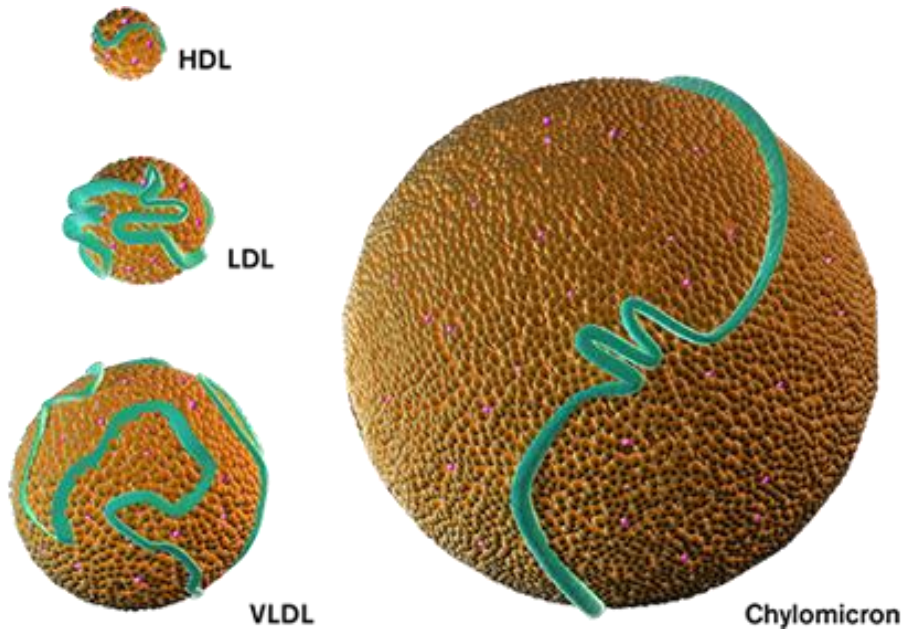


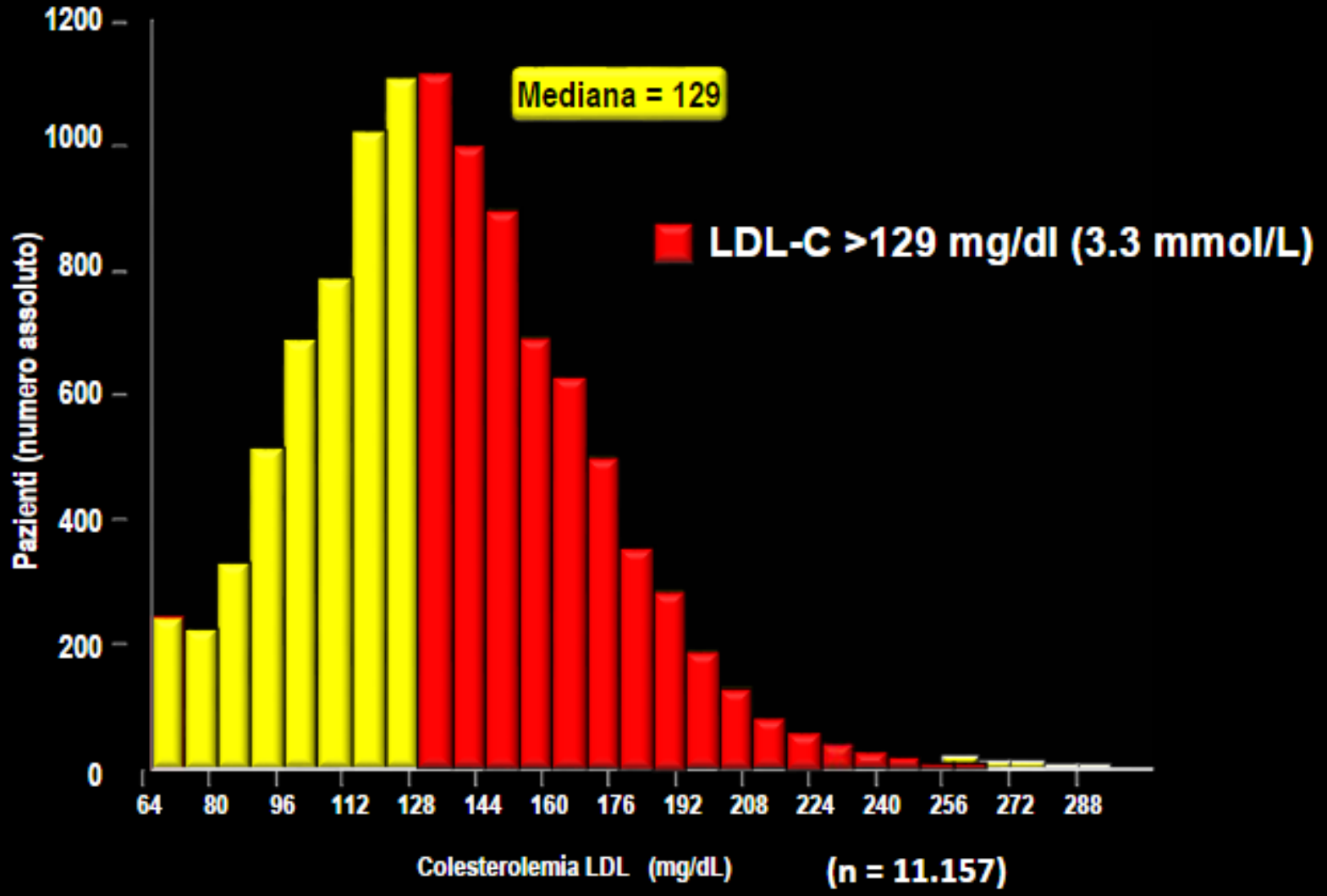
Management of Dyslipidemia in Diabetes and Prediabetes

Natia Vashakmadze MD
Evex Medical Corporation
22/05/2017

What is characteristic for “diabetic dyslipidemia” ?

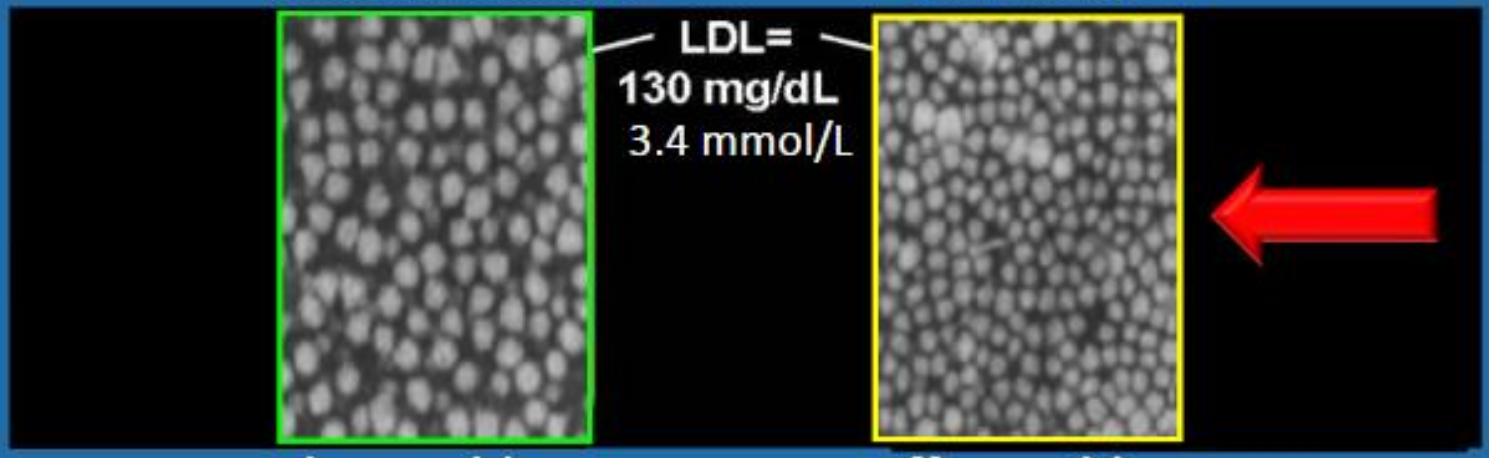
- High LDL + High Tot. cholesterol
- Low HDL
- High TG
- High TG + low HDL

Cardiovascular risk factors and metabolic control in type 2 diabetic subjects attending outpatient clinics in Italy
The SFIDA (survey of risk factors in Italian diabetic subjects by AMD) study



Nutr Met Cardiovasc Dis 2005, 15;204-2011

Small Dense LDL Particles – Same LDL-C Level but Different CVD Risk



Correlates with:		Correlates with:	
TC	198 mg/dL	TC	210 mg/dL
LDL-C	130 mg/dL	LDL-C	130 mg/dL
TG	90 mg/dL	TG	250 mg/dL
HDL-C	50 mg/dL	HDL-C	30 mg/dL
Non-HDL-C	148 mg/dL	Non-HDL-C	180 mg/dL

