</table>
**Effects on Incidence of Edema and Dyspnea**

- **Edema**: Placebo (PLB) vs. Rosiglitazone (RSG), 40% vs. 30% respectively, p = 0.065
- **Dyspnea**: Placebo (PLB) vs. Rosiglitazone (RSG), 30% vs. 20% respectively, p = 0.197

**Effect on LVEF & CI**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline EF</td>
<td>36.3 ± 7.7</td>
<td>34.1 ± 7.4</td>
</tr>
<tr>
<td>52-week EF</td>
<td>37.1 ± 8.4</td>
<td>36.3 ± 7.5</td>
</tr>
<tr>
<td>Change from baseline EF</td>
<td>0.8 ± 5.9 (p=0.2)</td>
<td>2.2 ± 5.6 (p&lt;0.001)</td>
</tr>
<tr>
<td>Baseline CI</td>
<td>1.64 ± 0.74</td>
<td>1.69 ± 0.45</td>
</tr>
<tr>
<td>52-week CI</td>
<td>1.66 ± 0.68</td>
<td>1.73 ± 0.43</td>
</tr>
<tr>
<td>Change from baseline CI</td>
<td>0.01 ± 0.51 (p=0.8)</td>
<td>0.03 ± 0.49 (p=0.5)</td>
</tr>
</tbody>
</table>

**Incretins: GLP-1**

- **Liver** produces GLP-1, which stimulates GLP-1 receptors in various tissues:
  - **Adipose tissue**: Lipogenesis
  - **Skeletal muscle**: GLP-1 activates GLP-1R on muscle cells, increasing glucose uptake and glycogen synthesis.
  - **Brain**: GLP-1 modulates appetite and satiety, reducing food intake.
  - **Small intestine**: GLP-1 delays gastric emptying, reducing postprandial glucose levels.

**Circulation 2003**

- **Consideration of TZD therapy**
  - History and physical examination to establish presence and severity of cardiac disease
  - Consider TZD therapy appropriate
  - Edema occurs or increases compared to baseline
  - Identify potential non-TZD causes and eliminate if appropriate
  - Venous insufficiency
  - Nephrotic syndrome

- **Symptoms or signs of CHF**
  - No CHF
  - Continue TZD treatment
  - May or may not be tolerated
  - Administer diuretics if tolerated

- **Discontinue TZD**
  - Consider alternative hypoglycemic drugs
  - Neprilysin-contraindicated in patients with CHF requiring drug therapy

- **Re-evaluate**
  - If cardiac disease intervenes (new MI, etc.)
  - If LVEF is < 40%: Suspect 1st systolic dysfunction
  - If LVEF is 40% or more: Suspect 1st diastolic dysfunction
Incretins: GIP

GLP-1:
- Naturally occurring peptide produced by small intestine
- Binds to GLP-1 receptor on beta-cell
- Potentiate glucose-stimulated insulin secretion
- Suppress glucagon secretion
- Slow gastric motility
- Stimulate proliferation & differentiation of beta-cell
- Improve satiety
- Current available agent: exenatide (exendin-4 analog of Gila monster)

Exenatide

- Lower postprandial glucose
- Lower A1C by 0.5-1.0%
- Weight loss of ~2-3 kg over 6 mo
- Approved for use in combination with SU, metformin, TZD, SU+metformin or Metformin+TZDs
- ADR: Nausea, vomiting, diarrhea, report of pancreatitis, hypoglycemia when combined with SU
- Dosing: 5-10 mcg SC within 60 min before meal BID  (6-h apart for each meal)
- Drug interaction: delay absorption of PO drugs, other drugs should be taken 1 hour before exenatide or when exenatide not given
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- DPP-4 degrade GLP-1 and glucose-dependent insulinotropic peptide (GIP)
- DPP-4 inhibitors enhance effects of GLP-1 and GIP, increase glucose-mediated insulin secretion, suppress glucagon secretion
- Available agents: sitagliptin
- Advantages: weight neutral, well-tolerated, no drug interaction report
- Decrease A1C by 0.6-0.9%

