Diabetes & Dyslipidemia: Early Treatment for Optimum Outcomes
I. Type 1 diabetes* (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defects of β-cell function
   B. Genetic defects in insulin action
   C. Diseases of the exocrine pancreas
   D. Endocrinopathies
   E. Drug- or chemical-induced
   F. Infections
   G. Uncommon forms of immune-mediated diabetes
   H. Other genetic syndromes sometimes associated with diabetes

IV. Gestational diabetes mellitus (GDM)

[Diabetes Care 26:S5-S20, 2003]
Cell Morphology in the Pancreas: β-Cell Disorders in T1DM

- Normal
- T1DM

- β-Cells (insulin)
- α-Cells (glucagon)

- Autoimmune process/unknown origin
- β-cell amount is very little/depleted

Pancreatic Islet Morphology: Structural Defects are Evident in T2DM

- Disorganized and misshaped
- Marked reduction in β-cell number
- Amyloid plaques

Insulin Deficiency is Often Already Established when T2DM is Diagnosed

Organs Involved with Glucose Homeostasis

- Liver
- Pancreas
  - Sulfonylureas
  - Glinides, GLP-1RA
  - DPP-4 Inhibitors
- Kidneys
  - SGLT2 Inhibitors
- Adipose
  - Metformin
  - TZDs
  - GLP-1RA
- Gut
  - Insulin
  - TZDs
  - GLP-1RA
  - Bromocriptine
  - α-glucosidase inhibitors
  - GLP-1RA, Colesevelam
- Muscle
- Brain

Modifikasi pola hidup sehat

**HbA1c < 7.5%**
- Monoterapi* dengan salah satu obat di bawah ini
  - Metformin
  - Agonis GLP-1
  - Penghambat DPP-IV
  - Penghambat Glukosidase Alfa
  - Penghambat SGLT-2**
  - Tiazolidindion
  - Sulfonilurea
  - Glinid

Jika HbA1c > 6.4% dalam 3 bulan tambahan obat ke 2 (kombinasi 2 obat)

**HbA1c ≥ 7.5%**
- Kombinasi 2 obat* dengan mekanisme kerja yang berbeda
  - Agonis GLP-1
  - Penghambat DPP-IV
  - Tiazolidindion
  - Penghambat SGLT-2
  - Insulin Basal
  - SU/Glinid
  - Kolsevelam**
  - Bromokriptin-QR
  - Penghambat Glukosidase Alfa

Jika belum memenuhi sasaran dalam 3 bulan, masuk ke kombinasi 3 obat

**HbA1c ≥ 9.0%**
- Kombinasi 2 obat
  - Insulin ± obat jenis lain

Gejala (-) Gejala (+)

Kombinasi 3 obat

Keterangan
*Obat yang terdaftar, pemilihan dan penggunaannya disarankan mempertimbangkan faktor keuntungan, kerugian biaya, dan ketersediaan sesuai tabel 11
**Kolsevelam belum tersedia di Indonesia
Bromokriptin QR umumnya digunakan pada terapi tumor hipofisis
Detection and Diagnosis of Gestational DM

- Screen for undiagnosed T2DM at the first prenatal visit in those with risk factors, using standard diagnostic criteria
- In pregnant women not previously known to have diabetes, screen for GDM at 24–28 weeks’ gestation, using a 75-g OGTT and specific diagnostic cut points
- Screen women with GDM for persistent diabetes at 6-12 weeks’ postpartum, using a test other than A1C
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years
- Women with a history of GDM found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes

ADA. III. Detection and Diagnosis of GDM. *Diabetes Care* 2012;35(suppl 1):S15.
# PERKENI: Diabetes Prevention

