Con il patrocinio di

SIO Società Italiana dell'Obesità

3° Workshop 07/03/2014 L'integrazione tra terapia medica e chirurgica nel trattamento del paziente obeso diabetico

S.I.C.OB.

Padova, 7 Marzo 2014 - Ex Ospedale Militare

Terapia Farmacologica del Paziente Diabetico Dopo Chirurgia

Controllo della Dislipidemia

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DIPARTIMENTO DI MEDICINA

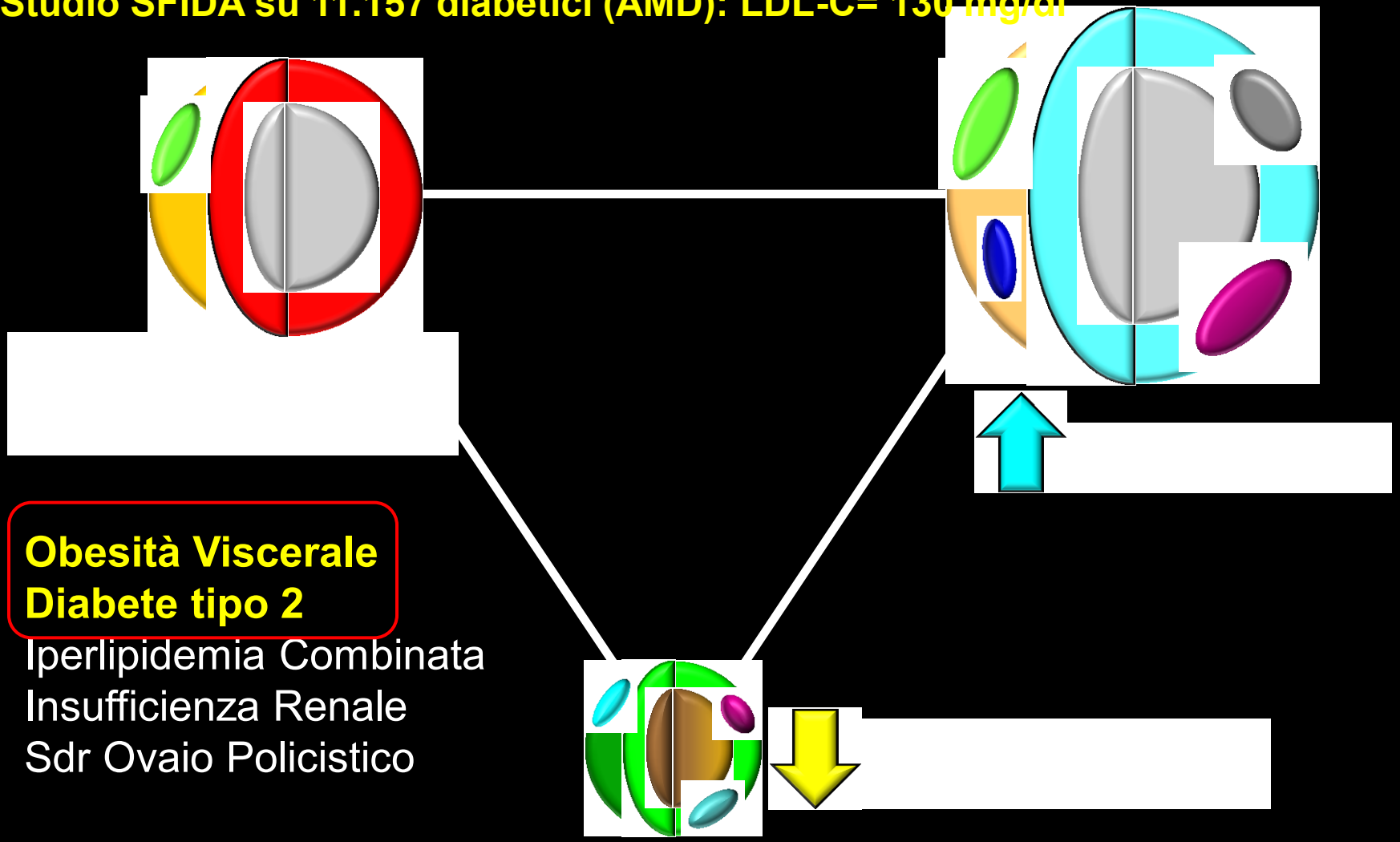
UNIVERSITA' DI PADOVA

Terapia dell'Obeso Diabetico dopo Chirurgia
CONTROLLO DELLA DISLIPIDEMIA

- **Background:**
  1) Quale dislipidemia nel diabetico
  2) Livello di rischio CV del diabetico
- **Chirurgia Bariatrica e Lipidi**
- **Rischio CV post Chirurgico nel diabetico:**
  - Cosa suggeriscono le Società Scientifiche (ADA)
- **Il Trattamento Farmacologico**

Dislipidemia Aterogena

Studio SFIDA su 11.157 diabetici (AMD): LDL-C= 130 mg/dl



Obesità Viscerale
Diabete tipo 2
Iperlipidemia Combinata
Insufficienza Renale
Sdr Ovaio Policistico

Nutr Met Cardiovasc Dis 2005, 15;204-2011

(Austin et al. Circulation 1990)

Rischio CV nel Paziente Diabetico

Linee Guida	Rischio Eventi Cardiovascolari			
	Basso	Intermedio	**Elevato**	**Molto Elevato**
EAS/ESC[1]				X
ACC/AHA[2]			X[a]	X[b]
ADA[3]			X[a]	X[b]
IAS[4]			X	
CANADIAN[5]			X	

a= Diabetici senza CVD; b= Diabetici con CVD o altri fattori di rischio CV

EAS: European Atherosclerosis Society; ESC: European Society of Cardiology; AHA: American Heart Association; ACC: American College of Cardiology; ADA: American Diabetes Association; IAS= International Atherosclerosis Society