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: Sitagliptin

- Approved for use as monotherapy or used in combination with metformin or TZDs
- ADRs: long-term safety not known
- Dosing
  - Normal renal function 100 mg/d taken with or without food
  - CrCl 30-50 ml/min, decrease dose to 50 mg/d
  - CrCl <30 ml/min, decrease dose to 25 mg/d

α-Glucosidase Inhibitors

- Available agents: acarbose, voglibose, miglitol
- Actions
  - Reduce rate of carbohydrate digestion
  - Lower postprandial glucose
  - Do not cause hypoglycemia
  - Malabsorption & weight loss do not occur
- Lower A1C by 0.5-0.8%

Acarbose

- One of the oral hypoglycemic drugs shown to decrease MI in type 2 DM
- Disadvantage:
  - 3 times dosing
  - GI side effects
  - Lower A1C by 0.5-1.0%
  - Expensive
Amylin Agonists: Pramlintide

- Synthetic analog of amylin (beta-cell hormone)
  - Inhibit gastric emptying
  - Inhibit glucagon production
  - Decrease postprandial glucose
  - Induce weight loss 1-1.5 kg/6 mo
- Lower A1C by 0.5-0.7%
- Approved for use with regular insulin or rapid acting insulin analog
- ADRs
  - GI side effects: nausea
- Dosing: SC before meal

Inhibitors of RAS Preferred in DM

- Reduce CVD outcomes in high risk patients including DM (HOPE trial)
- Reduce CVD outcomes in patients with heart failure
- Prevent progression of diabetic nephropathy

ADA/AHA: Management of Hypertension in Diabetes

- Goal BP in DM: <130/80 mm Hg
- If BP 130-139/80-89 mmHg ให้ lifestyle modification 3 เดือน ถ้ายัง ≥ 130/80 ให้เริ่มยา
- If BP ≥ 140/90 mmHg ให้เริ่มยาได้เลยพร้อมแนะนำ lifestyle modification
- ยาลดความดันเสือที่ผู้ป่วยควรได้รับควรประกอบด้วยยา ACEIs หรือ ARBs

Inhibitors of RAS Preferred in DM

- Reduce CVD outcomes in high risk patients including DM (HOPE trial)
- Reduce CVD outcomes in patients with heart failure
- Prevent progression of diabetic nephropathy

ADA/AHA: Management of Hypertension in Diabetes

- If BP ไม่สามารถควบคุมได้ ให้เลือกยาอื่นๆ ที่สามารถลดโรคหัวใจและหลอดเลือดใน DM ได้แก่
  - Thiazides
  - Beta-blockers
  - CCBs
- Safety Follow up: serum K, serum creatinine, orthostatic hypotension

Circulation. 2007; 115: 14-16; Diabetes Care Supplement 1, 2008
ADA Recommendation on lipid Management

- Lifestyle intervention: low saturated fat, trans fat, and cholesterol intake, increase physical activity
- Recommend statins for DM with
  - Overt CHD, regardless of LDL-C baseline level
  - Age >40 y + at least 1 CHD factor, regardless of LDL-C baseline level
  - LDL-C >100 mg/dL
  - Multiple CHD risk factors

ADA Recommendation on lipid Management

- Goals of therapy
  - LDL-C <70 mg/dL in patients with CHD
  - LDL-C <100 mg/dL in patients without CHD
  - Reduction in LDL-C 40% from baseline
- Other lipid goals
  - TG <150 mg/dL
  - HDL-C >40 mg/dL in men, >50 mg/dL in women

AHA Recommendation on Lipid Management in DM

- Same recommendation as ADA in LDL-C management
- After achieving LDL-C goal, AHA recommend non-HDL-C goal (30 mg/dL above LDL-C goal) as secondary target (=NCEP ATP III) instead of TG and HDL-C goal recommended by ADA

ADA recommendation on Antiplatelet Therapy in Diabetes

- Recommend aspirin 75-162 mg/day
  - Patients with CHD
  - Patients at increased CHD
    - >40 years
    - Family history of CHD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria
- Not recommended in pt <30 years

Circulation 2007; 115: 114-126
AHA Recommendation on Antiplatelet Therapy in Diabetes

- Same recommendation as ADA on aspirin therapy
- In primary prevention, aspirin only recommended in patients with 10-y risk for CHD >10%

