# Optimal Management of Dyslipidemia in Diabetes Mellitus

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## 1. Importance of Lowering LDL-Cholesterol in Diabetes Patients & Lipid Guidelines

## **Prevalence of dyslipidemia in Korea**





KSLA. Diabete fact sheet in Korea 2015

Prevalence of dyslipidemia in patients with DM in Korea

Dyslipidemia in DM



#### Comparison of Influence of Multiple Risk Factors\* on CVD Death Rates in Diabetic and Non-diabetic Men



Research design and methods: Participants in this cohort study were screened from 1973 to 1975; vital status has been ascertained over an average of 12 yr of follow-up (range 11-13 yr). Participants were 347,978 men aged 35-57 yr, screened in 20 centers for MRFIT. The outcome measure was CVD mortality.

#### CVD = Cardiovascular Disease

<sup>\*1)</sup> Plasma cholesterol ≥200mg/dl, 2) smoking, 3) systolic blood pressure ≥ 120mmHg

#### Increased CV events and PCI in patients with DM



Korean Diabetes Fact Sheet 2015

# Major lipid guidelines for patients with T2D

ACC/AHA(2013) Guideline	ESC/EAS(2011) Guideline
<ol> <li>ASCVD</li> <li>Off-treatment LDL-C ≥ 190</li> <li>mg/dl (without ASCVD or diabetes)</li> </ol>	Documented CVD, previous MI, ACS, coronary or other arterial revascularization, ischemic stroke, PAD, <b>type2 diabetes</b> or type1 diabetes with target organ damage, moderate to severe CKD, or a calculated 10 year risk SCORE ≥10%
<ul> <li>③ Diabetes (without ASCVD) LDL-C = 70-189 mg/dl</li> <li>④ 10-year ASCVD risk ≥ 7.5%</li> </ul>	LDL-C <70mg/dL (1.8 mmol/L) or 50% reduction in LDL-C

ACC: American College of Cardiology. AHA: American Heart Association. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society. ASCVD: Atherosclerotic cardiovascular disease. CVD: Cardiovascular disease.

LDL-C: Low-density lipoprotein Cholesterol. LDL: Low-density lipoprotein. FCH: Familial combined hyperlipidaemia. FH: Familial hypercholesterolaemia.

# 2013 ACC/AHA Cholesterol guidelines

- "Treat to risk" strategy using fixed-dose statin medications, rather than the previous "treat to LDL-C target" strategy
- Not recommend use of non-statin therapies
- Not recommend treatment to target LDL-C lipid levels

#### **Application of new cholesterol guidelines to Koreans**

### • Aim of study

: Annual change in the proportion of Korean adults eligible for lipid management using ACC/AHA guideline 2013

### Study population

- Korea National Health and Nutrition Examination Survey (KNHANES) between 1998 and 2012
- 42,954 Korean adults, aged ≥ 20 year

Annual changes in the proportions of adults eligible for lipid management guideline criterion by ACC/AHA in the KNHANESs during 1998-2012



### Korean Society of Lipidology and Atherosclerosis (KSLA) guideline (2015)

Target LDL-C and non-HDL-C goal		
Risk	<b>LDL-C</b> (mg/dL)	Non-HDL-C (mg/dL)
Very high risk		
CHD Ischemic stroke TIA PAOD	<70	<100
High risk		
Carotid a. stenosis Aortic aneurysm	<100	<130
Divi Mederate rick		
	(120	(100
KISK Tactor ≥ 2	<130	<160
Low risk		
Risk factor $\leq 1$	<160	<190

1. Korea Society of Lipidology and Atherosclerosis. Dyslipidemia treatment guideline 2015

# 2. Features of dyslipidemia in diabetes

Lipid profile of diabetes represents high TG, low HDL-C, and moderately elevated LDL