[1] **European Heart Journal (2011) 32, 1769–1818**

[2] **Circulation 12 Novembre 2013, e-pub**

[3] **Diabetes Care 2014, 37: S14-S80**

[4] **www.athero.org Dicembre 2013**

[5] **Canadian Journal of Cardiology 29 (2013) 151–167**

Terapia dell'Obeso Diabetico dopo Chirurgia
CONTROLLO DELLA DISLIPIDEMIA

- **Background:** 1) LDL-C±elevato, basso HDL-C, elevati TG
  2) Livello di rischio CV elevato-molto elevato
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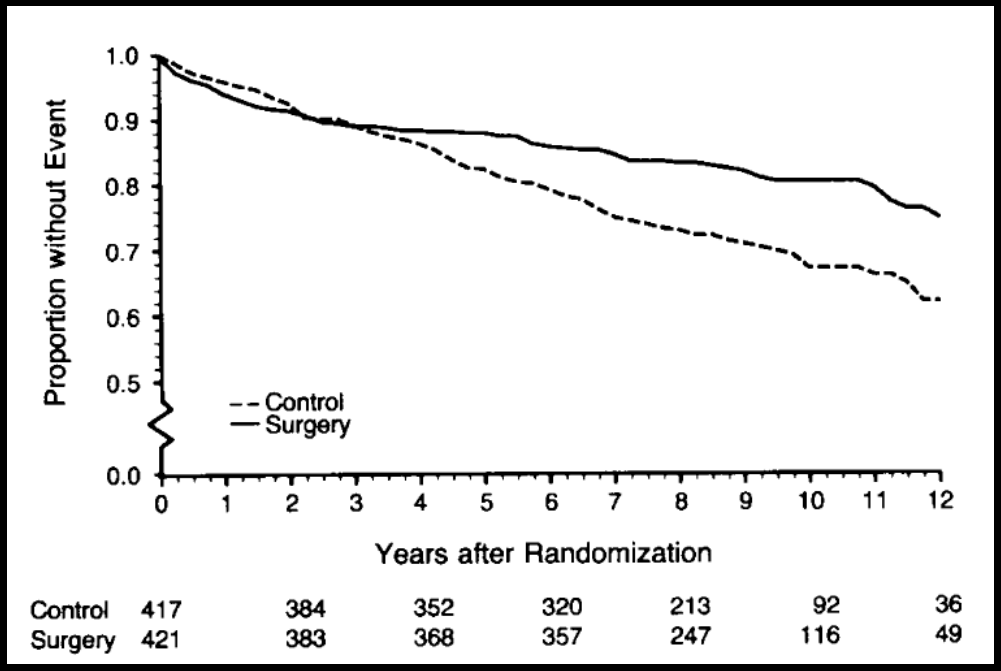
Lo Studio POSCH

(Program On Surgical Control of Hyperlipidemias)

PAZIENTI: 838 (421 surgery, 417 controls), age 51 yrs, survivors of first myocardial infarction
FOLLOW-UP: 9.7 anni
INTERVENTO: By-pass ileale parziale

ASSETTO LIPIDICO (Pre vs post):

Colesterolo totale:	-23,3% (p<0.0001)
LDL-C:	**-37,7%** (p<0.0001)
HDL-C:	+4,3% (p=0.02)
TG:	-20% (p=0.003)



Confirmed Myocardial Infarction and Death Due to CVD in the Study Groups

Control group: 125 events
Surgery group: 82 events

DECREASE IN EVENTS: **-35%** (p<0.001)

Buchwald H et al NEJM 1990; 323:946-55

Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials

11 randomized controlled studies, 796 pazienti, BMI ≥30, **n= 294 diabetici tipo 2, follow-up 6 mesi-2 anni**

Change in plasma lipid concentration (mg/dl) after bariatric surgery versus non-surgical treatment (control) for obesity: PATIENTS WITH DIABETES

Lipid Changes	**Adjustable gastric banding**	**Other bariatric surgery techniques***
Cholesterol Total	-8,0 (-19 to 8)	-23 (-46 to 4)
Triglycerides	-35 (-53 to -18)^	-80 (-106 to -44) ^
LDL-C	**-7,0** (-15 to 8)	**-22** (-46 to 1,0)
HDL-C	4,0 (4,0 to 8) ^	8,0 (8 to 12) ^

* Roux-en-Y gastric by-pass, sleeve gastrectomy, biliopancreatic diversion; **^p<0.01**

- Results are limited to two years of follow-up and based on a small number of studies and individuals
- The lack of evidence beyond two years' follow-up, in particular on adverse events, cardiovascular diseases, and mortality calls for further research

Gloy VL et al BMJ October 22, 2013

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  1) Dati a 6-24 mesi (calo ponderale stabilizzato?)
  2) Riduzione LDL-C variabile (10-25 mg/dl); insufficiente?

- **Rischio CV post-chirurgico nel diabetico:**
  - Cosa suggeriscono le Società Scientifiche (ADA)

- **Il Trattamento Farmacologico**

HOW DO WE DEFINE CURE OF DIABETES?
ADA Consensus Statement

- No robust surgical data beyond 5 years of follow-up on outcomes of diabetes, glucose control, or macrovascular and microvascular outcomes.