Circulation 2007; 115: 114-126

ADA Management of Diabetic Kidney Disease

- To reduce risk or slow progression of nephropathy
  - Optimize glucose control
  - Optimize blood pressure control
- Pharmacotherapy
  - Type 1 DM with any degree of albuminuria, ACEIs delay progression of nephropathy
  - Type 2 DM with microalbuminuria, both ACEIs and ARBs delay progression to macroalbuminuria
  - Type 2 DM with macroalbuminuria and Scr>1.5 mg/dL, ARBs delay progression of nephropathy

ADA Management of Diabetic Kidney Disease

- Monitor albumin excretion for assessment of response to therapy and disease progression
- Spot urine albumin-to-creatinine ratio
  - Normal <30 µg/mg
  - Microalbuminuria 30-299 µg/mg
  - Macroalbuminuria ≥300 µg/mg
- Using Scr to estimate GFR and staging of kidney disease

Definition of CKD

1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either
   - Pathological abnormalities; or
   - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

2. GFR <60 mL/min/1.73 m² for ≥3 months, with or without kidney damage

Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

K/DOQI Definition and Staging of CKD
K/DOQI: ความสำคัญของภาวะ Proteinuria

- เลือก ACEIs หรือ ARBs as preferred agents
- ใช้ติดตามการตอบสนองของผู้ป่วยเมื่อดื่มยาคุมความดันเลือด
- เป็นปัจจัยเสี่ยงสำคัญใน progression of CKD และการเกิดโรคหัวใจและหลอดเลือด
- ถ้าพบ protein-to-creatinine > 500-1000 mg/g ให้ลดเป้าหมายความดันให้ต่ำกว่าคิวตีมีกิ้น (BP<125/75 mmHg) และ intensify ยาที่มีผลลด proteinuria

K/DOQI: ACEIs and ARBs

- ใช้ยาในขนาด moderate to high dose
- ใช้แทนกันได้ระหว่าง ACEIs และ ARBs ในผู้ป่วย CKD
- ใช้ยาทั้ง 2 ตัวร่วมกันได้ เพื่อเสริมฤทธิ์ลด proteinuria
- Monitor BP, serum K+, creatinine, GFR
- Discontinue ถ้า
  - GFR ลดลง >30% จาก baseline ในช่วงเวลา 4 เดือน
  - Serum K+ > 5.5 mEq/L
- ไม่มีการกำหนด baseline creatinine ที่ห้ามใช้ยา

Interventions:
- Ramipril 10 mg/day (n=8576)
- Telmisartan 80 mg/day (n=8542)
- Combination of both drugs (n=8502)

Median follow-up time: 56 months

Outcomes: Death from CV, MI, stroke, hospitalization for HF

ONTARGET Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ramipril (N = 8576)</th>
<th>Telmisartan (N = 8542)</th>
<th>Combination Therapy (N = 8502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical History — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6382 (74.4)</td>
<td>6367 (74.5)</td>
<td>6353 (74.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4146 (48.3)</td>
<td>4124 (49.3)</td>
<td>4139 (49.3)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>3039 (35.4)</td>
<td>2958 (34.6)</td>
<td>2960 (34.8)</td>
</tr>
<tr>
<td>Unstable</td>
<td>1257 (14.7)</td>
<td>1296 (15.2)</td>
<td>1264 (14.9)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attacks</td>
<td>1805 (21.0)</td>
<td>1758 (20.6)</td>
<td>1779 (20.9)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1136 (13.2)</td>
<td>1161 (13.6)</td>
<td>1171 (13.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5918 (69.0)</td>
<td>5862 (68.6)</td>
<td>5827 (68.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3146 (37.6)</td>
<td>3246 (38.0)</td>
<td>3220 (37.9)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1085 (12.7)</td>
<td>1120 (13.1)</td>
<td>1082 (12.7)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>929 (13.1)</td>
<td>923 (13.2)</td>
<td>929 (13.3)</td>
</tr>
</tbody>
</table>

ONTARGET: Result

Composite primary outcomes: death from CV causes, MI, stroke or hospitalization for HF