## Management

<table>
<thead>
<tr>
<th>Early Detection</th>
<th>Lifestyle Changes</th>
<th>Pharmacology Therapy</th>
<th>Periodic Blood Glucose &amp; Risk Factor Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk population at &lt; 30-year old</strong></td>
<td><strong>Medical Nutritional Therapy</strong></td>
<td><strong>Not yet recommended</strong></td>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>• Family history of DM</td>
<td>• Physical activity</td>
<td></td>
<td><strong>Dyslipidemia</strong></td>
</tr>
<tr>
<td>• Cardiovascular disorder</td>
<td>• Weight reduction</td>
<td></td>
<td><strong>Physical health</strong></td>
</tr>
<tr>
<td>• Overweight</td>
<td></td>
<td></td>
<td><strong>Body weight control</strong></td>
</tr>
<tr>
<td>• Sedentary life style</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Known IFG or IGT</td>
<td>• If overweight, reduce body weight by 5-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Physical exercise for 30 minutes, 5 times/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elevated triglyceride, low HDL or both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• History of Gestational DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• History of given birth &gt; 4000g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 2-hour OGTT is the most sensitive method for early detection and a recommended screening test procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Management**

- **Periodic Blood Glucose & Risk Factor Monitoring**
  - Hypertension
  - Dyslipidemia
  - Physical health
  - Body weight control

---

**Pharmacology Therapy**

- Not yet recommended

---

**Lifestyle Changes**

- Medical Nutritional Therapy
- Physical activity
- Weight reduction
- If overweight, reduce body weight by 5-10%
- Physical exercise for 30 minutes, 5 times/week

---

**Early Detection**

- High-risk population at < 30-year old
- Family history of DM
- Cardiovascular disorder
- Overweight
- Sedentary life style
- Known IFG or IGT
- Hypertension
- Elevated triglyceride, low HDL or both
- History of Gestational DM
- History of given birth > 4000g
- PCOS

---

**2-hour OGTT is the most sensitive method for early detection and a recommended screening test procedure**
# Target of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Risk CVD (-)</th>
<th>Risk CVD (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>18.5 – &lt;23</td>
<td>18.5 – &lt;23</td>
</tr>
<tr>
<td><strong>Blood Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FPG (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>• Post Prandial BG (mg/dL)</td>
<td>&lt;140</td>
<td>&lt;140</td>
</tr>
<tr>
<td><strong>A1C (%)</strong></td>
<td>&lt;7.0</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt;130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td><strong>Lipid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>&lt;200</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>&gt;40 / &gt;50</td>
<td>&gt;40 / &gt;50</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

PERKENI GUIDELINES 2011
Dyslipidemia in Indonesia

- International Diabetes Management Practices Study (IDMPS)
  - Study of 674 patients with T2DM

- 53.5% had dyslipidemia
  - 44.5% were receiving treatment

- Demonstrated that the metabolic control of diabetes is not good enough to prevent complications

Current practice in the management of type 2 diabetes in Indonesia. Results from IDMPS. J Indon Med Assoc 2011
Percentage of Patients at LDL-C goals recommended by the 2004 updated NCEP ATP III* guidelines

% of Patients at LDL-C goals recommended by 2004 updated NCEP ATP III* guidelines

- For patients in Hong Kong the treatment goal attainment rate was 82.9% while patients in other countries had very low LDL-C attainment rate (31.3 – 52.7%).

CLASSIFICATION

• Primary Dyslipidemia
• Secondary Dyslipidemia
  – Diabetes melitus
  – Hipothyroidism
  – Obstructive liver disease
  – Nephrotic Syndrome
  – Medication that could increase LDL and decrease HDL such as: progestin, anabolic steroid, corticosteroid, beta-blocker
# Abnormal Lipid Metabolism

<table>
<thead>
<tr>
<th>Increased:</th>
<th>Decreased:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Triglycerides</td>
<td>• HDL</td>
</tr>
<tr>
<td>• Very-low-density lipoprotein (VLDL)</td>
<td>• Apolipoprotein A-I</td>
</tr>
<tr>
<td>• LDL and small dense LDL</td>
<td></td>
</tr>
<tr>
<td>• Apolipoprotein B</td>
<td></td>
</tr>
</tbody>
</table>

Major Risk Factors Affecting Lipid Goals

- Cigarette smoking
- Hypertension (≥140/90 mm Hg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL)
- Family history of early heart disease
- Age (men ≥45 years; women ≥55 years)
Screening for Dyslipidemia