Buse JB et al Diabetes Care 2009; 11:2013-35

Terapia dell'Obeso Diabetico dopo Chirurgia
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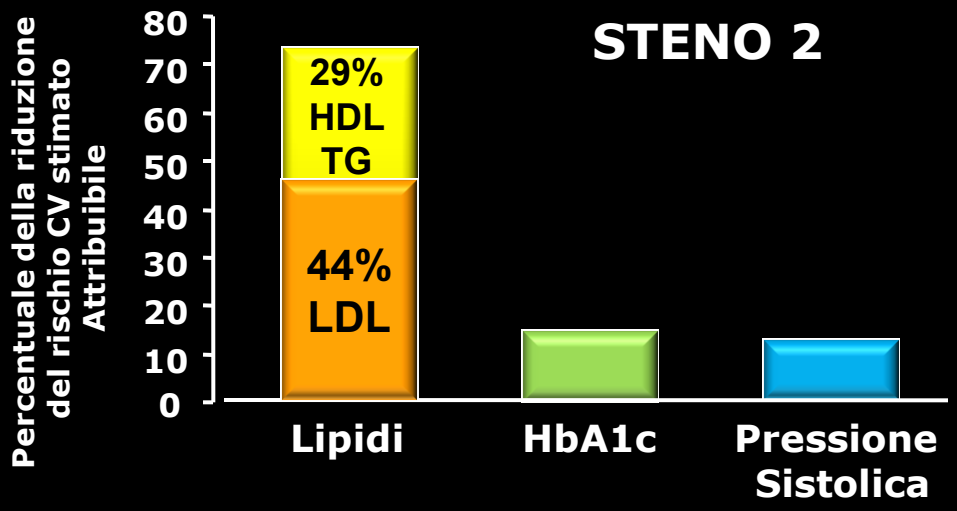
- **Rischio CV post-chirurgico nel diabetico:**
  1) Rischio CV resta elevato anche post-chirurgia bariatrica e va trattato di conseguenza (ADA)

- **Il Trattamento Farmacologico**

UKPDS –STENO 2: Riduzione del Rischio Cardiovascolare Rilevanza Clinica della Correzione dei Fattori di Rischio (Pazienti Diabetici)

UKPDS – Eventi Coronarici (n=280)

Rilevanza nel Modello	Variabile	P Valore
Primo	Colesterolo LDL	<0.0001
Secondo	Colesterolo HDL	0.0001
Terzo	Emoglobina Glicata (HbA_{1c})	0.0022
Quarto	Pressione Arteriosa Sistolica	0.0065
Quinto	Fumo di Sigaretta	0.056