ONTARGET Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ramipril (N = 8576)</th>
<th>Telmisartan (N = 8542)</th>
<th>Combination Therapy (N = 8502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>5234 (61.0)</td>
<td>5294 (62.0)</td>
<td>5255 (61.8)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>4847 (56.5)</td>
<td>4860 (56.9)</td>
<td>4876 (57.4)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6473 (75.3)</td>
<td>6469 (75.7)</td>
<td>6461 (76.0)</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine</td>
<td>927 (10.8)</td>
<td>966 (11.3)</td>
<td>931 (11.0)</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>6003 (68.5)</td>
<td>6026 (68.1)</td>
<td>6098 (61.1)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2454 (28.6)</td>
<td>2359 (27.6)</td>
<td>2351 (27.7)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>2821 (32.9)</td>
<td>2787 (32.6)</td>
<td>2864 (33.7)</td>
</tr>
</tbody>
</table>

ONTARGET: Result

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N = 8576)</th>
<th>Telmisartan (N = 8542)</th>
<th>Combination Therapy (N = 8502)</th>
<th>Telmisartan vs. Ramipril</th>
<th>Combination Therapy vs. Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure</td>
<td>1412 (16.5)</td>
<td>1423 (16.7)</td>
<td>1386 (16.3)</td>
<td>1.01 (0.94–1.09)</td>
<td>0.99 (0.92–1.07)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, or stroke</td>
<td>1210 (14.1)</td>
<td>1190 (13.9)</td>
<td>1200 (14.1)</td>
<td>0.99 (0.91–1.07)</td>
<td>1.00 (0.93–1.09)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413 (4.8)</td>
<td>440 (5.2)</td>
<td>438 (5.2)</td>
<td>1.07 (0.94–1.22)</td>
<td>1.08 (0.94–1.23)</td>
</tr>
<tr>
<td>Stroke</td>
<td>405 (4.7)</td>
<td>369 (4.3)</td>
<td>373 (4.4)</td>
<td>0.91 (0.79–1.05)</td>
<td>0.93 (0.81–1.07)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>354 (4.2)</td>
<td>394 (4.6)</td>
<td>332 (3.9)</td>
<td>1.12 (0.97–1.29)</td>
<td>0.95 (0.82–1.10)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>603 (7.0)</td>
<td>598 (7.0)</td>
<td>620 (7.3)</td>
<td>1.00 (0.89–1.12)</td>
<td>1.04 (0.93–1.17)</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
<td>411 (4.8)</td>
<td>391 (4.6)</td>
<td>445 (5.2)</td>
<td>0.96 (0.83–1.10)</td>
<td>1.10 (0.96–1.26)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1014 (11.8)</td>
<td>989 (11.6)</td>
<td>1065 (12.5)</td>
<td>0.98 (0.90–1.07)</td>
<td>1.07 (0.98–1.16)</td>
</tr>
</tbody>
</table>
Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial

Johannes F Meier, Roland E Schmidt, Matthew McQueen, Leanne Dyer, Helmut Schumacher, Janice Payne, Xingyu Wang, Aldo Maggioni, Andrea Buja, Syed Ali Raza Khan, Kenneth Volstein, Marion Keitz, Kyri Metziner, Ali Obe, Alexandre Parikh, Leonel Silver, Tapani Vartiainen, Koen K Teo, Salem Yusuf, on behalf of the ONTARGET investigators

- **Interventions:**
  - Ramipril 10 mg/day (n=8576)
  - Telmisartan 80 mg/day (n=8542)
  - Combination of both drugs (n=8502)

- **Median follow-up time:** 56 months

- **Outcomes:** renal function and proteinuria

Lancet 2008; 372: 547–553
ONTARGET

- Combination of telmisartan and ramipril did not improve cardiovascular and renal outcomes compared to either drug alone
- Telmisartan did not increase MI or cardiovascular outcome compared to ramipril

BENEDICT

- Intervention (f/u 3 yr, target BP 120/80 mmHg)
  - Trandolapril (2 mg/d) + verapamil (SR 180 mg/d)
  - Trandolapril alone (2 mg/d)
  - Verapamil alone (SR 240 mg/d)
  - Placebo
- Outcomes:
  - Development of persistent microalbuminuria (overnight albumin excretion ≥20 µg/min at two consecutive visits)
### BENEDICT

