Contents
(Treatment of 2 Cases)

❖ Type 2 Diabetes Mellitus

❖ Hypertension
Case 1

- Male / 58 years old
- 15 years history of hypertension and diabetes
- Ex-smoker; quit 15 years ago (daily 0.5 pack)
Physical Exam

- BWt 72 kg, Height 167 cm
- BMI 25.8 kg/m²,
- Waist circumference 98 cm
- Blood pressure: 194/128 mmHg
Laboratory results

- **HbA1c**: 10.1 %, **FBS**: 198mg/dl
- **Lipid profile (mg/dl)**
  - TC: 218, LDLc: 143, TG: 282, HDLc: 44
- **Echo**:
  - LVH 14.3/13.3 mm
  - EF: 60-65%
- **U/A**: proteinuria 1+
- **Micro-albumin**: 16.26mg/dL
Medication

- Exforge (amlodipine/valsartan 5/80 mg) od
- Rosuvastatin 10 mg od
- Metformin 500mg od
Two weeks later

- Blood pressure: 138/96 mmHg
- PP2: 256mg/dl, HbA1c: 10.6%

Medication

- Exforge 5/80 mg od
- Rosuvastatin 10 mg od
- Metformin 500mg bid
- Indapamide 1.5mg bid
- Galvus 50mg bid
Two month later

- Blood Pressure: 122/76 mmHg
- HbA1c: 6.8%
- PP2: 173 mg/dl
Diabetes vs. Dysglycemia

- **Diagnostic criteria of Diabetes (ADA, 2011)**
  - FPG $\geq 126$ mg/dl
  - PP2hr glucose $\geq 200$ mg/dl after OGTT
  - Random glucose $\geq 200$ mg/dl with 3P’s Sx
  - HbA1C $\geq 6.5$
  - IFG: 100-125 / IGT: PP2h of 140-199 mg/dl
Prevalence of diabetes

- 6.2% of total population
- 20% of persons over 65
- Highest in ethnic groups
  - African American (up to 12%)
  - Asian American (up to 22%)
  - Latin American (up to 20%)
  - Native American (up to 60%)
Prevalence of Dysglycemia in General Population, KNHANES 2008, >20 yo

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>7.4%</td>
</tr>
<tr>
<td>30-39</td>
<td>17%</td>
</tr>
<tr>
<td>40-49</td>
<td>30.4%</td>
</tr>
<tr>
<td>50-59</td>
<td>47.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>44%</td>
</tr>
<tr>
<td>70+</td>
<td>18.7%</td>
</tr>
<tr>
<td>IFG</td>
<td>8.4%</td>
</tr>
<tr>
<td>DM</td>
<td>27.1%</td>
</tr>
<tr>
<td>Total</td>
<td>909.4만</td>
</tr>
<tr>
<td></td>
<td>(627.8만)</td>
</tr>
<tr>
<td></td>
<td>(281.5만)</td>
</tr>
</tbody>
</table>
People with both diabetes and hypertension have approximately **twice the risk of cardiovascular disease** as non-diabetic people with hypertension.

In the UKPDS epidemiological study, each 10-mmHg decrease in mean SBP was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications.
HRs for vascular outcomes by Fasting Glucose

* CHD (n=279,290), Ischemic stroke (n=175,542)
* Reference group : 5.0-5.5 mmol/L (90-99 mg/dL)

Lancet 2010;375:2215-22
HRs for vascular outcomes by Glucose, Cholesterol and BP

Lancet 2010;375:2215-22
Fasting Blood Glucose and Risk of Ischemic Stroke

*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819
Fasting Blood Glucose and Risk of Hemorrhagic Stroke

*after excluding diabetes,*
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence*

Circulation 2009;119;812-819
Fasting Blood Glucose and Risk of Myocardial Infarction

*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819
HbA1C and Cardiovascular Death in non-DM

Reference: 0.0427 (4.27%)

Results for total CV events were similar

Diabetologia. 2011 Feb
HbA1c was significantly associated with cardiovascular events and deaths in persons without diabetes.
## Glycemic control and CVD in Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

- Initial Trial: Down
- Long-term F/U: Red Border
Clinical trials of glucose-lowering therapies in people with dysglycemia

- Intensive versus standard glycemic control in people with well-established diabetes have not proved whether either strategy has cardiovascular benefit (ACCORD, VADT, ADVANCE)