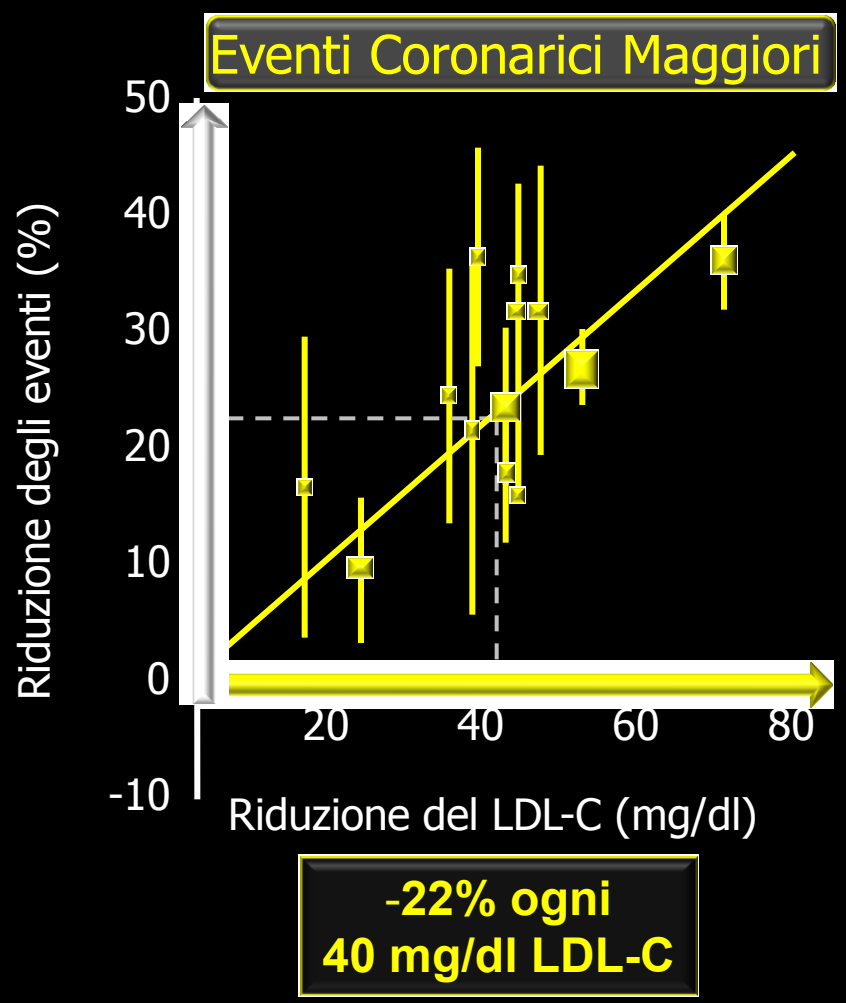


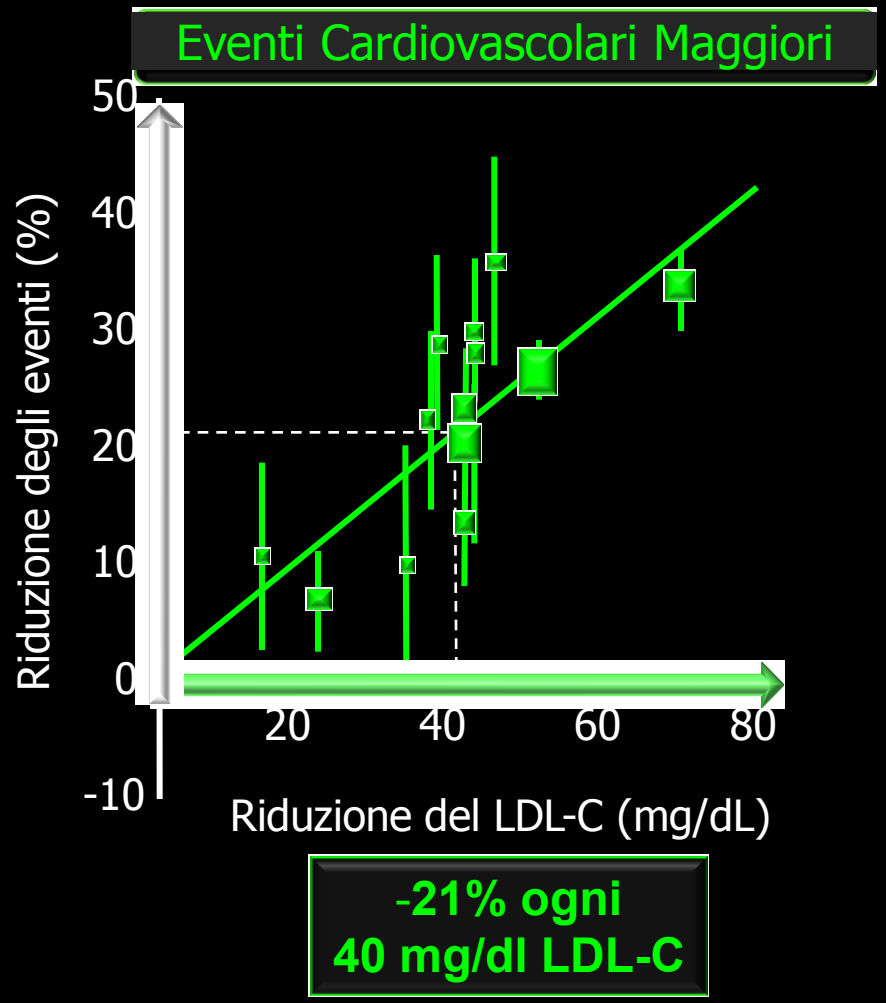
Gaede P, and Pedersen O, Diabetes 2004;53:S39-S47

UKPDS -Lancet 1998;352:837–853

Riduzione dell'incidenza degli **eventi coronarici** e **cardiovascolari** maggiori e riduzione media del LDL-C

(Meta-analisi di 14 trials, n=18.686 **PAZIENTI DIABETICI**, 1994-2004)





Lancet 2008; 371:117-125

Somiglianze e differenze nella terapia farmacologica tra il documento 2011 ESC-EAS Management of Dyslipidaemias Guidelines e Linee Guida 2013 ACC/AHA su Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk

	EAS/ESC *	AHA/ACC
Prevenzione primaria in soggetti diabetici	Diabete con altri fattori di rischio o danno d'organo: Target c-LDL <70 mg/dL (1,8 mmol/L) o almeno una riduzione del 50%. Diabete non complicato: Target c-LDL <100 mg/dL (2,5 mmol/L)	Diabete e alto rischio: terapia intensiva con statine. Diabete e basso rischio: terapia con statine a moderata intensità.

1. **Importanza della riduzione del LDL-C**
2. **Statine come approccio terapeutico prioritario**

EAS e ESC continuano a raccomandare le attuali linee guida come più adatte per l'Europa.

* Stessi target suggeriti da Raccomandazioni American Diabetes Association 2014

EAS: European Atherosclerosis Society; ESC: European Society of Cardiology
AHA: American Heart Association; ACC: American College of Cardiology

EAS/ESC website Novembre 22, 2013

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

High- Moderate- and Low-Intensity Statin Therapy
(Used in the RCTs reviewed by the Expert Panel)

High-Intensity Statin	Moderate-Intensity Statin Therapy	Low-Intensity Statin
Daily dose lowers LDL–C average by ≥ 50%	Daily dose lowers LDL–C on average by 30% to < 50%	Daily dose lowers LDL–C on average by < 30%
Atorvastatin 40-80 mg **Rosuvastatin 20-40 mg**	**Atorvastatin 10-20 mg** **Rosuvastatin 5-10 mg** **Simvastatin 20–40 mg** Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Statina+Ezetimibe

Specific statins and doses are noted in **bold** that were evaluated in RCTs and the CTT 2010 meta-analysis, and that demonstrated a reduction in major cardiovascular events.

Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*

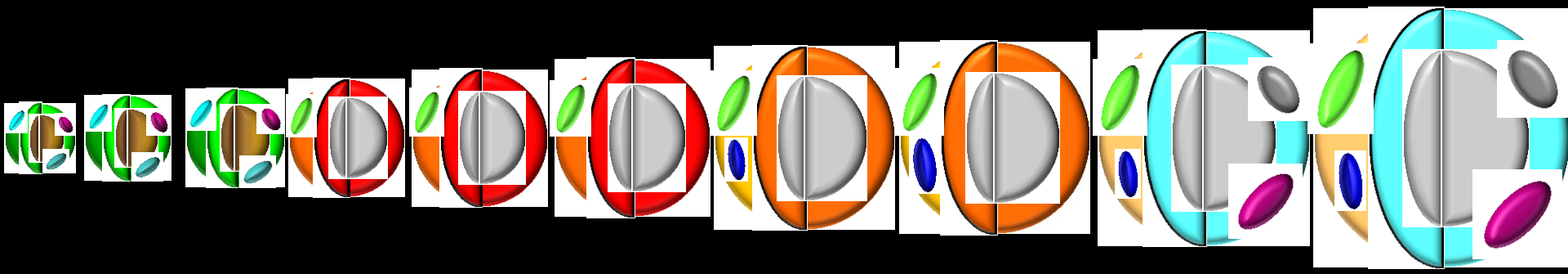
Modificato da Circulation 12 Novembre 2013, e-pub