Diabetic dyslipidemia triad



LDL : Low Density Lipoprotein, VLDL : Very Low Density Lipoprotein, sdLDL :: small, dense LDL, TG : Triglyceride, HDL-C : High density lipoprotein-cholesterol, CMR : Chylomicron remnant, ApoB : Apolipoprotein B, ApoA1 : Apolipoprotein A1

# LDL particle size and numbers Non diabetes vs. Diabetes



Small, dense LDL particles increase risk of atherosclerosis.<sup>1</sup>

# LDL particle sizes and glucose metabolism

- Features of Diabetes mellitus in Asian populations
  - : has a younger age of onset
  - : is accompanied by more visceral fat for the same BMI with western populations
- Lipoprotein abnormalities may occur in the prediabetic state.
- We evaluate the lipoprotein subfraction profile in patients with impaired glucose metabolism (IFG, IGT, IFG/IGT and DM) in Korean population.

# **Study population**

- Study population
  - N = 2889
  - Duration: 2006.11. 2015.3.
  - Seoul National University Bundang Hospital
- Parameters
  - Age, BMI, FBS, PP2, HbA1c
  - fasting insulin
  - LDL particle pattern by LDL subfraction analysis



# sdLDL(%), sdLDL/lb/LDL, and LDLSF score





#### Postprandial TG levels and incident CV events

- Prospective study of 26,509 initially healthy US women (20,118 preprandial and 6,391 postprandial) participating in the Women's Health Study.
- Undergoing follow-up for a median of 11.4 years.
- Hazard ratios for incident cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death).



CVD, cardiovascular disease; TG, triglyceride; CV, cardiovascular; MI, myocardial infarction; CVA, cerebrovascular accident; F/U, follow-up; US, united states

1. Bansal S, et al. JAMA. 2007;298:309-316.

#### Postprandial dyslipidemia after lipid meal challenge

## • Aim of study

: Postprandial dyslipidemia after a standardized 70g fat meal test in BMI-matched healthy individuals, prediabetes, and Type 2 diabetes

#### Methods

- Study subjects: NGT/ IGT / T2D (25 in each group)
- A standardized high fat meal containing 70g of fat
- Measurement: fasting and postmeal load glucose, insulin, C-peptide, ApoA1, ApoB, and TG levels at 1, 2, 3, 4, 5, 6, and 8 h.



**Unpublished data** 



**Unpublished data** 

### **Postprandial lipid lowering agents**

Drug	Reducing ApoB48
High dose statin	YES
Statin + Ezetimibe	YES
Statin + Fenofibrate	YES
Incretin therapy (GLP-1 analogues and DPP-4I)	YES
DGAT1 inhibitor	YES
MTP inhibitor (lomitapide)	YES
Antisense oligonucleotides to ApoB (Mipomersen)	unlikely due to liver-specific effect
Orlistat	probable but no data
PCSK9 mAb	probable but no data

# Conclusion

### **Dyslipidemia in Diabetes**

• >90% of patients with DM have dyslipidemia

### Lipid management guidelines

- Aggressive treatment
- <70 mg/dl of LDL-C or >50% reduction

#### Atherogenic dyslipidemia in DM

- Increased sdLDL
- High TG and low HDL
- Postprandial TG

# THANK YOU!!!

# Pathogenesis in diabetic dyslipidemia



VLDL, very low-density lipoprotein; TG, triglyceride; CE, cholesteryl ester; CETP, cholesterylester transfer protein; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein

#### 1. Solano MP, et al. Cardiol Rev. 2006;14:125-135.



# **Study Population**

- 5 mutually exclusive risk groups on the basis of the new guidelines
  - 1 ASCVD
  - ② Diabetes (without ASCVD) LDL-C = 70-189 mg/dl
  - ③ Off-treatment LDL-C  $\geq$  190 mg/dl (without ASCVD or diabetes)
  - ④ 10-year ASCVD risk ≥ 7.5% (without ASCVD, diabetes, or offtreatment LDL-C ≥ 190 mg/dl)