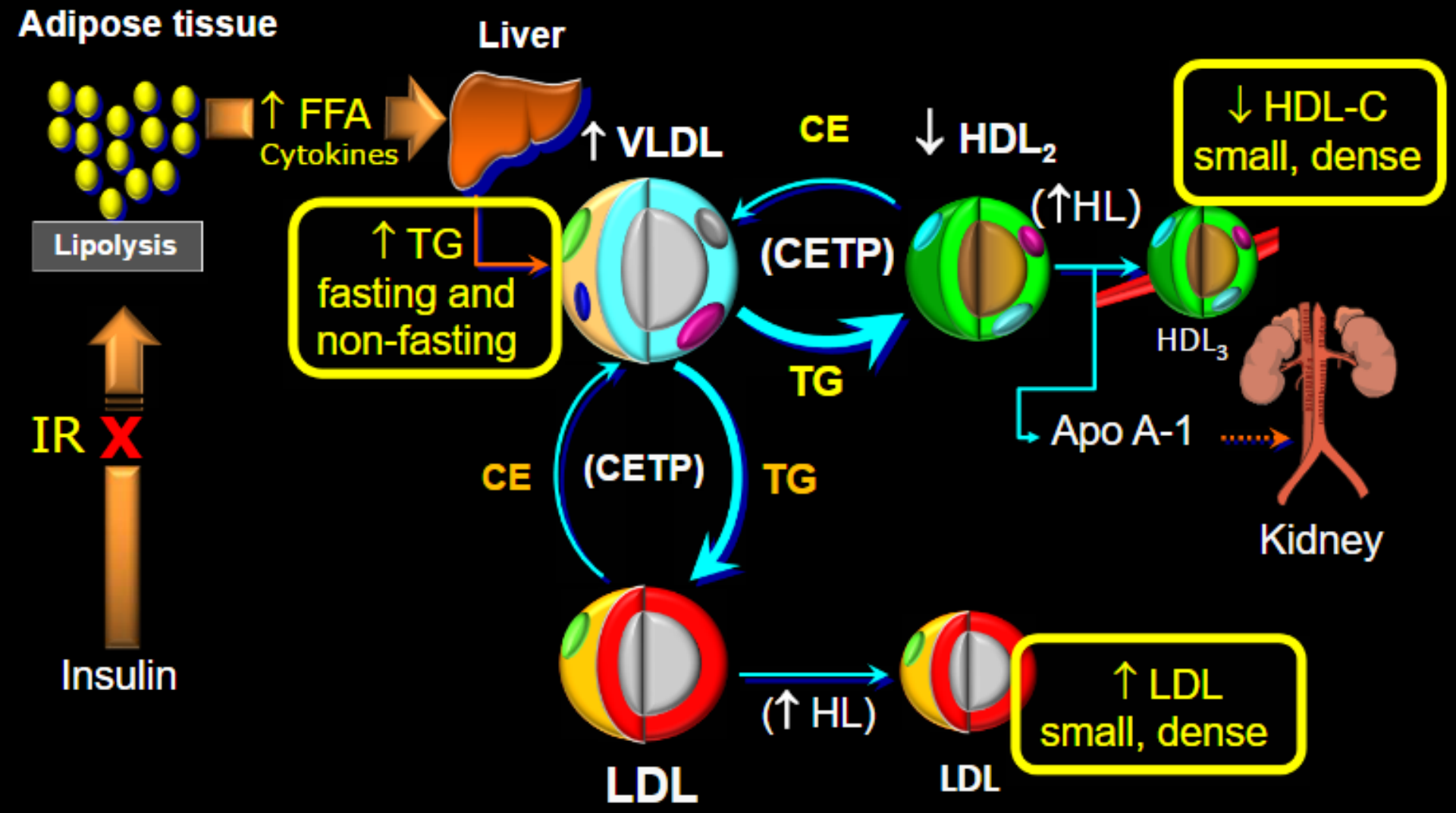
Otvos JD et al. Am J Cardiol. 2002;90:22i-29i

Chapman MJ et al. Eur Heart J 2011;332:1345-1361.

What is main cause of Diabetic Dyslipidemia?

- Hyperglycemia
- Insulin resistance
- Relative Insulin insufficiency
- Altered incretin response

Pathophysiology of Diabetic Dyslipidemia (Atherogenic Dyslipidaemia)



HL= hepatic lipase; CETP = cholesteryl ester transfer protein

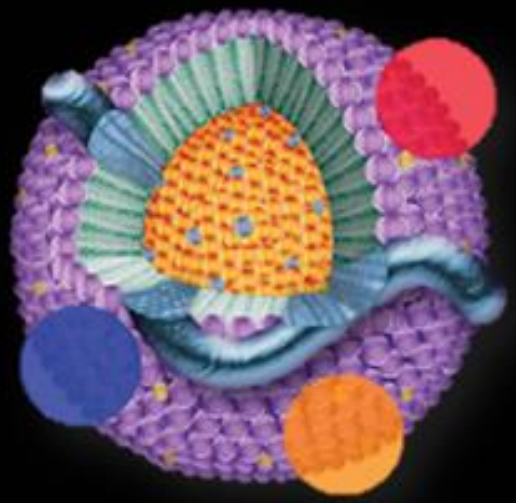
HDL FUNCTIONAL PROPERTIES

«FUNCTIONAL» HDL

↑ Cholesterol efflux
↓ Inflammation
↓ Thrombosis
↓ Oxidation

● Apo AI, Apo E, PON1, AH

«DYSFUNCTIONAL» HDL



↓ Cholesterol efflux
↑ Inflammation
↑ Thrombosis
↑ Oxidation

● Apo CIII, Lp-LPLA2, SAA1

J Am Soc Nephrol 22,1631,2011;
JACC 60,2372,2012; JACC 60,2380,2012

What would you treat first to reduce CVD risks in diabetic patient?

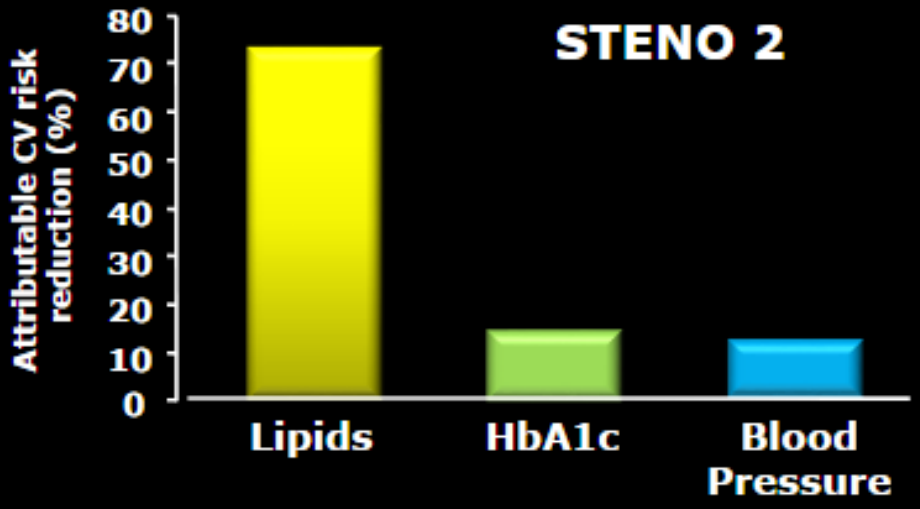
- Glucose
- Lipids
- Hypertension
- Cigarette smoking

UKPDS –STENO 2: Cardiovascular Risk Reduction as it is Accounted for by Changes in Risk Factors on Therapy

(Patients with Type 2 Diabetes)

UKPDS – Coronary Events (n=280)

Ranking in the model	Variable	P Value
First	LDL Cholesterol	<0.0001
Second	HDL Cholesterol	0.0001
Third	Glycated Hemoglobin (HbA_{1c})	0.0022
Fourth	Systolic blood pressure	0.0065
Fifth	Cigarette smoking	0.056



Gaede P, and Pedersen O, Diabetes 2004;53:S39-S47

UKPDS -Lancet 1998;352:837–853

Recommendations for Statin and Combination Treatment in Persons With Diabetes

Risk Factors, by Age	Recommended Statin Intensity*
<40 y	
None	None
ASCVD risk factors†	Moderate or high (C rating)
ASCVD	High
40-75 y	
None	Moderate (A rating)
ASCVD risk factors	High (B rating)
ASCVD	High
ACS, LDL cholesterol level >1.3 mmol/L (>50 mg/dL), and inability to tolerate high-dose statin therapy	Moderate plus ezetimibe (A rating)
>75 y	
None	Moderate (B rating)
ASCVD risk factors	Moderate or high (B rating)
ASCVD	High
ACS, LDL cholesterol level >1.3 mmol/L (>50 mg/dL), and inability to tolerate high-dose statin therapy	Moderate plus ezetimibe (A rating)

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein.
* In addition to lifestyle therapy. † LDL cholesterol level ≥2.6 mmol/L (≥100 mg/dL), high blood pressure, smoking, overweight or obesity, and family history of premature ASCVD.

ADA Standards of Care in Diabetes 2016, Diabetes Care January 2016 Volume 39, Suppl. 1

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

Differences vs 2011 ESC/EAS Guidelines

- **……or a reduction of at least 50% if the baseline LDL-C is between 70 and 135 mg/dL** (1.8 and 3.5 mmol/L) **is recommended.**
- **……or a reduction of at least 50% if the baseline LDL-C is between 100 and 200 mg/dL** (2,6 and 5,2 mmol/L) **is recommended.**

European Heart Journal online published August 27, 2016

Patients With Diabetes Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[1]* (CHD patients)	19.8%	25.7%	**33.4%**	37.8%
CARE[2]†	19.4%	24.6%	**28.7%**	36.8%
LIPID[3]‡	11.7%	15.2%	**19.2%**	22.8%
PROSPER[4]§	13.1%	16.0%	**23.1%**	18.4%
ASCOT-LLA[5]‡	4.9%	8.7%	**9.6%**	11.4%
TNT[6]‖	7.8%	9.7%	**13.8%**	17.9%

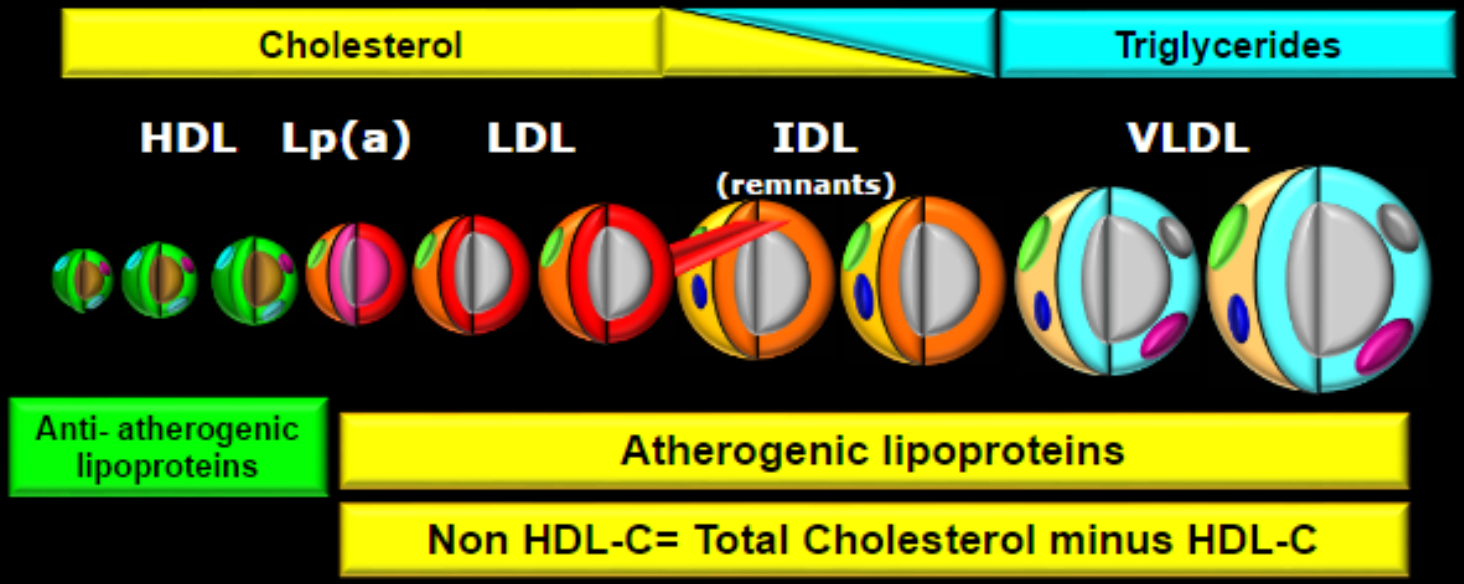
*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
‖CHD death, nonfatal MI, resuscitated cardiac arrest, stroke
(80 mg versus 10mg atorvastatin)

[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
[2]Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
[3]LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.
[4]Shepherd J, et al. *Lancet*. 2002;360:1623-1630.
[5]Sever PS, et al. *Lancet*. 2003;361:1149-1158.
[6]Shepherd J, et al. *Diabetes Care*. 2006;29:1220-1226.