- Intensive glycemic control in people with newly diagnosed diabetes reduces their long-term risk of cardiovascular disease (UKPDS, UKPDS-FU)

# Current Targets for Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>ACE</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1C (%)</strong></td>
<td>&lt;7.0</td>
<td>≤6.5</td>
<td>≤6.5</td>
</tr>
<tr>
<td><strong>Fasting (mg/dL)</strong></td>
<td>90-130</td>
<td>&lt;110</td>
<td>&lt;100</td>
</tr>
<tr>
<td><strong>Postprandial</strong></td>
<td>&lt;180*</td>
<td>&lt;140</td>
<td>&lt;135</td>
</tr>
</tbody>
</table>


Determining the optimal HbA1c goal

The goal: HbA1c < 7%

Adjust according to the following criteria:

1. Risk OF HYPOGLYCEMIA
2. Risk FROM HYPOGLYCEMIA
3. LOW BENEFIT from tight glycemic control

If 1-2 TRUE, HbA1c < 7%

If 2-3 TRUE, Set individual goal. Generally: HbA1c < 7.5-8%

HbA1c < 6.5%
Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

STEP 1

STEP 2
Lifestyle + Metformin + Basal insulin
Lifestyle + Metformin + Sulfonylurea

STEP 3
Lifestyle + Metformin + Intensive insulin

Tier 2: Less well-validated therapies

Lifestyle + Metformin + Pioglitazone
- No hypoglycemia
- Oedema/CHF
- Bone loss

Lifestyle + Metformin + GLP-1 agonist
- No hypoglycemia
- Weight loss
- Nausea/vomiting

Lifestyle + Metformin + Pioglitazone + Sulfonylurea

Lifestyle + Metformin + Basal insulin
### Recently Diagnosed Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Young 15-40</th>
<th>Middle 40-70</th>
<th>Elderly &gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications, Duration of disease &gt; 10Yrs</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;6</td>
<td>&lt;6.5</td>
<td>&lt;6.5</td>
</tr>
</tbody>
</table>

### 당화혈색소 목표치 개별화의 예

<table>
<thead>
<tr>
<th>당화혈색소(%)</th>
<th>위험요소</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.0</td>
<td>40세 이하, 당뇨병 초기, 합병증 없는 경우</td>
</tr>
<tr>
<td>&lt; 6.5</td>
<td>65세 이하, 당뇨병 10년 이하, 합병증이 없는 경우</td>
</tr>
<tr>
<td>7.0 -</td>
<td>65세 이상, 당뇨병 10년 이상, 합병증을 동반 경우</td>
</tr>
</tbody>
</table>

DIABETES/METABOLISM RESEARCH AND REVIEWS  
Case 2

- F / 53 yo
- Long hypertension history since 15 yo
- Treat hypertension with short acting nifedipine since 43 yo
- Diagnose T2 DM at 3 years ago
P/Ex

(1) 165cm, 82Kg,  BMI 30.1
(2) W/H ratio: 1.1
(3) BP 150/95mmHg

Lab

(1) CBC, Electrolyte, LFT, BUN/Cr : WNL
(2) HbA1c: 7.3 %, FBS: 138mg/dl
(3) T-Chol 257 mg/dl, TG 204 mg/dl, HDL 42mg/dl, LDL 198 mg/dl
(4) CK-MB 7.8 mg/dl, Troponin-I 0.07 mg/dl
(5) Microalbuminuria: 55mg/min
Echocardiography

(1) normal LV wall motion (EF=65%)
(2) No valvular abnormality
(3) mild LVH
RAO-Caudal View

RAO-Cranial View
What is the clinical diagnosis?