• Persons without diabetes
  – Test at least every 5 years, starting at age 20, including adults with low-risk values

• Persons with diabetes
  – In adults, test at least annually
  – Lipoproteins: measure after initial BG control is achieved as hyperglycemia may alter results
Low HDL-C: Independent Predictor of CHD Risk, Even When LDL-C is Low
Lowering Lipid Blood Level
Accounted for >70% of CV Risk Reduction in Diabetes

Multifactorial therapy in type 2 DM, to achieve:
BP <130/80, HbA1c < 6.5%, total cholest < 175 mg/dL

The most of the CV benefit was attributable to the use of lipid-lowering therapy

### Table 8.1—Recommendations for statin treatment in people with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin dose*</th>
<th>Monitoring with lipid panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
<td>Annually or as needed to monitor for adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factor(s)**</td>
<td>Moderate or high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD***</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
<td>As needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate or high</td>
<td>As needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

*In addition to lifestyle therapy.

**CVD risk factors include LDL cholesterol $\geq 100$ mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.

***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.
## Tata Laksana Dislipidemia

Berdasarkan ATP III dan ACC/AHA 2013

<table>
<thead>
<tr>
<th>Molekul</th>
<th>Efek pada Lipid</th>
<th>Efek Samping</th>
<th>Kontra Indikasi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATIN</strong></td>
<td>LDL 18-55%</td>
<td>Myopati, peningkatan enzim hati</td>
<td>Absolut: gangguan hati akut dan kronis</td>
</tr>
<tr>
<td></td>
<td>HDL 5-15%</td>
<td></td>
<td>Relatif: Penggunaan beberapa obat tertentu</td>
</tr>
<tr>
<td></td>
<td>TG 7-30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BILE ACID SEQUESTRANT</strong></td>
<td>LDL 15-30%</td>
<td>Gangguan gastrointestinal, konstipasi, penurunan absorbsi obat lain</td>
<td>Absolute: dysbetalipoproteinemia TG &gt; 400mg/dl</td>
</tr>
<tr>
<td></td>
<td>HDL 3-5%</td>
<td></td>
<td>Relatif: TG &gt; 200 mg/dl</td>
</tr>
<tr>
<td></td>
<td>TG no change</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NICOTINIC ACID</strong></td>
<td>LDL 5-25%</td>
<td>Flushing, hiperglikemia, gangguan gastrointestinal, hepatotoxic</td>
<td>Absolute: Gangguan hati kronis, gout</td>
</tr>
<tr>
<td></td>
<td>HDL 15-35%</td>
<td></td>
<td>Relatif: diabetes, hiperurisemia, ulkus peptikum</td>
</tr>
<tr>
<td></td>
<td>TG 20-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FIBRATE</strong></td>
<td>LDL 18-55%</td>
<td>Dispepsia, myopati, batu empedu</td>
<td>Absolut : gangguan ginjal dan hati yang berat</td>
</tr>
<tr>
<td></td>
<td>HDL 5-15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG 7-30%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Statin direkomendasikan sebagai pilihan utama pencegahan primer dan sekunder
- Obat lain dapat digunakan jika terdapat kontraindikasi statin
# TATA LAKSANA DISLIPIDEMIA

## Rekomendasi Statin (Berdasarkan ACC/AHA 2013)

<table>
<thead>
<tr>
<th>HIGH INTENSITY</th>
<th>MODERATE INTENSITY</th>
<th>LOW INTENSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penurunan LDL-C ≥ 50%</td>
<td>Penurunan LDL-C 30 – 50%</td>
<td>Penurunan LDL-C &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin 40 – 80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20 – 40 mg</td>
<td>Atorvastatin 10 – 20 mg</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 5 – 10 mg</td>
<td>Simvastatin 20 – 40 mg</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 – 80 mg</td>
<td>Pravastatin 10 – 20 mg</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 20 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 20 – 40 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 40 mg bid</td>
<td>Pitavastatin 2 – 4 mg</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 1 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACC/AHA Guidelines identify 4 statin benefit groups