Which additional parameter could we use for better prediction of residual CVD risks in diabetic patients?

- Low HDL
- High Tg
- High VLDL
- Non-HDL-Cholesterol

Non-HDL Cholesterol: Emerging Target for the Treatment of (Residual) CV Risk

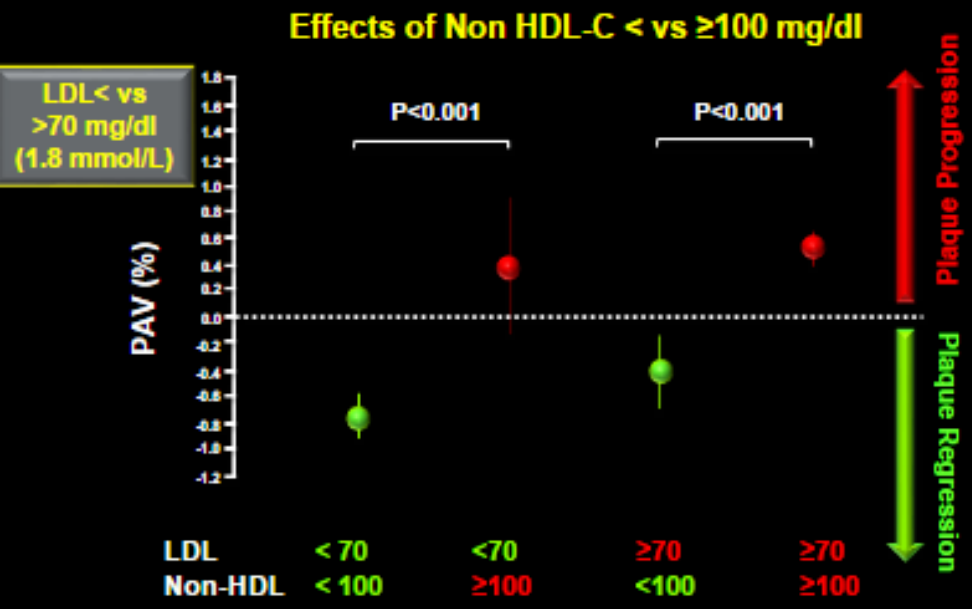


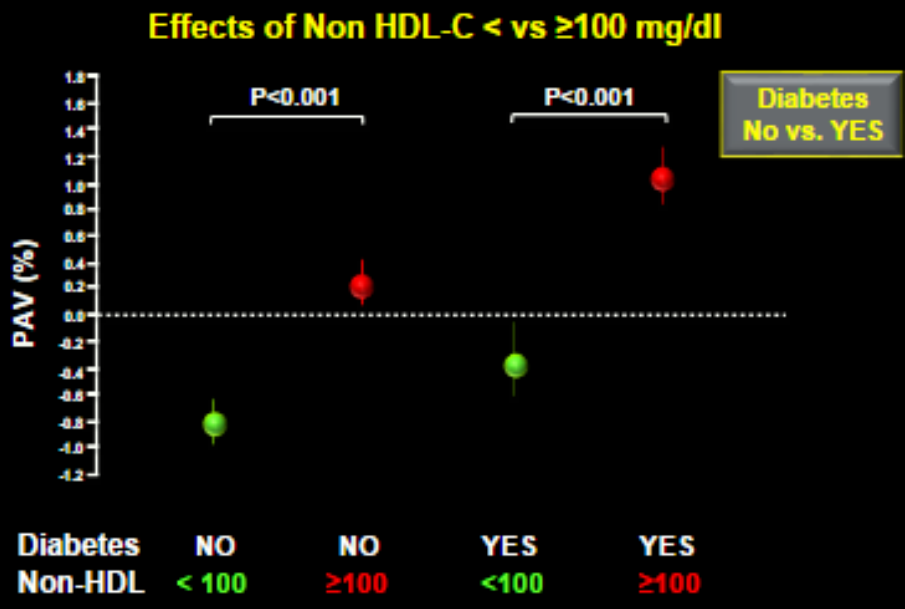
- ✓ **Accounts for all atherogenic lipoproteins** and may provide an improved estimate of CV risk in patients with diabetes, metabolic syndrome or chronic kidney disease
- ✓ Recommended as **secondary target** by national/international guidelines
- ✓ Target levels= **LDL-C goal + 30 mg/dl** (0.8 mmol/L)
- ✓ **Easy to calculate**: Total cholesterol minus HDL-C

Non-HDL Cholesterol and Triglycerides

Implications for Coronary Atheroma Progression and Clinical Events

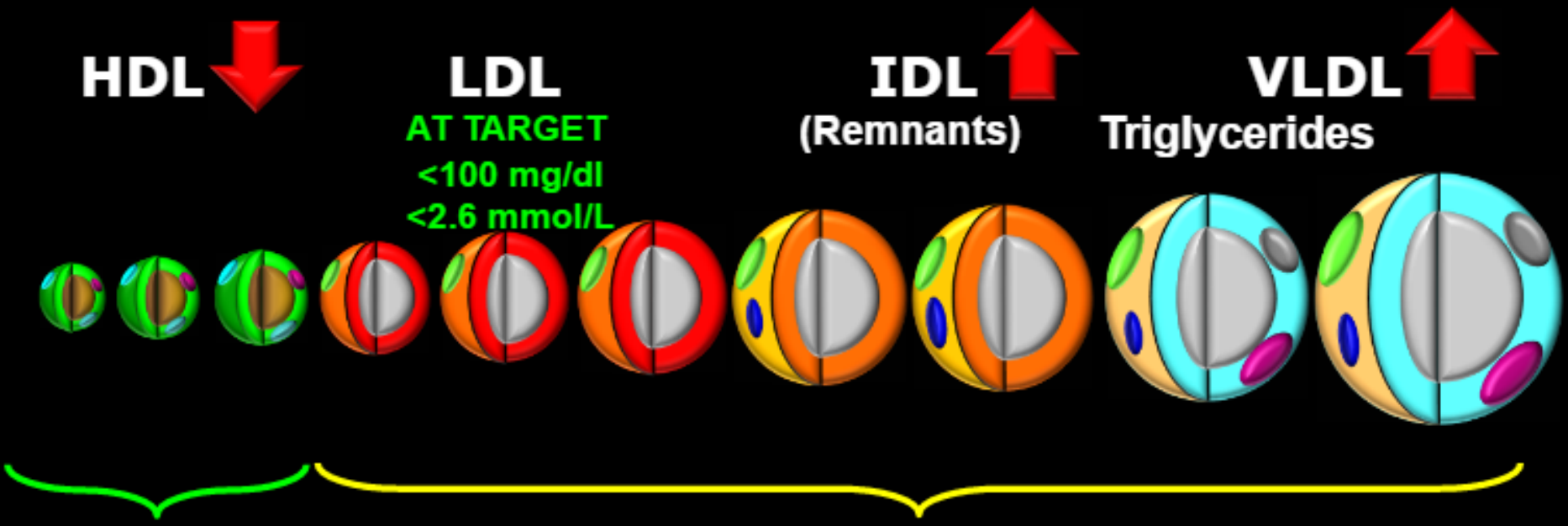
- 9 clinical trials involving 4957 patients with coronary disease undergoing serial intravascular ultrasonography to assess changes in percent atheroma volume (ΔPAV).
- Follow-up 18-24 months
- Evaluated against on-treatment non-HDLC < 100 mg/dl (<2.6 mmol/L) vs >100 mg/dl (>2.6 mmol/L)





Puri R, Nissen SE et al Arterioscler Thromb Vasc Biol. 2016 Aug 11. pii: ATVBAHA.116.307601. [Epub ahead of print]