Multiple choice

① Hypertension

② T2 DM with nephropathy

③ Dyslipidemia; high TG 204, low HDL 43

④ Abdominal obesity

⑤ Metabolic syndrome

⑥ Coronary heart disease
What is the choice of antihypertensive drugs? Multiple choice

① Diuretic
② B-blocker
③ CCB
④ ACEI
② ARB
### First choice of antihypertensive drug (JNC-7)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Diuretic</th>
<th>B-blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>○</td>
</tr>
<tr>
<td>CHF</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>○</td>
</tr>
<tr>
<td>Post MI</td>
<td>○(antialdosterone)</td>
<td>○</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○</td>
</tr>
</tbody>
</table>
Table 1

Recommended Target Blood Pressure and Drugs in Patients With Diabetes Mellitus and Nephropathy

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Blood Pressure Goal, mm Hg</th>
<th>Hypertension</th>
<th>Type 1 Diabetic Nephropathy</th>
<th>Type 2 Diabetic Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC VII(^1)</td>
<td>2004</td>
<td>(&lt;130/85, 125/75) if proteinuria present</td>
<td>ACE, ARB, (\beta)-blockers, CA, diuretic</td>
<td>ACE/ARB</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>American Diabetes Association(^8)</td>
<td>2002</td>
<td>(&lt;130/80)</td>
<td>ACE, ARB, (\beta)-blockers, CA, diuretic</td>
<td>ACE/ARB</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>National Kidney Foundation(^5)</td>
<td>2002</td>
<td>(&lt;130/80, 125/75) if proteinuria present</td>
<td>—</td>
<td>ACE/ARB</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>European Society of Hypertension(^4)</td>
<td>2003</td>
<td>(&lt;130/80)</td>
<td>ACE, ARB, (\beta)-blockers, CA, diuretic</td>
<td>ACE/ARB</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>British Hypertension Society(^7)</td>
<td>2004</td>
<td>(&lt;130/80)</td>
<td>ARB, diuretic</td>
<td>ACE</td>
<td>ACE</td>
</tr>
</tbody>
</table>

JNC VII = Joint National Committee on Prevention, Detection, Valuation, and Treatment of High Blood Pressure; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CA = calcium antagonist.
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Treated (n/n)</th>
<th>Control (n/n)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPP (28)</td>
<td>337/5183</td>
<td>380/5230</td>
<td>0.888 (0.762-1.033)</td>
</tr>
<tr>
<td>STOP-2 (29)</td>
<td>93/1969</td>
<td>192/3926</td>
<td>0.964 (0.748-1.243)</td>
</tr>
<tr>
<td>HOPE (30)</td>
<td>102/2837</td>
<td>155/2883</td>
<td>0.656 (0.508-0.847)</td>
</tr>
<tr>
<td>ALLHAT (32)</td>
<td>241/4605</td>
<td>319/3979</td>
<td>0.634 (0.533-0.753)</td>
</tr>
<tr>
<td>SOLVD Montreal Substudv (33)</td>
<td>9/153</td>
<td>31/138</td>
<td>0.632 (0.543-0.796)</td>
</tr>
<tr>
<td>ANBP-2 (37)</td>
<td>163/2718</td>
<td>202/2721</td>
<td>0.216 (0.099-0.472)</td>
</tr>
<tr>
<td>LIFE</td>
<td>220/4096</td>
<td>883/10720</td>
<td></td>
</tr>
<tr>
<td>CHARM overall</td>
<td>138/3044</td>
<td>200/3039</td>
<td></td>
</tr>
<tr>
<td>SCOPE</td>
<td>690/5308</td>
<td>845/5152</td>
<td></td>
</tr>
<tr>
<td>ALPINE</td>
<td>335/3432</td>
<td>399/3472</td>
<td></td>
</tr>
<tr>
<td>VALUE</td>
<td>567/7072</td>
<td>799/7040</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2989/42780</td>
<td>4528/50671</td>
<td></td>
</tr>
</tbody>
</table>

DM developed in 8.2% with ARBs, compared with 10.5% with placebo or other agents (OR 0.73, 95% CI 0.64 to 0.84, p < 0.001)
The mechanism of prevention of DM by inhibition of the RAS

- Hemodynamic benefits
  - antagonizing the Ang II–mediated hypoperfusion of skeletal muscle or pancreatic islet cells.