Non-HDL Colesterolo e Apo B

Colesterolo

Trigliceridi

HDL LDL IDL VLDL



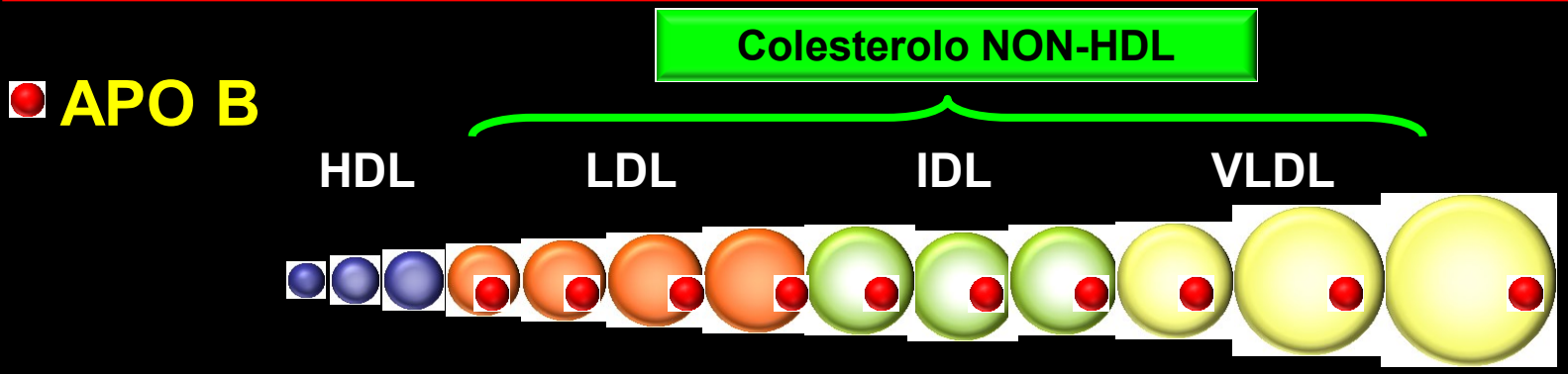
Lipoproteine Anti Aterogene

Lipoproteine Aterogene

= Tutte le Lipoproteine meno le HDL

= Non HDL Colesterolo

Non-HDL-C e Apo B nelle Linee Guida del Diabete



ESC/EAS Guidelines for the management of dyslipidaemias

Recommendations	Class[a]	Level[b]
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for [redacted] mg/dL) and the secondary goal for [redacted] (100 mg/dL) and for apo B is <80 mg/dL.	I	B
In all people with type 2 diabetes [redacted] <2.5 mmol/L [redacted] is the primary target. [redacted] and apo B <100 mg/dL are the secondary targets.	I	B

European Heart Journal (2011) 32, 1769–1818

NON-HDL C

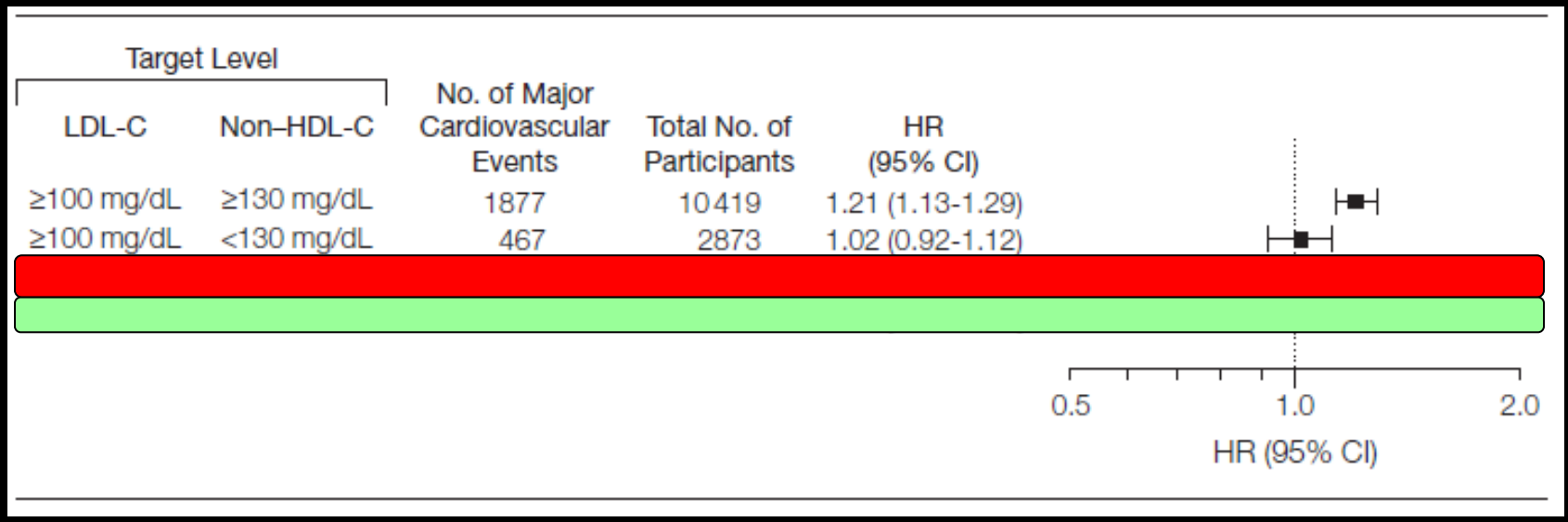
- ✓**Target Secondario**: ADA-ACC, EAS/ESC
- ✓**Economico, facile da calcolare**:
  Colesterolo totale – HDL-C= Non-HDL C
- ✓**Livelli Target facili da ricordate**:
  Target Non-HDL-C: target LDL-C + 30 mg/dl
- ✓**Predice rischio CV meglio di LDL-C in diabetici poichè comprende TUTTE** le lipoproteine aterogene!!!