Non-HDL Cholesterol



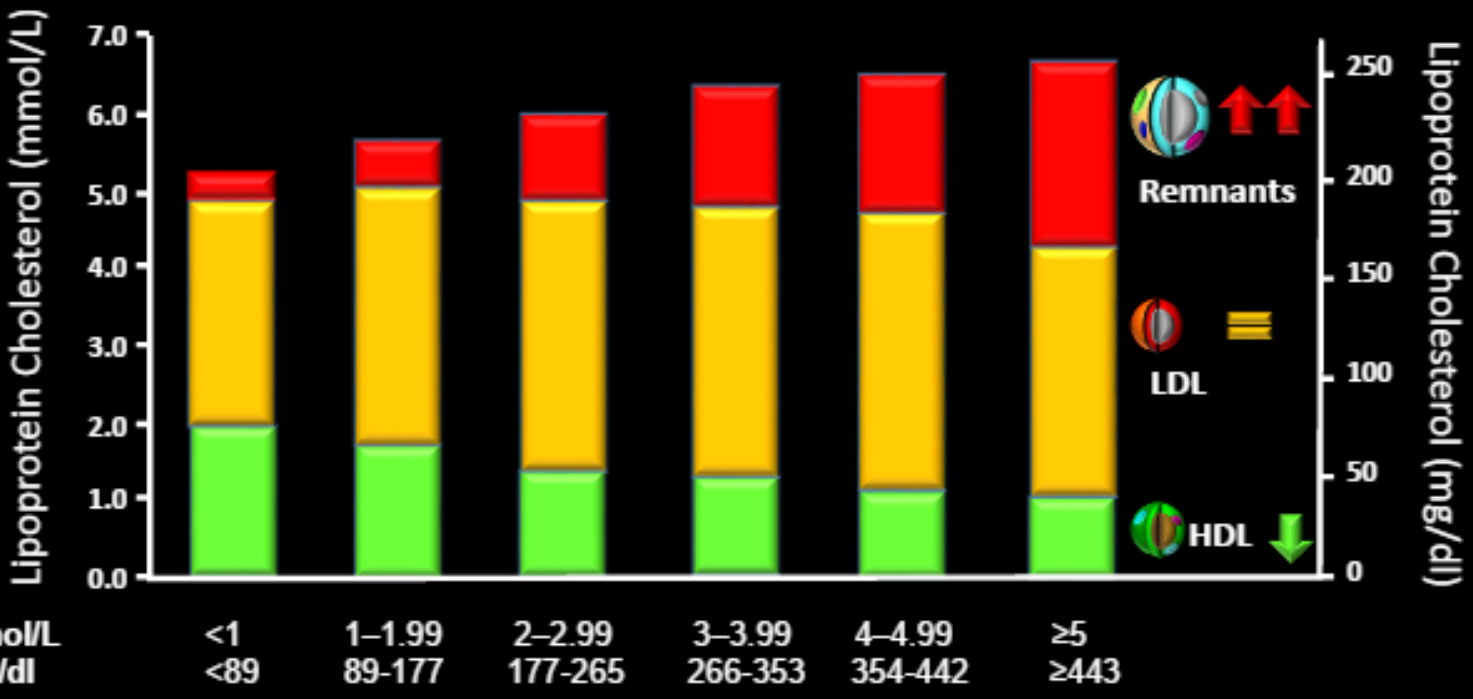
Anti Atherogenic Lipoproteins

Non HDL-C ≥130 mg/dl or 3.4 mmol/L NOT AT TARGET

Atherogenic Lipoproteins

Non-HDL cholesterol: Emerging # 1 TARGET for treatment of (Residual) Cardiovascular Risk

Lipoprotein cholesterol as a function of increasing levels of non-fasting triglycerides in the general population



- Based on non-fasting samples from *36 160 men and women from the Copenhagen General Population Study* collected over the period 2003–2007
- Remnant cholesterol is calculated from a non-fasting lipid profile as total cholesterol minus HDL cholesterol minus LDL cholesterol; under these conditions, remnant cholesterol represents the total cholesterol transported in IDL, VLDL, and chylomicron remnants.

Chapman MJ et al. Eur Heart J. 2011 Jun;32(11):1345-61.

What can we do to improve our patient care in special situations?

- What can we do when LDL is not on target with maximal dose statin therapy?

- What Can we do when LDL is on target, but non-HDL is not on target?

Lipid Targets and Combination Therapy

Statin + Ezetimibe
Statin + Bile acid sequestrant
Statin + Ezetimibe + Bile AS

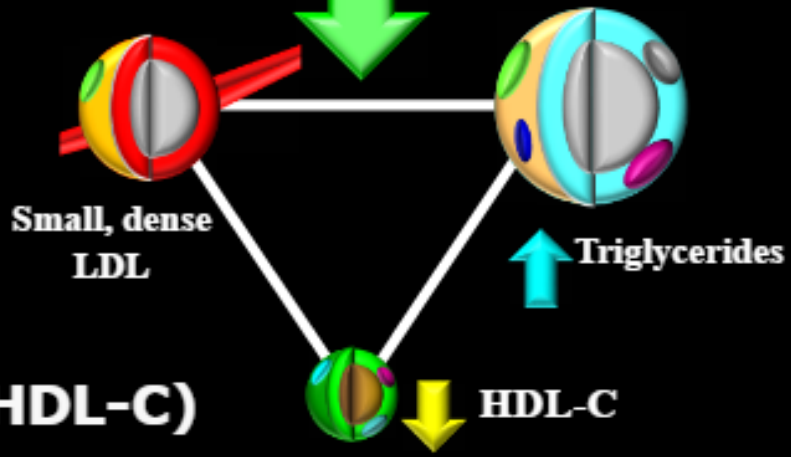
Target LDL-C

At target LDL-C: NO

STATIN → **Combination statin + 2° lipid lowering agent IF..**

At target LDL-C: YES, but…..

Statin + Fenofibrate
Statin + Nicotinic ac.
Statin + Omega 3 fatty acids



Target HDL-C and TG (Non HDL-C)

Statin usage in associated with increased incidence of diabetes:

- 10-12%
- 12-20%
- 20-25%
- 30%

New onset diabetes mellitus and statins

- Development of NODM during statin therapy seems to occur most frequently among individuals with pre-existing risk factors, such as components of the metabolic syndrome, the elderly (age >70 years), women and those of Asian ethnicity.
- The meta-analysis shows that for every 255 patients treated with a statin for 4 years 1 additional patient would develop diabetes.
- One study estimated that 4 years' treatment with a standard dose of statins would lead to one additional case of T2DM but prevent nine major CVD events.

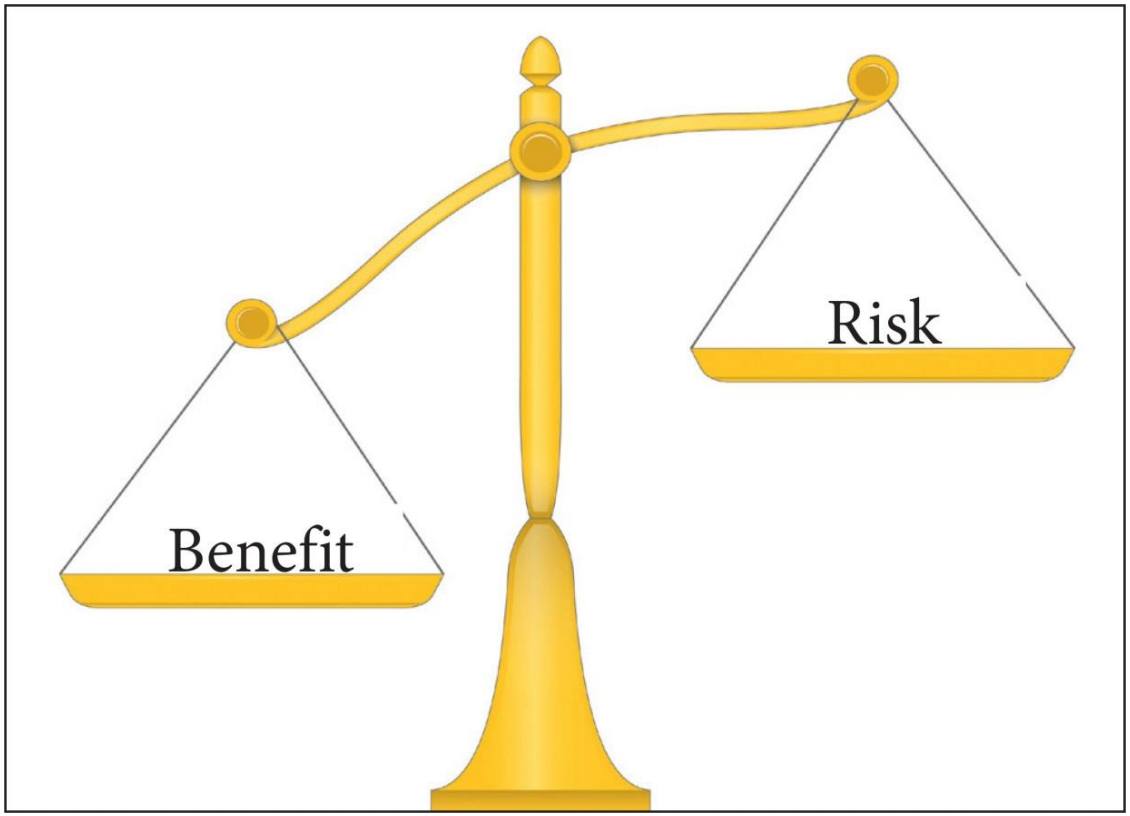
Should we avoid statin usage in high to moderate CVD risk prediabetic patient?

- Yes, we should not prescribe statins at all in these group

- No, but we should try minimal effective dose

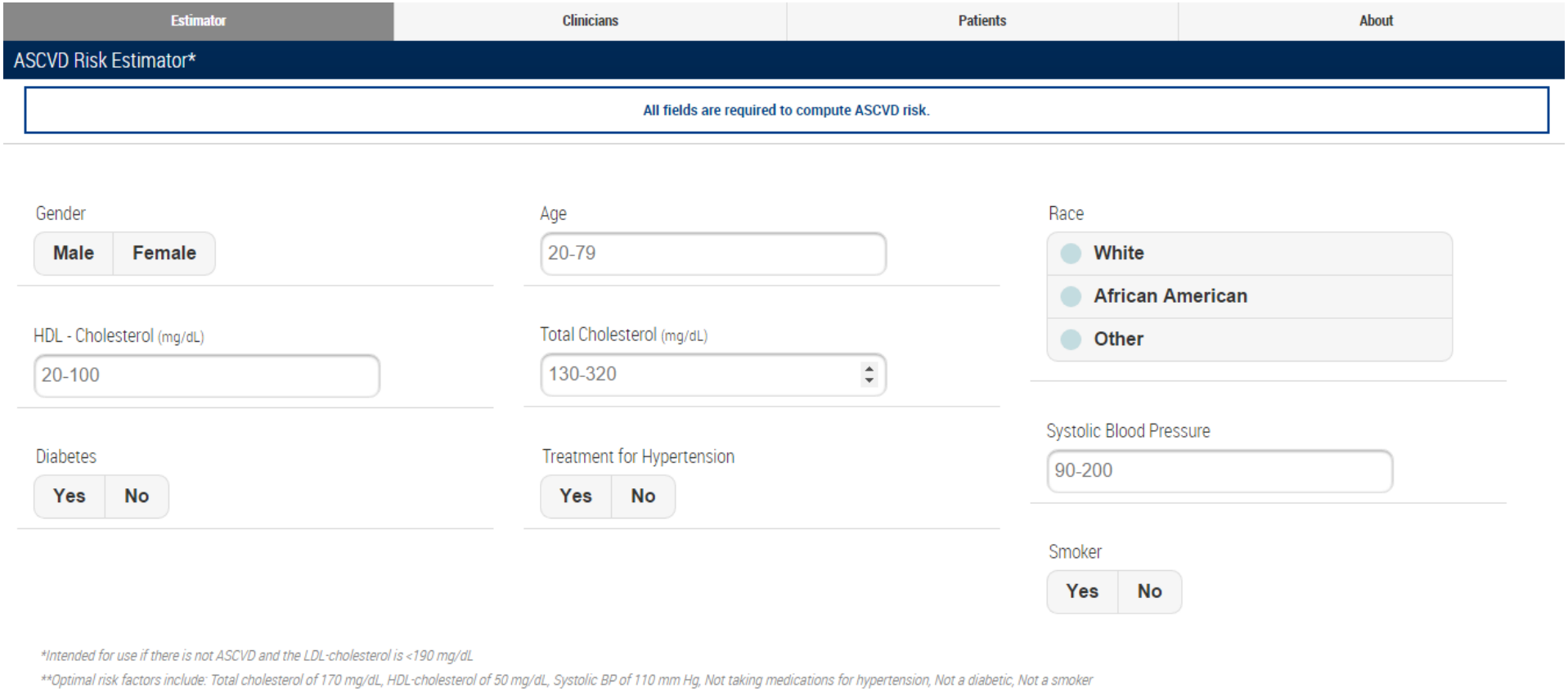
- No, we should not change our clinical approach as statin CVD benefits significantly outweigh diabetogenic risks

Consequently, in the case of the statins the benefits markedly outweigh the risks.