**Group 1**
Clinical ASCVD
- CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

**Group 2**
LDL-C ≥190 mg/dL (~5 mmol/L)

**Group 3**
Diabetes mellitus
- age of 40–75 years
- LDL-C 70–189 mg/dL (1.8–4.9 mmol/L)

**Group 4**
ASCVD risk ≥7.5%
- No diabetes
- age of 40–75 years
- LDL-C 70–189 mg/dL (1.8–4.9 mmol/L)

---

ASCVD, atherosclerotic cardiovascular disease
CHD, coronary heart disease
LDL-C, low-density lipoprotein-cholesterol

Who is a High-risk Patient?

**European Society of Cardiology Guidelines**

- **Very high risk**
  - Documented CVD
  - DM (type 1 or 2) with one or more CV risk factors and/or target organ damage
  - Severe CKD
  - A calculated SCORE ≥10%.

- **High risk**
  - Markedly elevated single risk factors
  - DM (type 1 or 2) but without CV risk factors or target organ damage
  - Moderate CKD
  - SCORE of ≥5% and 10% for 10-year risk of fatal CVD

**ACC/AHA Guidelines**

- **Patients with clinical ASCVD**
- **Patients with primary elevation of LDL-C of >190 mg/dL**
- **Patients with diabetes aged 40-75 years with LDL-C of 70-189 mg/dL without clinical ASCVD**
- **Patients without clinical ASCVD or diabetes with LDL-C of 70-189 mg/dL and estimated 10-year ASCVD risk of >7.5%**

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, Low density lipoprotein-cholesterol; SCORE, Systematic Coronary Risk Evaluation Project.

2013 ACC/AHA Guideline Recommendations for Statin Therapy

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL-C ≥190 mg/dL</th>
<th>Diabetes; age 40-75 years*</th>
<th>Estimated 10-yr ASCVD risk ≥7.5%; age 40-75 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-Intensity statin (age ≤75 years)</td>
<td>• High-intensity statin</td>
<td>• Moderate-intensity statin</td>
<td>• Moderate- to high-intensity statin</td>
</tr>
<tr>
<td>• Moderate-intensity statin if &gt;75 years or not a candidate for high-intensity statin</td>
<td>• Moderate-intensity statin if not a candidate for high-intensity statin</td>
<td>• High-intensity statin if estimated 10 year ASCVD risk ≥7.5%</td>
<td></td>
</tr>
</tbody>
</table>

ASCVD prevention benefit of statin therapy may be less clear in other groups. Consider additional factors influencing ASCVD risk, potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

* With LDL-C of 70-189 mg/dL
† Estimated using the Pooled Cohort Risk Assessment Equations

Cardiovascular Risk Reduction: Recommendations of ESC Guidelines

- Smoking cessation
- Dietary modification
- Weight management
- Physical activity

Lifestyle modification

Management of comorbid conditions

Lipid-lowering drugs

ESC, European Society of Cardiology

Summary

• Screening for risk factors for development of DM helps identify patients early
• T1DM & T2DM can be distinguished by age onset, weight, and progression of signs and symptoms
• Each have different underlying pathophysiology and thus require different treatment and management strategies
• There are several different classes of anti-hyperglycemia medications available
  – Biguanides, SU, thiazolidinediones, alpha-glucosidase inhibitors, DPP-IV inh. and GLP-1 receptor agonists, SGLT2-inh.
• Each class differs in their target site, pharmacology, efficacy and safety profile
• Treatment algorithms aid in choosing which medication to use for each patient
Summary: Cardiometabolic Risk

- Assessing a patient’s cardiometabolic risk is important in the prevention of CVD and T2DM
- Dyslipidemia plays key role in the development of CVD especially with the presence of T2DM
- Identification of risk factors such as obesity, dyslipidemia and hypertension allow for the initiation of appropriate risk management strategies such as:
  - Lifestyle modification
  - Addition of pharmacologic agents in some clinical scenarios
Thank you