Association of LDL-C, Non–HDL Cholesterol, and Apo B With Risk of Cardiovascular Events Among Patients Treated With Statins

A Meta-analysis

62154 patients enrolled in 8 trials published between 1994 and 2008

Risk of Major Cardiovascular Events by LDL and non-HDL Cholesterol Categories



Data markers indicate hazard ratios (HRs) and 95% CIs for risk of major cardiovascular events. Results are shown for 4 categories of statin-treated patients based on whether or not they reached the LDL-C target of 100 mg/dL (2.6 mmol)L) and the non–HDL-C target of 130 mg/dL (3.4 mmol/L).

HRs were adjusted for sex, age, smoking, diabetes, systolic blood pressure, and trial.

Boekholdt M et al. ***JAMA. 2012;307(12):1302-1309***

Dislipidemia Aterogena e Terapia di Associazione

	Statina + Acido Nicotinico	Statina + Acidi grassi Omega-3	Statina + Feno fibrato
Effetti su Dislipidemia Aterogena	+++	+	+++
HDL-C	++	-	+
Trigliceridi	++	++	+++
Profilo di Sicurezza	-	+++	++
Evidenza clinica su CVD	-	-	+
Diabetici alti TG, basso HDL-C	-	-	+++
Presente nelle Linee Guida	Yes	Yes	Yes

Acidi grassi omega-3: Evidenza su pazienti in post-IMA alla dose di 1 gr/die

Acido Nicotinico: Assenza di beneficio in associazione a statina: AIM-HIGH - HPS2-THRIVE

Terapia della Dislipidemia nell'Obeso Diabetico dopo Chirurgia:
TAKE HOME MESSAGE

- **Background:**
  1) LDL-C±elevato, basso HDL-C, elevati TG
  2) Livello di rischio CV elevato-molto elevato

- **Chirurgia bariatrica e lipidi**
  1) Dati a 6-24 mesi (calo ponderale stabilizzato?)
  2) Riduzione LDL-C variabile (10-25 mg/dl); insufficiente?

- **Rischio CV post-chirurgico nel diabetico:**
  1) Rischio CV resta elevato anche post-chirurgia bariatrica

- **Il Trattamento Farmacologico**
  1) Target #1 LDL-C; Target emergente Non HDL-C
  2) Statine 1° scelta: elevata efficacia (↓LDL ≥50%), LDL target<70
     efficacia intermedia (↓LDL 30-50%), LDL target<100
  3) Casi selezionati (basso HDL-C, alti TG nonostante statina), considerare statina+fenofibrato

Old and New Lipid-lowering agents effective on plasma HDL-C and Triglycerides

	Δ LDL-C	ΔHDL-C	ΔTG	ΔLp(a)
CETP* Inhibitors	↓ by 0-40%	↑ by 35-140%	Variable	--------
Niacin (2g/day)	↓ 20%	↑ up to 30%	↓ up to 35%	↓ 30-40%
Fibrates	Variable	↑ by 10-20%	↓ by 25-50%	No Effect
Omega-3 Fatty acids	↑/no change	↑/no change	↓ by 25-50	No Effect