How can we calculate ASCVD risk for individual patient?

- http://tools.acc.org/ASCVD-Risk-Estimator/



Case Report N1

- 61 years old male patient
- DMT2 diagnosed 8 years ago
- With long standing history of Hypertension, Dyslipidemia and Coronary Artery Disease
- Sedentary lifestyle, poor diet, no smoker
- Strong Family predisposition toward Cardio-Vascular diseases

On first visit 11/08/2016

- **Complains:** frequent night urination, high blood pressure;
- high blood sugars + frequent hypoglycemia.

- **Average fasting glucose** -130-150 mg/dL
- **Average PP glucose** 190-220 mg/dl

- Medications: Metformin 850 mg 2X day
  Gliclazide MR 60 mg 1Xday
  Enalapril 10 mg 2 Xday
  Aspirin 75 mg 1Xday
  Bisoprolol 5 mg 1 Xday

- Blood pressure 150/90 mmhg
- Pulse – 60 bits per minute

- Height – 168 sm; weight – 86 kg BMI – 32 kg/m2

Lab. Results 11/08/2016

Lab. Test	Result	References
HbA1c	7.8%	<5.6%
Tot. Cholesterol	274 mg/dl	<200 mg/dl
HDL	28.67 mg/dl	40-60 mg/dl
LDL	176.21 mg/dl	<100 mg/dl
VLDL	85 mg/dl	5-40 mg/dl
Tg	425 mg/dl	<150 mg/dl
Non-HDL	246 mg/dl	<130 mg/dl
Creatinine	79 mkmol/l	62-115 mkmol/l
eGFR	92 ml/min/1.73 m2	>90 ml/min/1.73 m2
TSH	1.11	0.4-4.4 mkIU/ml

What about Targets?

What is target HbA1c for this patient?

<7% with drugs that do not cause hypoglycemia

What are target lipids for this patient?

LDL < 70 mg/dl; non HDL <100 mg/dl

What is target blood pressure for this patient?

<140/90 mmhg

Diagnosis

- Diabetes Mellitus type 2 with frequent iatrogenic hypoglycemia

- Coronary artery disease
- Arterial hypertension
- Central Obesity, Grade I
- Hypercholesterolemia
- Diabetic (Atherogenic) dyslipidemia HDL ⬇ + TG ⬆

Estimator | Clinicians | Patients | About

ASCVD Risk Estimator*

10-Year ASCVD Risk

44.4 % calculated risk

6.3 % risk with optimal risk factors**

Lifetime ASCVD Risk

Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years of age.

Recommendation Based On Calculation

Gender

Male | Female

Total Cholesterol (mg/dL)

274.78

Treatment for Hypertension

Yes | No

Age

61

Note: Lifetime risk is only calculated for the 20 to 59 year range

HDL - Cholesterol (mg/dL)

28.67

Diabetes

Yes | No

Race

- White
- African American
- Other

Systolic Blood Pressure

150

Smoker

Yes | No

Back

Recommendation

Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Male
- Age: 61
- Race: White/Other
- Total Cholesterol: 274.78
- HDL-Cholesterol: 28.67
- Systolic Blood Pressure: 150
- Hypertension Treatment: Yes
- Diabetes: Yes
- Smoker: No

Consider High-Intensity Statin

Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. (I A)

High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. (IIa B)

It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. (IIa C)

New treatment 08/2016

- Diet + physical exercise
- Metformin 1000 mg 2 X Day
- Sitagliptin 100 mg 1 X Day
- Rosuvastatin 20 mg 1 X day
- Aspirin 75 mg 1 X day
- Antihypertensive treatment

3 month later – 11/11/2016

- Patient had significant hyperglycemia and changed Sitagliptin to Gliclazide by himself
- Had several episodes of hypoglycemia on Gliclazide MR (blood sugars avarage - 63 mg/dl)
- Complains about frequent night urination and high blood pressure persist.

Lab Results 14/11/2016

Test	result	Targets
HbA1c	7.5%	<7%
Tot. Cholesterol	151.94 mg/dl	
HDL	34 mg/dl	>40 mg/dl
LDL	89.37 mg/dl	<70 mg/dl
VLDL	23.2 mg/dl	
Tg	116.8 mg/dl	<150 mg/dl
Non HDL	117.94 mg/dl	<100 mg/dl
eGFR	103 ml/min/1.73m2	>90

ASCVD Risk Estimator*

10-Year ASCVD Risk

26.2% calculated risk

6.3% risk with optimal risk factors**

Lifetime ASCVD Risk

⚠ Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years of age.

Recommendation Based On C

Gender

Male | **Female**

Total Cholesterol (mg/dL)

151.94

Treatment for Hypertension

Yes | **No**

Age

61

⚠ **Note:** Lifetime risk is only calculated for the 20 to 59 year range

HDL - Cholesterol (mg/dL)

34

Diabetes

Yes | **No**

Race

- (●) **White**
- ( ) **African American**
- ( ) **Other**

Systolic Blood Pressure

150

Smoker

Yes | **No**

New treatment 16/11/2016

- Metformin 1000 mg 2 X day
- Liraglutide 0.6 mg → 1.2 mg 1 X day subcutaneously
- Rosuvastatin 20 mg 1 X day

- **Prescription of Cardiologist:**
- Perindopril + indapamide 10/2.5 1 X day
- Aspirin 75 mg 1 X day
- Metoprolol 25 mg 1 X day

6 month later 10/05/2017

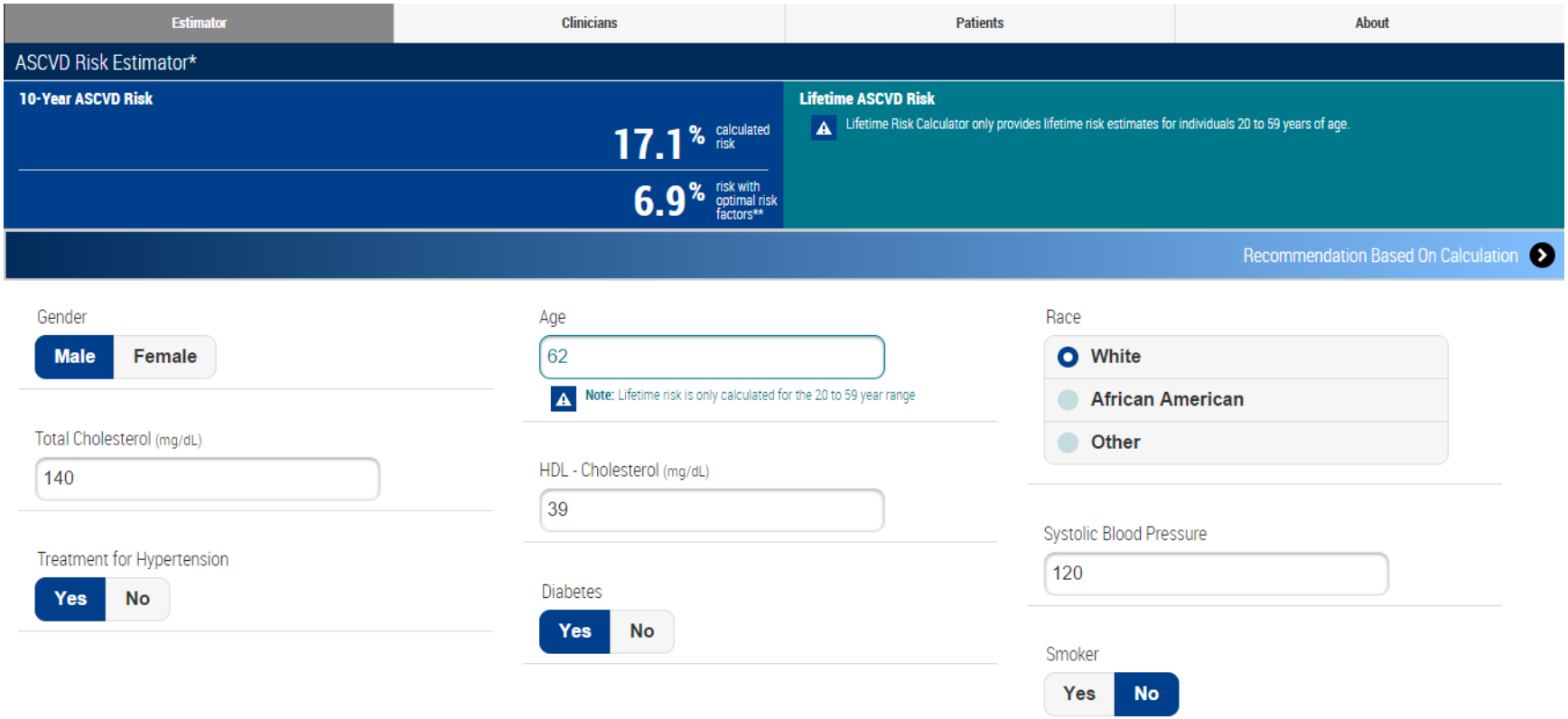
- No complains;