- Direct inhibitory effects of angiotensin II on insulin signaling and glucose transport

- Reduction in islet fibrosis and increased B-cell mass, by decreasing oxidative stress, apoptosis, and profibrotic pathways
Clinical course

- LAD stenosis → PTCA and stenting
- 100mg ASA, 75mg Clopidogrel
- 10mg Lipitor
- 2.5mg bisoprolol
- 8mg perindopril

BP 120~130/80~90mmHg
No chest pain
Good lipid and glucose level
Controversy for target BP in diabetic patients
Major guidelines in patients with diabetes or a history of CV or renal disease; ESH 2007, JNC 7 and ADA 2010

- Recommend drug treatment to be initiated within a lower BP range
  - a SBP between 130 and 139 mmHg and
  - a DBP between 85 and 89 mmHg,
- aiming at achieving SBP/DBP values 130/80 mmHg.
Classic diagram for antihypertensive management in diabetes

- **BP > 130/80 mmHg**
  - Start ACEI or ARB titrate upwards
    - **If BP still not 130/80 mmHg**
      - Add thiazide or long-acting CCB
        - **If BP still not 130/80 mmHg**
          - **HR > 84 bpm**
            - Add low-dose B-blocker or aB-blocker
          - **HR < 84 bpm**
            - Add other subgroup of long-acting CCB
ACCORD Blood Pressure Trial

Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus

ACCORD Study Design

Designed to independently test three medical strategies to reduce CVD in diabetic patients

• BP question: does a therapeutic strategy targeting SBP <120 mmHg reduce CVD events compared to a strategy targeting SBP <140 mmHg in patients with type 2 diabetes at high risk for CVD events
Systolic Pressures (mean ± 95% CI)

Average: 133.5 Standard vs. 119.3 Intensive, Delta = 14.2

Mean # Meds

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

N = 4382                        4050                       2391                        359
## Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive Events (%/yr)</th>
<th>Standard Events (%/yr)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.89 (0.73-1.07)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Total Mortality</strong></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><strong>Cardiovascular Deaths</strong></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><strong>Nonfatal MI</strong></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><strong>Nonfatal Stroke</strong></td>
<td>34 (0.30)</td>
<td>55 (0.47)</td>
<td>0.63 (0.41-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Total Stroke</strong></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>

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)
Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

Total Stroke

HR = 0.89
95% CI (0.73-1.07)

HR = 0.59
95% CI (0.39-0.89)

NNT for 5 years = 89

Intensive  Standard
# Adverse Events

<table>
<thead>
<tr>
<th>Event</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>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.0001</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 Arrhythmia</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 (1.2)</td>
<td>58 (1.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Dizziness on Standing†</td>
<td>217 (44)</td>
<td>188 (41)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

† Symptom experienced over past 30 days from HRQL sample of N=943 participants assessed at 12 and 48 months post-randomization.
# Clinical Parameters assessed at last clinic visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intensive</th>
<th>Standard</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mean mg/dl)</td>
<td>4.3</td>
<td>4.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Creatinine (mean mg/dl)</td>
<td>1.1</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estimated GFR (mean mL/min/1.73m²)</td>
<td>74.8</td>
<td>80.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary Alb/Cr (median mg/g)</td>
<td>11.0</td>
<td>13.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macroalbuminuria (%)</td>
<td>6.6</td>
<td>8.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

JAMA. 2010;304:61-68
Primary Outcome

Composite endpoint of all-cause death, nonfatal myocardial infarction, or nonfatal stroke

Overall log-rank $P < .001$

Tight control vs usual control log–rank $P = .19$

Cumulative Event Rate, %

Systolic blood pressure control
- Uncontrolled
- Tight
- Usual

Time to Event, y
Cumulative Event Rates

Nonfatal myocardial infarction

- Systolic blood pressure control
  - Uncontrolled
  - Tight
  - Usual

Overall log-rank $P < .001$
Tight control vs usual control log-rank $P = .49$

Nonfatal stroke

Overall log-rank $P < .001$
Tight control vs usual control log-rank $P = .38$
All-cause mortality

Overall log-rank $P < .001$
Tight control vs usual control log-rank $P = .04$

Overall log-rank $P < .001$
Tight control vs usual control log-rank $P = .06$

Extended follow-up
2009 Reappraisal of ESH guidelines: hypertension treatment initiation

- Initiation of antihypertensive drug therapy in diabetic patients with high normal BP is presently unsupported by prospective trial evidence.

- For the time being, it appears prudent to recommend treatment initiation in high normal BP diabetic patients if subclinical organ damage (particularly microalbuminuria or proteinuria) is present.
Strategy for management of Hypertensive Diabetic patients

- Proper blood sugar control.
- Achieve target level of BP control for diabetic patients.
- Early Detection of both diabetes and hypertension complications & manage them as well as delay their progression.
- Improve patient’s quality of life.
Thanks for your attention!