Che cosa c'è di nuovo nella gestione della dislipidemia nei pazienti con diabete: il futuro della terapia ipolipemizzante

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Disclosure of Maurizio Averna

In the last two years

Lecturing:

Akcea, Amgen, Amryt, Aurora Biopharma, Daichii, Genzyme, Novartis, Piam, Sanofi, Takeda, Sobi

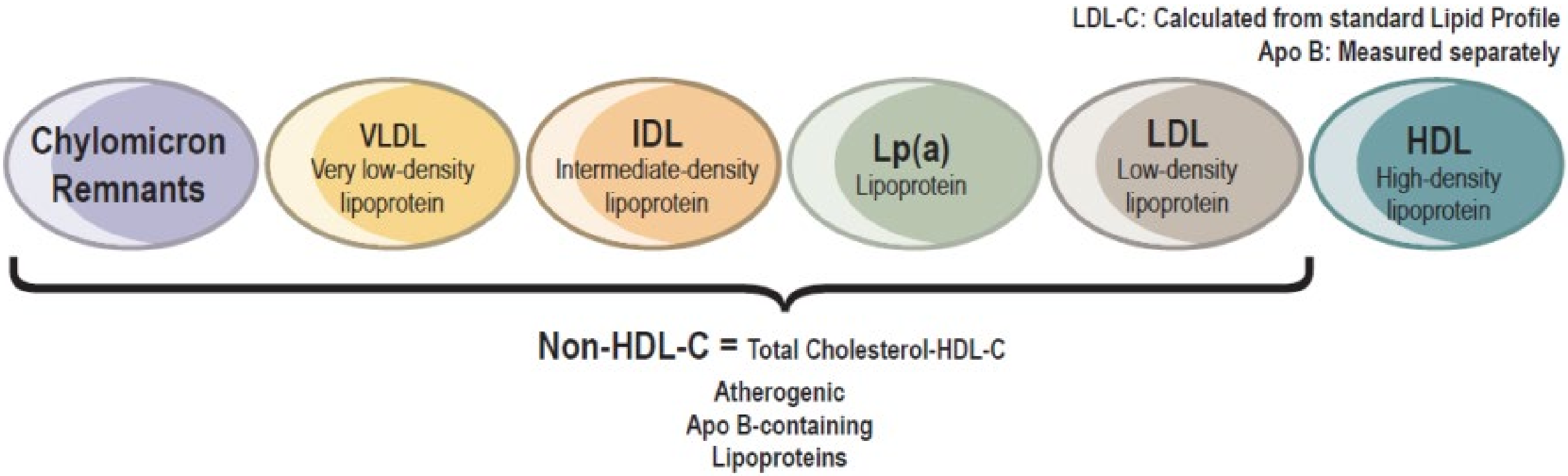
Consultant:

Akcea, Amgen, Amryt, Aurora Biopharma, Daichii, Genzyme, Novartis, Piam, Sanofi, Takeda, Sobi

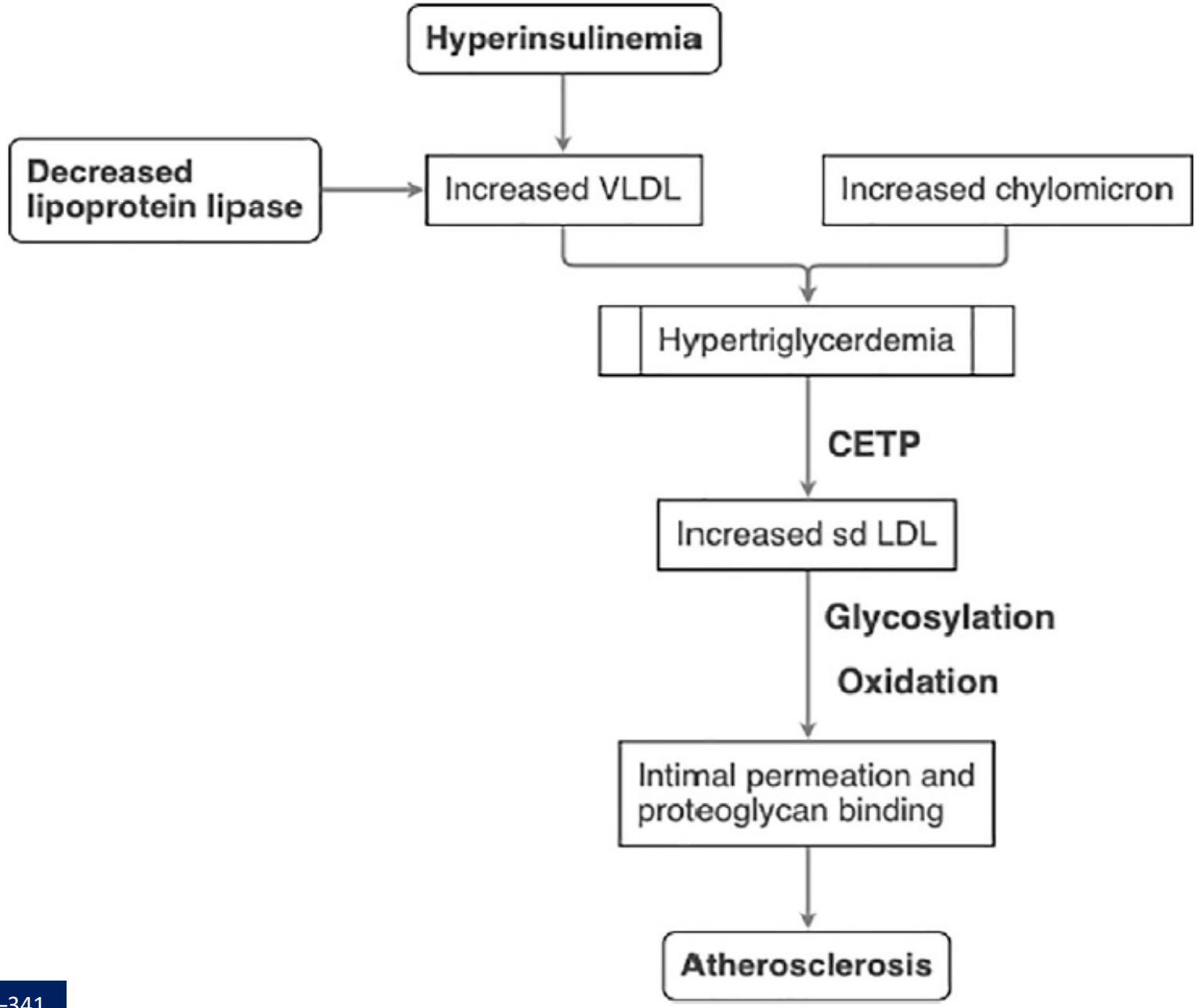
I have no actual or potential conflict of interest in relation to this presentation