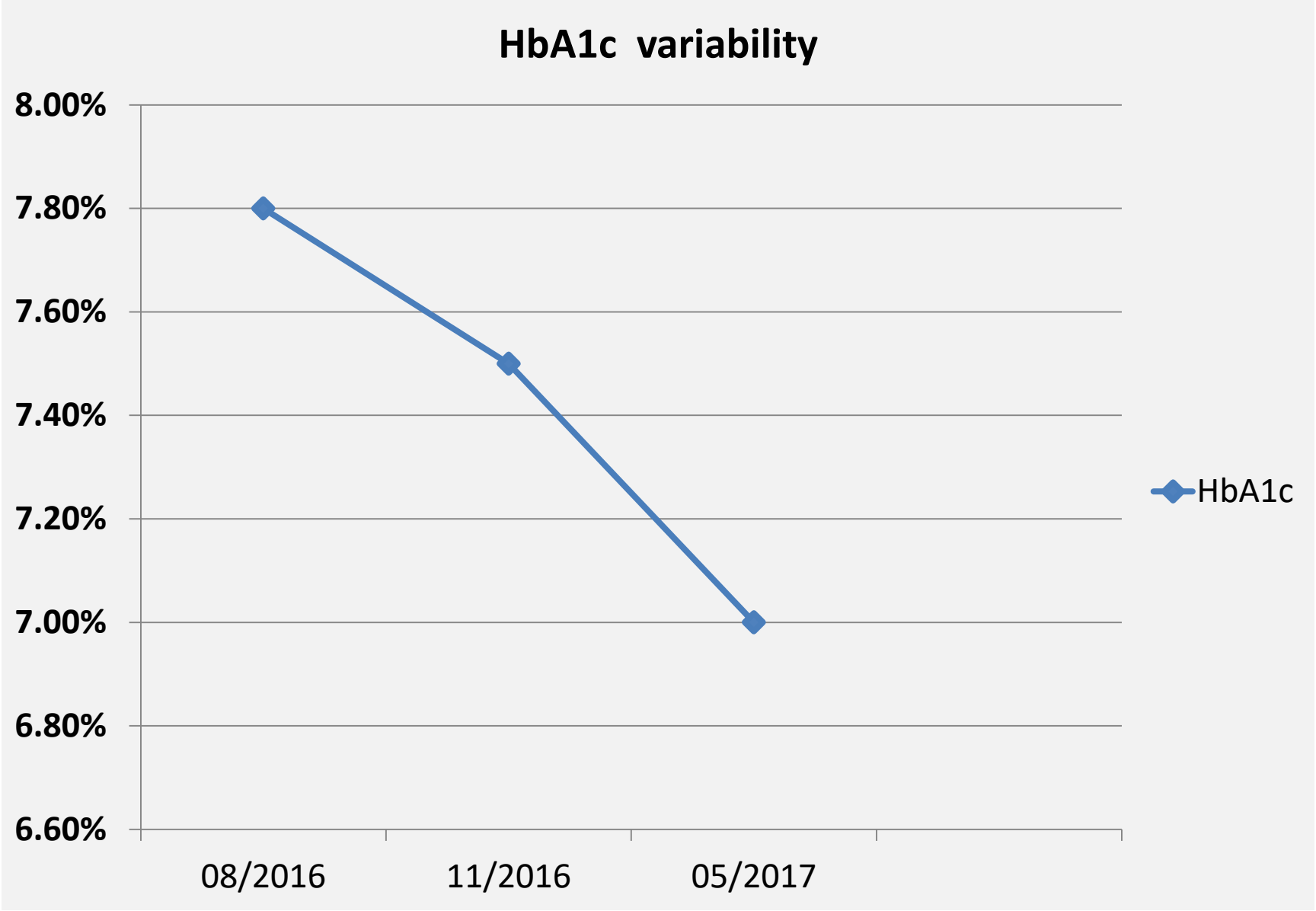
- Fasting Blood glucose 110-150 mg/dl
- Postprandial blood glucose 140-160 mg/dl

- Poor Diet
- Minimal physical activity

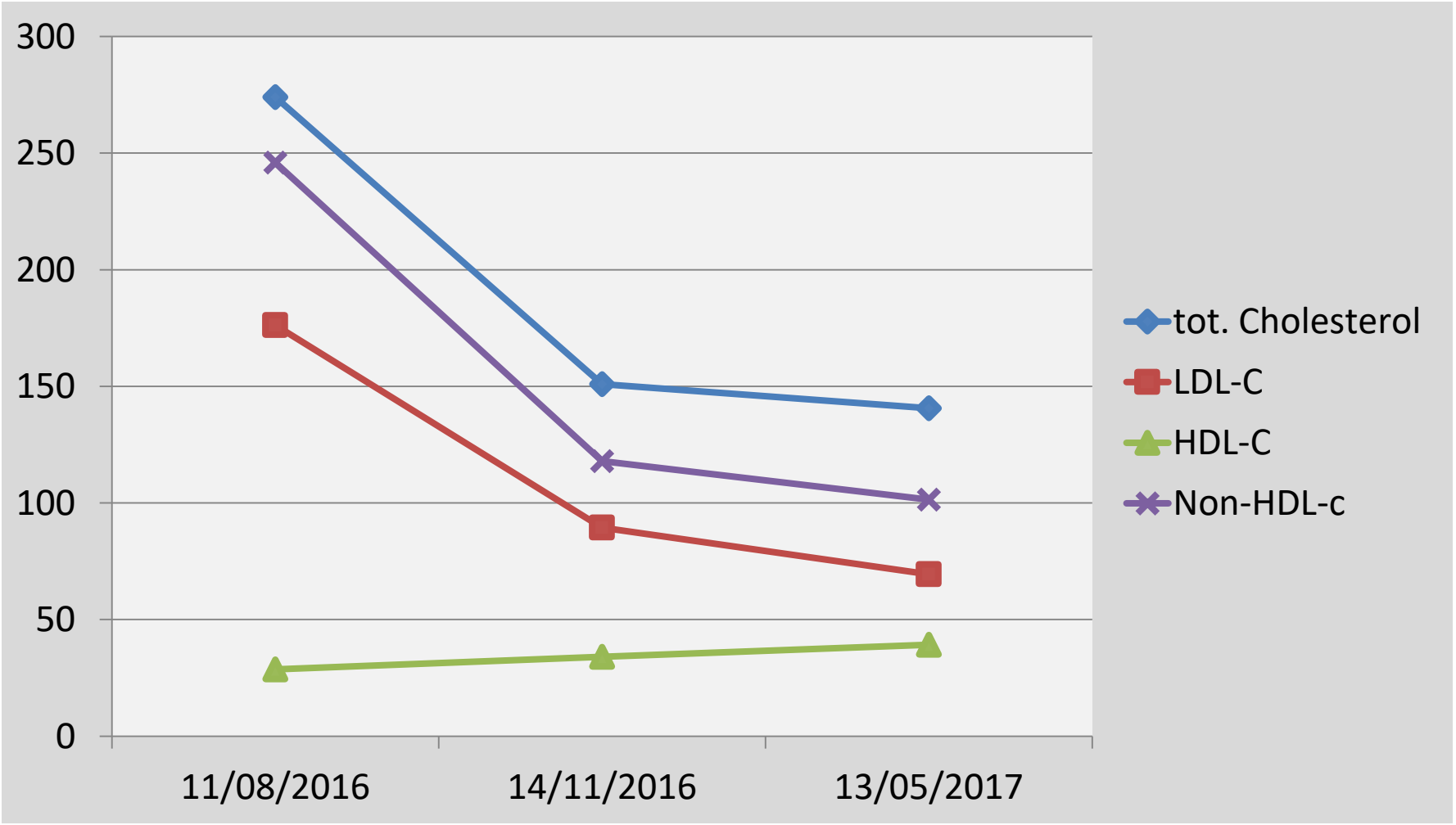
Lab results 13/05/2017

Test	Result	Targets
HbA1c	7.0%	<7%
Tot. Cholesterol	140.6 mg/dl	
HDL –Chol	39.2 mg/dl	>40 mg/dl
LDL	69.4mg/dl	<70 mg/dl
VLDL	32 mg/dl	
Tg	158 mg/dl	
Non-HDL	101.4 mg/dl	<100 mg/dl
eGFR	103 ml/min/1.73m2	>90 ml/min/1.73m2
25(OH)D3	12.9 ng/dl	30-100 ng/dl

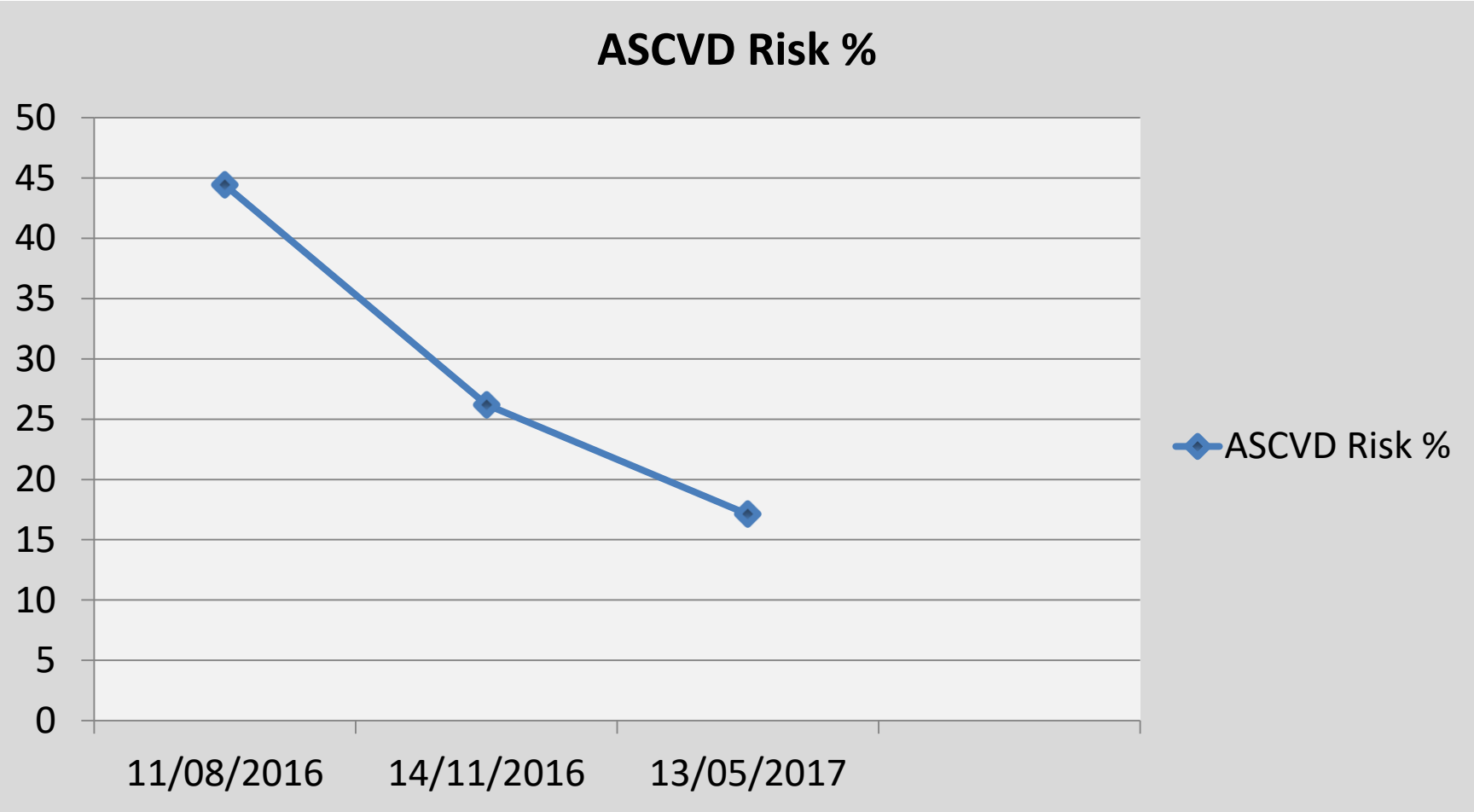

Estimator
Clinicians
Patients
About
ASCVD Risk Estimator*
10-Year ASCVD Risk
17.1 % calculated risk
6.9 % risk with optimal risk factors**
Lifetime ASCVD Risk
Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years of age.
Recommendation Based On Calculation
Gender
Male
Female
Total Cholesterol (mg/dL)
140
Treatment for Hypertension
Yes
No
Age
62
Note: Lifetime risk is only calculated for the 20 to 59 year range
HDL - Cholesterol (mg/dL)
39
Diabetes
Yes
No
Race
White
African American
Other
Systolic Blood Pressure
120
Smoker
Yes
No