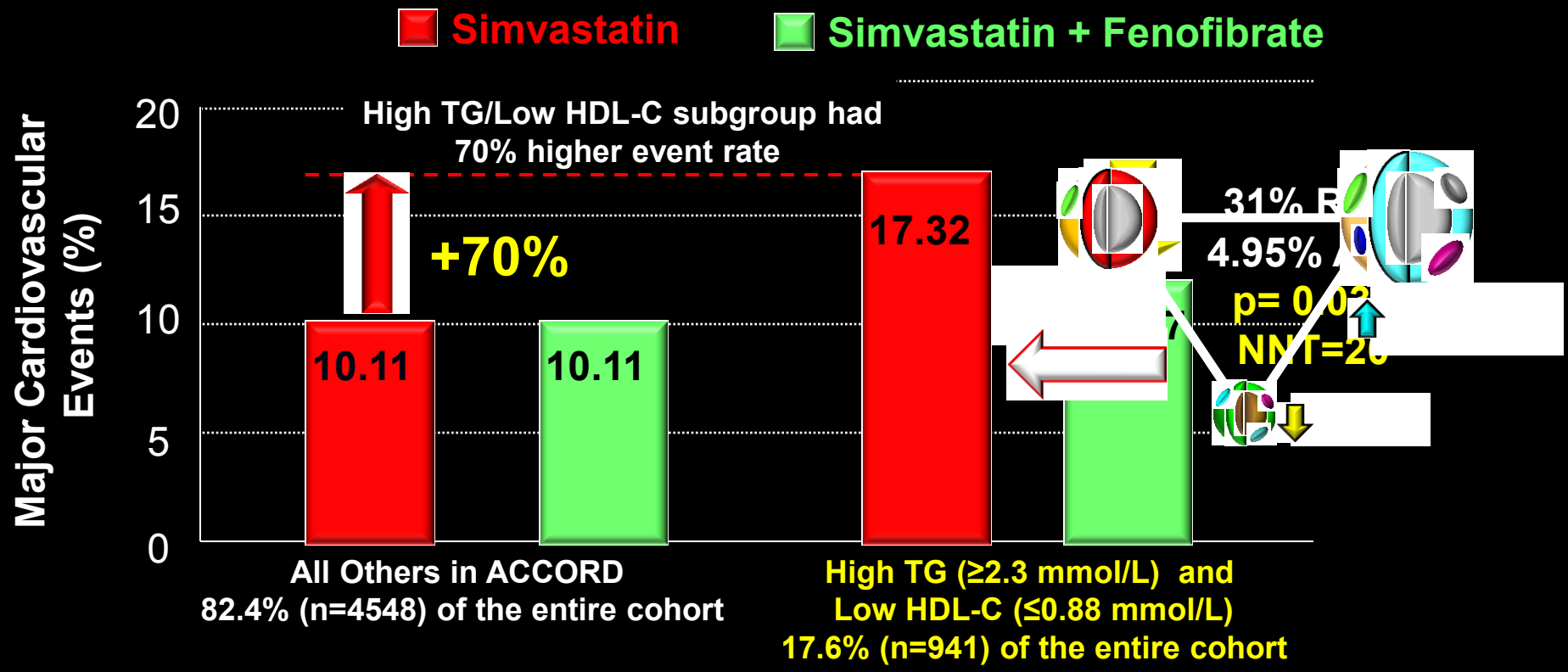
* Advanced Phase III trials

Modified from EAS Consensus, Eur.Heart J 29 aprile 2011 e-pub

ACCORD

Patients with Elevated TG and Low HDL-C

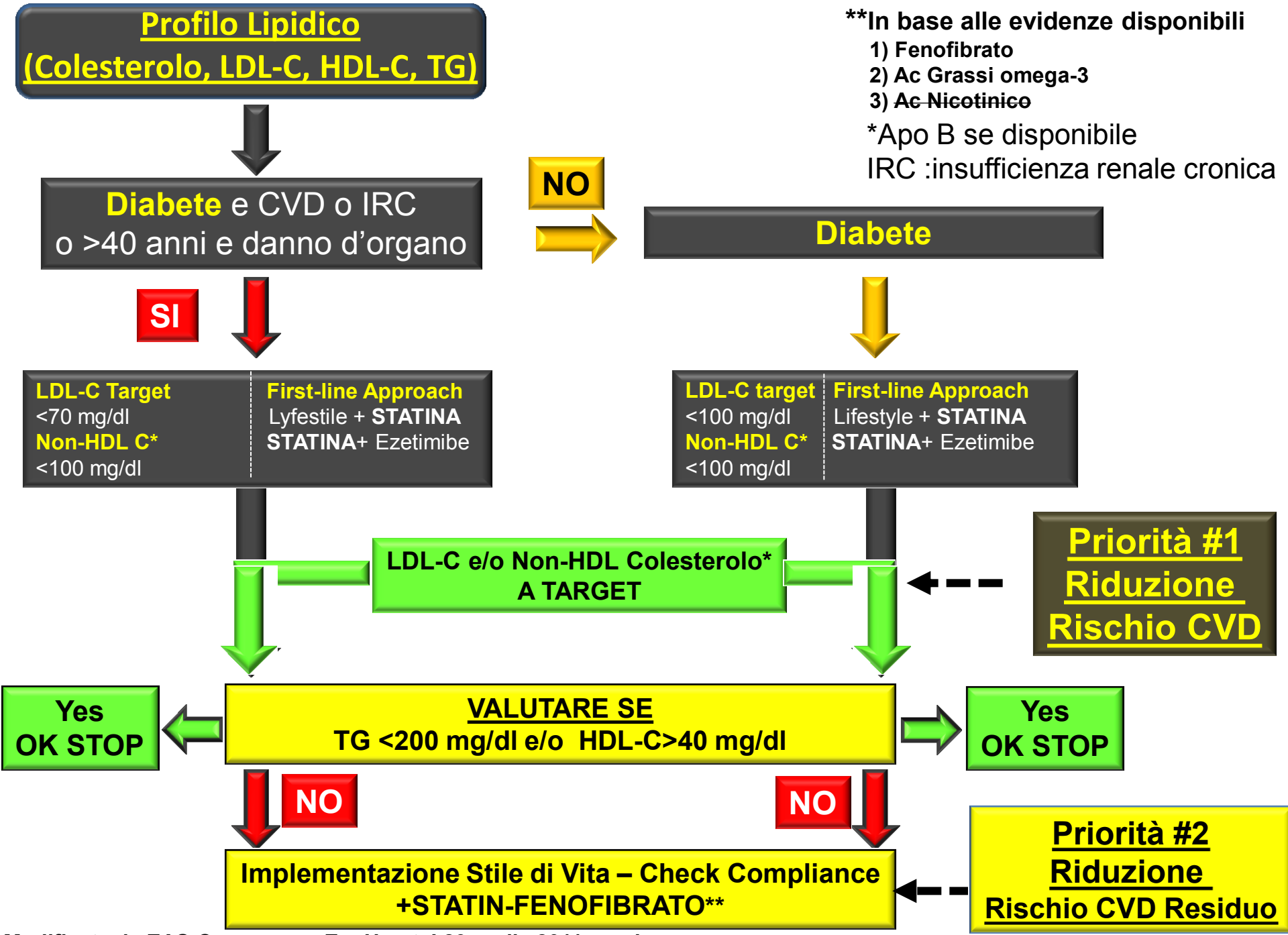
- Similar selection criteria
-Same lipid-lowering therapy: simvastatin 20-40 mg
-Same LDL-C on therapy: 80 mg/dl (2.0 mmol/l)



**Major CV events defined as CV death, nonfatal MI and nonfatal stroke

TG

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.