#### Characteristic

<table>
<thead>
<tr>
<th></th>
<th>Trandolapril (N=301)</th>
<th>Verapamil (N=303)</th>
<th>Verapamil plus Trandolapril (N=300)</th>
<th>Placebo (N=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>61.6±8.1</td>
<td>62.5±8.2</td>
<td>62.7±7.7</td>
<td>62.6±8.2</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>157 (52.2)</td>
<td>164 (54.1)</td>
<td>165 (55.0)</td>
<td>149 (49.7)</td>
</tr>
<tr>
<td>Body-mass index — yr</td>
<td>29.1±4.7</td>
<td>29.5±4.6</td>
<td>29.2±5.3</td>
<td>28.6±4.2</td>
</tr>
<tr>
<td>Known duration of diabetes — yr</td>
<td>7.7±6.7</td>
<td>8.2±6.4</td>
<td>7.7±6.7</td>
<td>7.8±6.8</td>
</tr>
<tr>
<td>Smoking status — no. (%)</td>
<td>Never smoked</td>
<td>169 (56.1)</td>
<td>185 (61.1)</td>
<td>157 (52.3)</td>
</tr>
<tr>
<td></td>
<td>Former smoker</td>
<td>91 (30.2)</td>
<td>88 (29.0)</td>
<td>107 (35.7)</td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
<td>41 (13.6)</td>
<td>30 (9.9)</td>
<td>36 (12.0)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin — %</td>
<td>5.8±1.4</td>
<td>5.9±1.3</td>
<td>5.8±1.4</td>
<td>5.8±1.4</td>
</tr>
<tr>
<td>Glucose — mg/dl</td>
<td>160.9±66.8</td>
<td>162.6±77.7</td>
<td>160.8±67.0</td>
<td>161.4±47.2</td>
</tr>
<tr>
<td>Trough blood pressure — mm Hg</td>
<td>150.8±14.8</td>
<td>150.1±13.1</td>
<td>150.5±13.3</td>
<td>151.9±15.4</td>
</tr>
<tr>
<td></td>
<td>Systolic</td>
<td>87.4±7.7</td>
<td>87.5±7.2</td>
<td>87.3±8.1</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>87.4±7.7</td>
<td>87.5±7.2</td>
<td>87.7±7.6</td>
</tr>
<tr>
<td></td>
<td>Mean arterial pressure</td>
<td>108.6±8.6</td>
<td>108.4±7.7</td>
<td>108.3±8.4</td>
</tr>
</tbody>
</table>

#### Treatment

<table>
<thead>
<tr>
<th>Glucose-lowering regimen</th>
<th>Trandolapril (N=301)</th>
<th>Verapamil (N=303)</th>
<th>Verapamil plus Trandolapril (N=300)</th>
<th>Placebo (N=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet alone</td>
<td>79 (26.2)</td>
<td>92 (30.4)</td>
<td>96 (32.0)</td>
<td>88 (29.3)</td>
</tr>
<tr>
<td>Oral hypoglycemic agent</td>
<td>155 (46.8)</td>
<td>169 (55.8)</td>
<td>165 (53.0)</td>
<td>175 (58.3)</td>
</tr>
<tr>
<td>Insulin and oral hypoglycemic agent</td>
<td>15 (5.0)</td>
<td>25 (8.3)</td>
<td>19 (6.3)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>Insulin alone</td>
<td>12 (4.0)</td>
<td>17 (5.6)</td>
<td>20 (6.7)</td>
<td>18 (6.0)</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>Any</td>
<td>172 (57.1)</td>
<td>162 (53.5)</td>
<td>161 (51.7)</td>
</tr>
<tr>
<td>Duetic</td>
<td>66 (21.9)</td>
<td>70 (23.1)</td>
<td>58 (19.3)</td>
<td>65 (21.7)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>31 (10.3)</td>
<td>24 (7.9)</td>
<td>23 (7.7)</td>
<td>25 (8.3)</td>
</tr>
<tr>
<td>Calcium-channel blocker (dihydropyridine)</td>
<td>73 (24.3)</td>
<td>88 (29.0)</td>
<td>87 (29.0)</td>
<td>90 (30.0)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>Any</td>
<td>38 (12.6)</td>
<td>39 (12.9)</td>
<td>36 (12.0)</td>
</tr>
<tr>
<td>Statin alone</td>
<td>25 (8.3)</td>
<td>10 (3.3)</td>
<td>27 (9.0)</td>
<td>25 (8.3)</td>
</tr>
<tr>
<td>Fibrin alone</td>
<td>11 (3.7)</td>
<td>18 (5.9)</td>
<td>5 (1.7)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>Any</td>
<td>38 (12.6)</td>
<td>39 (12.9)</td>
<td>36 (12.0)</td>
</tr>
<tr>
<td>Statin and fibrin</td>
<td>25 (8.3)</td>
<td>10 (3.3)</td>
<td>27 (9.0)</td>
<td>25 (8.3)</td>
</tr>
</tbody>
</table>