HbA1c variability
8.00%
7.80%
7.60%
7.40%
7.20%
7.00%
6.80%
6.60%
08/2016
11/2016
05/2017
HbA1c

Lipid variability



10 year probability of ASCVD



- Do we need intensification of statin therapy?
- Do we need intensification of GLP-1 agonists?
- Did we met blood pressure targets?
- Any further recommendations or advice?

More aggressive approach toward extremely high CVD risk patients!!!

Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

CPG for Managing Dyslidemia and Prevention of CVD, Endocr Pract. 2017;23(Suppl 2)

Case N2

- 55 years old male
- Abdominal obesity grade I (BMI 32 kg/m2)
- Complains: general fatigue
- In 2015 first time was detected fasting hyperglycemia on screening tests: 130 mg/dl
- No family predisposition toward endocrine pathologies or CVDs.
- Sedentary lifestyle, poor diet;
- No hypertension, No smoking

On first visit 25/08/2016

Lab. Test	result	references
OGGT: fasting glucose	111 mg/dl	60-110 mg/dl
2 hrs. after glucose loading	191 mg/dl	<140 mg/dl
Tot. Cholesterol	340.23 mg/dl	<200 mg/dl
HDL	38.25 mg/dl	40-60 mg/dl
LDL	270 mg/dl	<100 mg/dl
VLDL	31 mg/dl	5-40 mg/dl
Tg	155.5 mg/dl	<150 mg/dl
Non-HDL	302 mg/dl	<130
Creatinine	81 mkmol/l	60-100 mkmol/l
eGFR	93 ml/min/1.73m2	>90 ml/min/1.73m2
TSH	1.31 mkIU/ml	0.35-4.94 mkIU/ml
ALT	48 U/L	16-63 U/L
AST	18.71 U/L	<50 U/L

Diagnosis

Metabolic syndrome:

- Impaired Glucose Tolerance
- Abdominal obesity grade I
- Atherogenic dislipidemia (⬇ HDL, ⬆ Tg)
- Severe Hypercholesterolemia

ASCVD Risk Estimator*

10-Year ASCVD Risk

9.3% calculated risk

3.6% risk with optimal risk factors**

Lifetime ASCVD Risk

50% calculated risk

5% risk with optimal risk factors

Recommendation Based On Calculation

Gender

Male | **Female**

Age

55

Race

- (•) **White**
- ( ) **African American**
- ( ) **Other**

HDL - Cholesterol (mg/dL)

38

Total Cholesterol (mg/dL)

320

Diabetes

Yes | **No**

Treatment for Hypertension

Yes | **No**

Systolic Blood Pressure

110

Smoker

Yes | **No**

Back

Recommendation

Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Male
- Age: 55
- Race: White/Other
- Total Cholesterol: 320
- HDL-Cholesterol: 38
- Systolic Blood Pressure: 110
- Hypertension Treatment: No
- Diabetes: No
- Smoker: No

Moderate to High-Intensity Statin Recommended

Before initiating statin therapy, it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. (IIa C)

Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL with no diabetes and estimated 10-year ASCVD risk ≥7.5% should be treated with moderate to high-intensity statin therapy. (I A)

- Does this patient need Metformin? (which dose? How long?)
- Does this patient need statins? (If yes, which statin, which dose?)
- Would you introduce statins immediately or after 3-6 month? (regarding diabetogenic effects of the drugs)

Treatment -25/08/2016

- Diet
- Regular physical exercise
- Metformin 850 mg X2 day for long term use
- Discussed statin risk benefit ratio with patient and decided to delay initiation of statin therapy for 3 month.

~ 3 month later - 20/12/2016

Patient could not tolerate metformin 850 mg 2Xday and stopped taking the medication Himself. Did not follow the diet recommendation and no physical activity.

Lab. Test	result	references
OGGT: fasting glucose	150 mg/dl	60-110 mg/dl
2 hrs. after glucose loading	256 mg/dl	<140 mg/dl
Tot. Cholesterol	327 mg/dl	<200 mg/dl
HDL	45.7 mg/dl	40-60 mg/dl
LDL	245.17 mg/dl	<100 mg/dl
VLDL	35.6 mg/dl	5-40 mg/dl
Tg	178.01 mg/dl	<150 mg/dl
Non-HDL-c	280 mg/dl	<130
HbA1c	7%	<5.6%

ASCVD Risk Estimator*

10-Year ASCVD Risk

15.0% calculated risk

3.6% risk with optimal risk factors**

Lifetime ASCVD Risk

69% calculated risk

5% risk with optimal risk factors

Recommendation Based On Calculation

Gender

Male | Female

Age

55

Race

- White
- African American
- Other

HDL - Cholesterol (mg/dL)

45

Total Cholesterol (mg/dL)

320

Systolic Blood Pressure

110

Diabetes

Yes | No

Treatment for Hypertension

Yes | No

Smoker

Yes | No

- What is a target HbA1c for this patient?
- <6.5%

- What is target lipids for this patient?
- LDL <100 *mg/dl* HDL >40 mg/dl
- Non-HDL<130 mg/dl

- Does this patient need aspirin therapy?
  probably, yes

New treatment 20/12/2016

- Focus on Diet + physical exercise
- Metformin 500 mg X2 per day for 1 week, then 850 mg X2 day – for long term use.
- Rosuvastatin 20 mg X1 day

- Consultation of Cardiologist (stress test to exclude Coronary artery disease)

5 month later 10/05/2017

- Patient feels better, follows the diet, regularly checks blood glucose levels;
- Mean fasting blood glucose 120-150 mg/dl;
- Stopped taking Rozuvastatin because of the reason that “statin intake was associated with increased fasting blood glucose“(?)
- Minimal physical activity

Lab results 13/05/2017

Test	Result	Target
HbA1c	7%	<6.5%
Tot. Cholesterol	282.7 mg/dl	
HDL	36 mg/dl	>40 mg/dl
LDL	211.9 mg/dl	<100 mg/dl
VLDL	34 mg/dl	
Tg	171.1 mg/dl	<150 mg/dl
Non-HDL-c	246.7	<130 mg/dl
eGFR	92 ml/min/1.73m3	> 90 ml/min/1.73m3
25(OH)D3	8.5 ng/dl	30-100 ng/dl

Lipid profile of 81 years old mother

Test	Result	References
Tot. Cholesterol	315.52 mg/dl	<200 mg/dl
HDL	78.69 mg/dl	40-60 mg/dl
LDL	232,99 mg/dl	<100 mg/dl
VLDL	12.8 mg/dl	5-40 mg/dl
Tg	64.35 mg/dl	<150 mg/dl

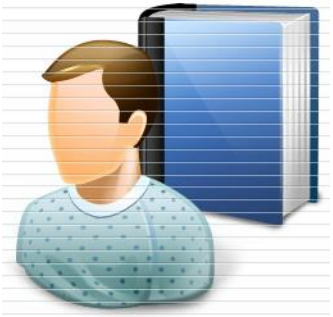
- Is it familiar hypercholesterolemia?
- What is best antidiabetic agent for this patient after metformin?
- Does this patient need aspirin?

New treatment 15/05/2017

- Diet
- Physical Exercise
- Can’t tolerate metformin, even with low dose and slow titration.

- Sitagliptin 100 mg 1X day
- Rozuvastatin 20 mg 1 Xday
- Aspirin?

Patient N3



- 42 years old man with uncontrolled diabetes Mellitus type 2 (duration of diabetes -9 years)
- 3 years ago started insulin therapy in Basis Bolus regimen combined with Metformin 1000 mg twice a day
- In 2010 patient developed non-STEMI, underwent PCI with angioplasty. 2 Stents were placed.
- Patient is noncompliant, intermittently stops all oral medications, including statins.
- Poor diet, sedentary lifestyle, Current Smoker (1 package per day)
- Occupation – Georgian actor, playing in movies and theater
- Family history: Genetic predisposition toward DMT2 – father and brother has DMT2; Genetic predisposition toward CVD – uncle had MI and sudden cardiac death at age 40.

On first visit

- Dry mouth
- Excessive thirst
- Frequent urination
- Nighttime urination

- Numbness and tingling in lower extremities

- Chest pain connected to excessive physical or emotional stress

- Recently noticed small skin rash all over the body.