Modificata da EAS Consensus, Eur.Heart J 29 aprile 2011 e-pub

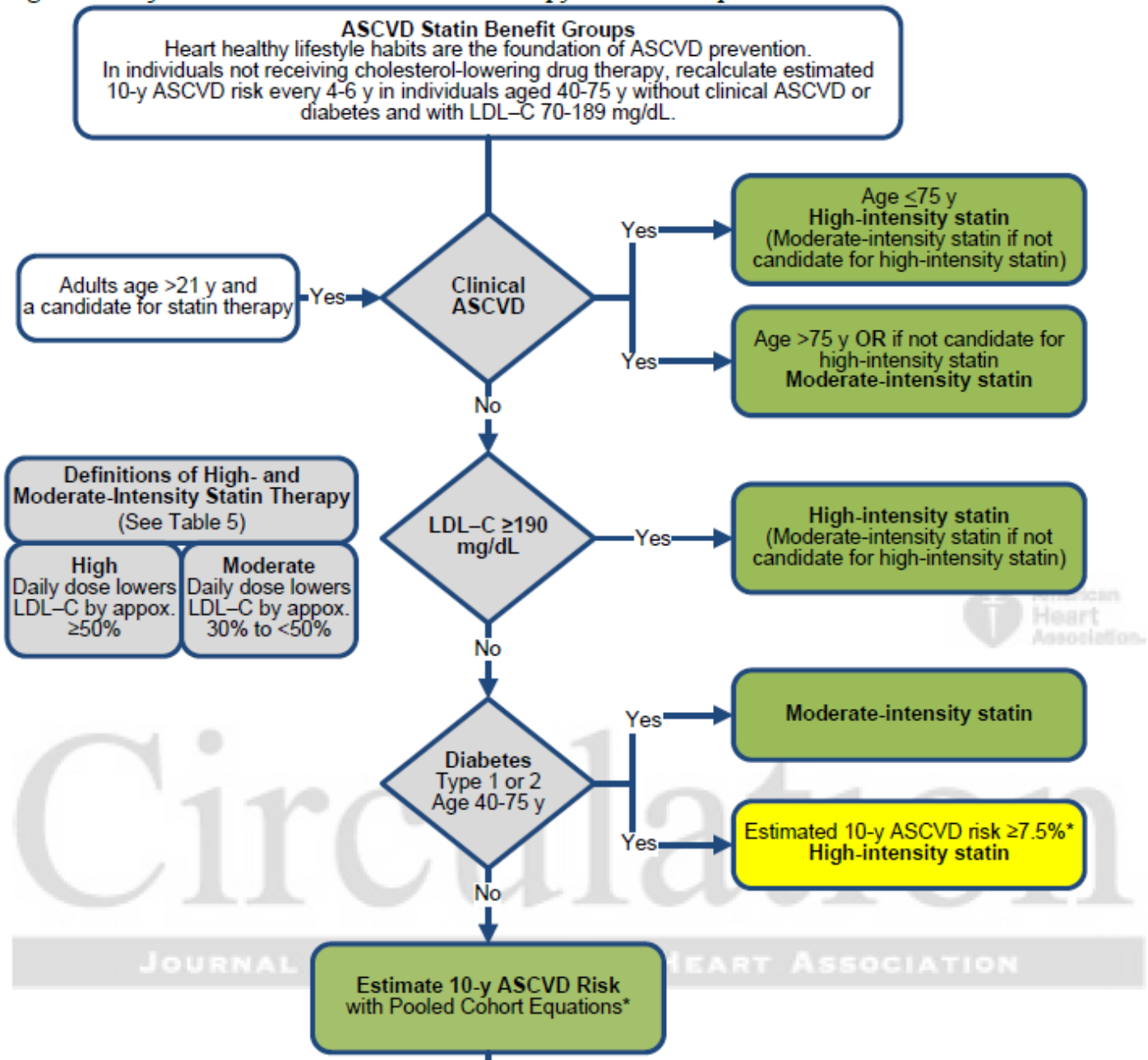
ADA 2014 Guidelines

Management of Dyslipidemia

Screening	Measure fasting lipids at least annually Every 2 yrs for adults with low-risk lipid values: LDL-C <100 mg/dL (2.6 mmol/L), HDL-C >50 mg/dL (1.3 mmol/L), TG <150 mg/dL (1.7 mmol/L)
Targets	• No overt CVD: LDL-C <100 mg/dL (2.6 mmol/L) • Overt CVD: LDL-C <70 mg/dL (1.8 mmol/L), with high-dose statin* • If targets not achieved on max statin therapy: ~30–40% LDL-C reduction from baseline
Treatment	Lifestyle modification •Reduce saturated fat, trans fat, cholesterol intake •Increase omega-3 fatty acids, viscous fiber, plant stenols/sterols intake •Weight loss (if indicated) •Increase physical activity
	Statin therapy* and lifestyle changes in patients with •Overt CVD •No CVD, aged >40 yrs, ≥1 CVD risk factor† •Consider statins in lower-risk patients (no overt CVD, aged <40 yrs) if LDL-C >100 mg/dL or if multiple CVD risk factors
	Combination therapy not recommended

*Contraindicated in pregnancy; †Hypertension, smoking, dyslipidemia, albuminuria, family history of CVD

Figure 2. Major recommendations for statin therapy for ASCVD prevention



Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials

11 randomized controlled studies, 796 pazienti, BMI ≥30, **n= 200 diabetici tipo 2, follow-up 1-2 anni**

Change in plasma lipid concentration (mmol/L) after bariatric surgery versus non-surgical treatment (control) for obesity: PATIENTS WITH DIABETES

Lipid Changes	Adjustable gastric banding	Other bariatric surgery techniques*
Cholesterol Total	-0,2 (-0,5 to 0,2)	-0,6 (-1,2 to 0,1)
Triglycerides	-0,4 (-0,6 to -0,2)	-0,9 (-1,2 to -0,5)
LDL-C	-0,17 (-0,4 to 0,2)	-0,6 (-1,2 to 0,0)
HDL-C	0,1 (0,1 to 0,2)	-0,2 (0,2 to 0,3)

* Roux-en-Y gastric by-pass, sleeve gastrectomy, biliopancreatic diversion

- Results are limited to two years of follow-up and based on a small number of studies and individuals
- The lack of evidence beyond two years' follow-up, in particular on adverse events, cardiovascular diseases, and mortality calls for further research

Gloy VL et al BMJ October 22, 2013