#### Treatment

| Urinary albumin excretion — µg/min | 5.02 (3.47—7.89) | 5.91 (3.76—10.55) | 5.31 (3.54—9.24) | 3.07 (5.55—8.78) |
| Serum creatinine — mg/dl           | 0.9±0.2            | 0.9±0.2            | 0.9±0.2            | 0.9±0.2           |
| Triglycerides — mg/dl              | 147.0±82.3         | 143.2±87.7         | 147.5±79.5         | 147.0±98.8        |
| Cholesterol — mg/dl                | 207.2±37.4         | 210.1±36.9         | 206.9±34.3         | 215.1±38.0        |
| Total                               | 160.2±36.4         | 161.4±36.0         | 159.7±34.0         | 168.0±37.5        |
| Low-density lipoprotein             | 46.9±12.2          | 46.9±12.1          | 47.0±12.2          | 46.9±11.9         |

#### Subjects with Microalbuminuria (%)

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Placebo (N=300)</th>
<th>Verapamil plus Trandolapril (N=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>300</td>
<td>429</td>
</tr>
<tr>
<td>Verapamil plus Trandolapril</td>
<td>249</td>
<td>232</td>
</tr>
<tr>
<td>Placebo</td>
<td>229</td>
<td>214</td>
</tr>
</tbody>
</table>
BENEDICT

- Use of trandolapril alone or plus verapamil reduce incidence of microalbuminuria in type 2 diabetes with HTN and normal UAE
- Verapamil alone was not different from placebo in reducing microalbuminuria in this study

Beneficial Effects of Adding Spironolactone to Recommended Antihypertensive Treatment in Diabetic Nephropathy

RCT, double-blind, crossover study
- N= 21 diabetes type 2 with nephropathy
- Intervention
  - Spironolactone 25 mg/d
  - Placebo
- Outcomes
  - Urinary albumin excretion

Diabetes Care 28:2106–2112, 2005

Spironolactone in Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo</th>
<th>Spironolactone</th>
<th>Mean Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria (mg/24h)</td>
<td>1566</td>
<td>1067</td>
<td>-33%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mg/24h) (655-4208)</td>
<td>(429-2358)</td>
<td>(-41to -25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-h albuminuria (mcg/min)</td>
<td>1301</td>
<td>741</td>
<td>-43%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mcg/min) (844-2005)</td>
<td>(455-1206)</td>
<td>(-27 to -56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>74±6</td>
<td>71±6</td>
<td>-3</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(455-1206)</td>
<td>(-6 to 0.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Spironolactone in Diabetic Nephropathy

- In small trial, spironolactone show beneficial effects on reducing albumin excretion in type 2 diabetes with nephropathy when added to concurrent antihypertensive therapy
- By average, spironolactone further reduce BP in the study by 10/5 mmHg for office BP
- 1 discontinue due to hyperkalemia

Summary

- Lifestyle intervention
- Glycemic control
  - A1C <7%
  - Metformin as initial agent with lifestyle intervention
- BP control
  - Goal BP <130/80 mm Hg
  - ACEI or ARB preferred initial agent
- Lipid management
  - LDL-C <100 mg/dL
  - Statins first line agent
- Antiplatelet
  - Aspirin in CHD or high-risk >40 years + risk factor
- Smoking cessation