- Weight - 113 kg; height – 1.85 m;
- BMI – 31 kg/m2; Abdominal circumference – 110 cm

- T/A 130/80 mmhg; HR – 95’ / per minute

Laboratory examination – 02/07/2016

- **Glucose profile:**
- Fasting glucose – 250-270 mg/dl,
- Postprandial glucose – does not measure at all ;
- HbA1c – 11.4%

- **Kidney function test**
- Crea – 84 μmol/l eGFR - 91 ml/min/1.73m2 according to CKD-EPI
- Microalbuminuria – 129mg/l (<15 mg/l)

- **Liver function test:**
- ALT - 27 U/l; AST - 30 U/l; γ-GT 35 U/l;

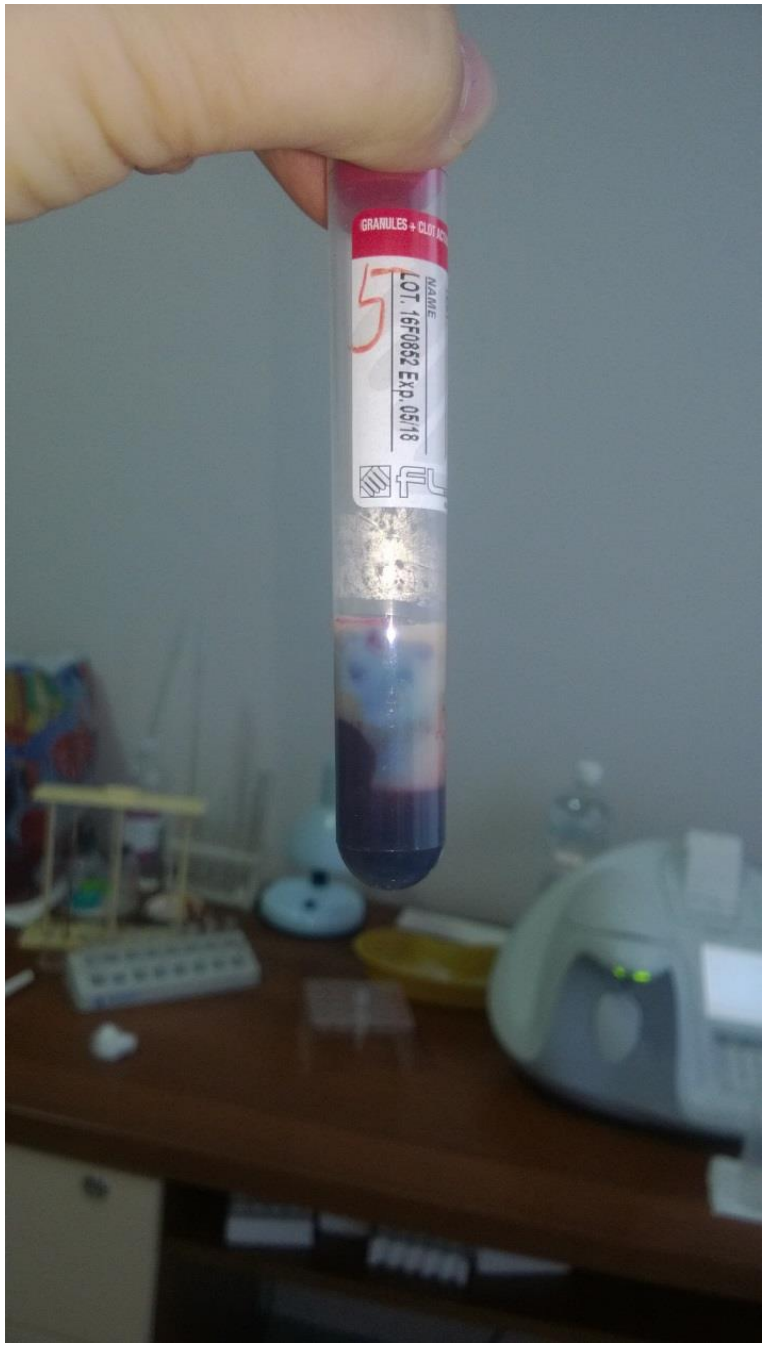
- **Urinalysis** – glycosuria, ketonuria "+"; other parameters without changes.

- **Thyroid function:** TSH – 0.84 μmol/L (0.4-4.4)

- **25(OH)D3 Vitamin** – 13 ng/ml (30-100 ng/ml)

Fasting lipids 02/07/2016

Lipid profile	Mg/dl	Mmol/l
Total cholesterol	694	18
HDL	45	1.16
LDL	418	10.85
VLDL	230	5.9
TG	1153	13.04
Non-HDL	650	16.54


GRANULES + CLOT
5
NAME
LOT. 16F0852 Exp. 05/18

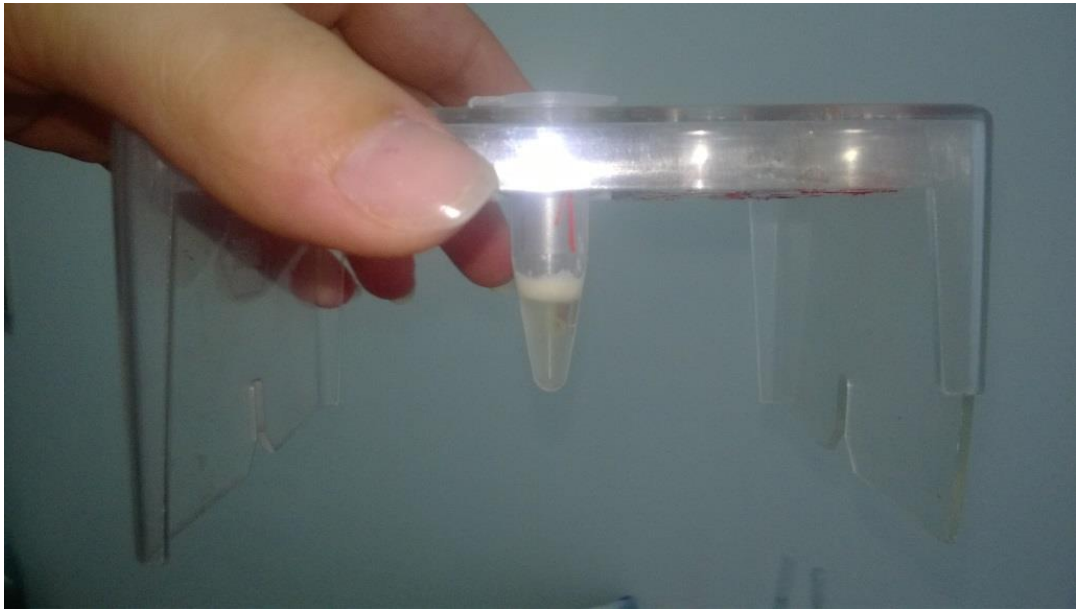


Table I **Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolaemia in adults**

	Points
Group 1: family history	
(i) First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD) OR	1
(ii) First-degree relative with known LDL cholesterol >95th percentile by age and gender for country	1
(iii) First-degree relative with tendon xanthoma and/or corneal arcus OR	2
(iv) Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: clinical history	
(i) Subject has premature (<55 years, men; <60 years, women) CHD	2
(ii) Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person <45 years	4
Group 4: biochemical results (LDL cholesterol)	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the *LDLR*, *APOB*, or *PCSK9* genes	8

Diagnosis

Familiar Hypercholesterolemia
Severe hypertriglyceridemia (due to decompensated diabetes)
or
Disbetalipoproteinemia

- **Diabetes mellitus type 2, uncontrolled**

- **Microvascular Complications of diabetes:**

Diabetic polyneuropathy
Diabetic autonomic neuropathy (ED, Sinus tachicardia)
Diabetic nephropathy, microalbuminuria, CKD1
Ophthalmological complications need to be specified

- **Macrovascular complications of FH and diabetes:**

CHD; Non-STEMI in 2010, Nonstable stenocardia

Abdominal obesity grade I
Vitamin D deficiency

Treatment – The main problem is Non-compliance

Previous treatment

- Metformin 1000 mg b.i.d.
- Ins. Glargine 20 U at bedtime
- Ins. Glulisine 10 U before each main meal

Patient was not taking Medications prescribed by cardiologist: statins, antiplatelet, ACE-inhibitors, B-Blockers, Spironolactone;

The reason of noncompliance is that he "hates to take pills, he would not be dependent on oral medication, he feels worse when taking pills" and similar stories.

Current treatment (last 3 month)

- **Rosuvastatin** 40 mg in the evening
- **Fenofibrate** 145 mg once a day
- **Cholecalciferol** 50 000 IU/weekly
- **Metformin 1000 mg** b.i.d.

(Liraglutide was suggested but patient refused to start injectable GLP-1 agonists.)

- **Ins. Glargine** 30 U at bedtime
- **Ins. Glulisine** 10 U before each main meal

Prescription by cardiologist:

Perindopril 5 mg at bedtime
Aspirin 100 mg after dinner
Spironolactone 25 mg once a day
Nebivolol 5 mg once a day

Laboratory examination

- **Glucose profile:**
- Fasting glucose – 180-250 mg/dl,
- Postprandial glucose – still does not measure;
- HbA1c – 9.5%

- **Kidney function test**
- Crea –60 μmol/l eGFR - 117 ml/min/1.73m2 according to CKD-EPI
- Urine dipstick - 2+

- **Liver function test:**
- ALT - 21 U/l; AST - 16 U/l; γ-GT 20 U/l;

- **Thyroid function:** TSH – 1.07 μmol/L (0.4-4.4)

- **25(OH)D3 Vitamin** – 26 ng/ml (30-100 ng/ml)

Fasting lipids 16/09/2016

Lipid profile	Mg/dl	Mmol/l	Target
Total cholesterol	147	3.81	
HDL	39	1.02	?
LDL	79	2.04	<70 mg/dl (<1.8)mmol/l
VLDL	44.2	1.13	?
TG	221	2.5	?
Non-HDL	108	2.79	<100 mg/dl (<2.6 mmol/l)

Lab results 15/05/2017

Test	Result	Target
HbA1c	9.4%	<7%
Tot. cholesterol	236 mg/dl	
HDL-c	26 mg/dl	>40 mg/dl
LDL-c	99 mg/dl	<70 mg/dl
Tg	902 mg/dl	<150 mg/dl
Non-HDL-c	210 mg/dl	<100 mg/dl

On Current treatment:
Metformin 1000 mg 2Xday
Ins. Glargine 30 U – at bedtime
Ins. Glulisine 10 U before main meals

Rozuvastatin 40 mg 1 Xday
Fenofibrate 145 mg 1X day

Poor diet
Sedentary lifestyle
Smoking

Lab results of 2 years old child

Test	Result	References
Tot. cholesterol	141 mg/dl	<140 mg/dl
HDL	41 mg/dl	>35 mg/dl
LDL	87 mg/dl	<90 mg/dl
Tg	104 mg/dl	<100 mg/dl

Questions

Omega 3 fatty acids were immediately added to current treatment as risk of acute pancreatitis is high when Tg >500

- Should 10 mg Ezetimibe also be added to his treatment regimen?

Concerns - 4 agents for lipid control? Drug to drug interactions?

- What is best hypoglycemic treatment for this patient?
- Should he and child be screened only for LDLR, PCSK-9 and Apo-B mutations or also Apo-E, LPL and Apo-CII as well?
- If 1.9 years boy has a genetic mutation, then what are further recommendations?
- Any comments or additional recommendations?