The State of Art

Le Lipoproteine ricche in ApoB sono causa di malattie cardiovascolari di natura aterosclerotica

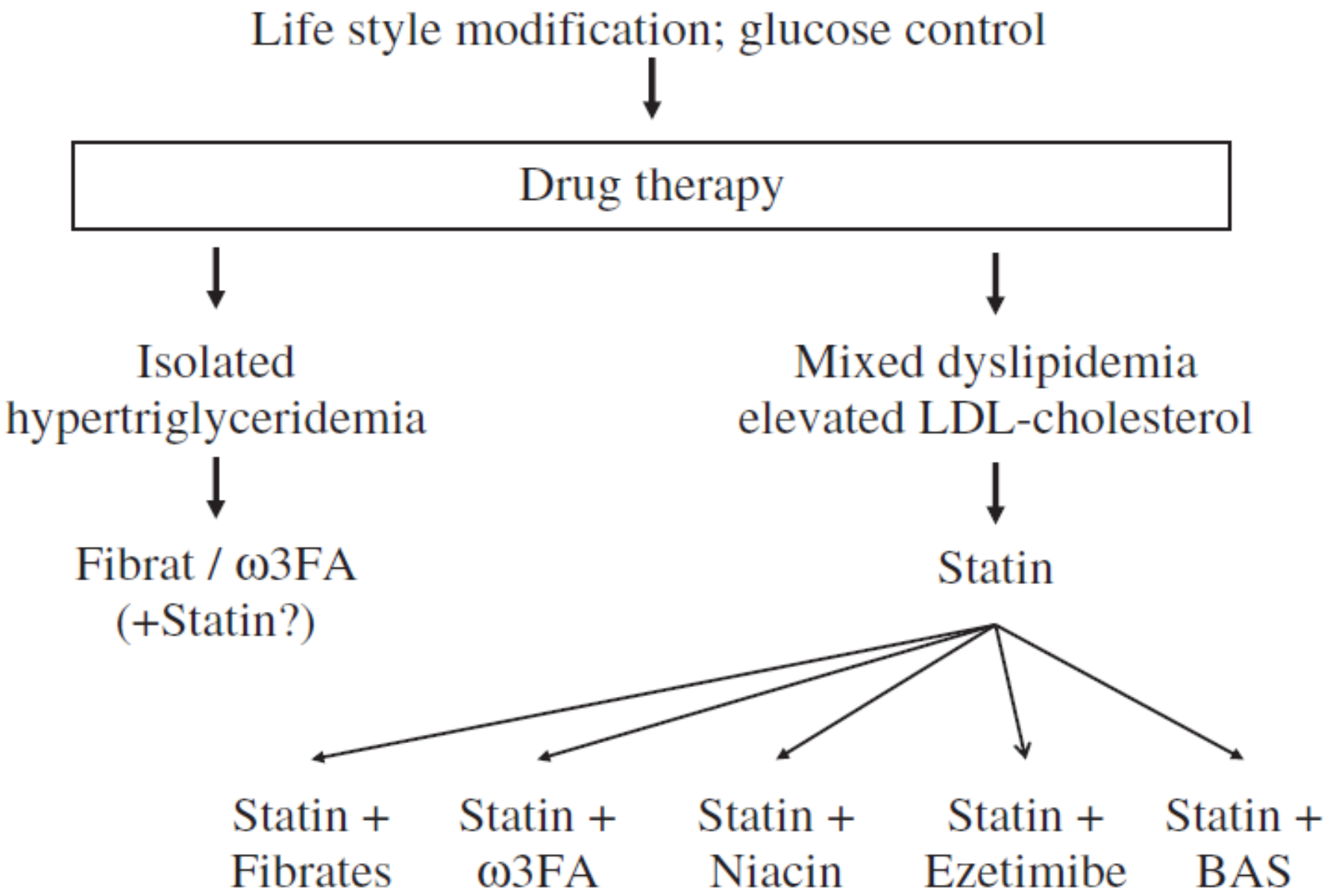


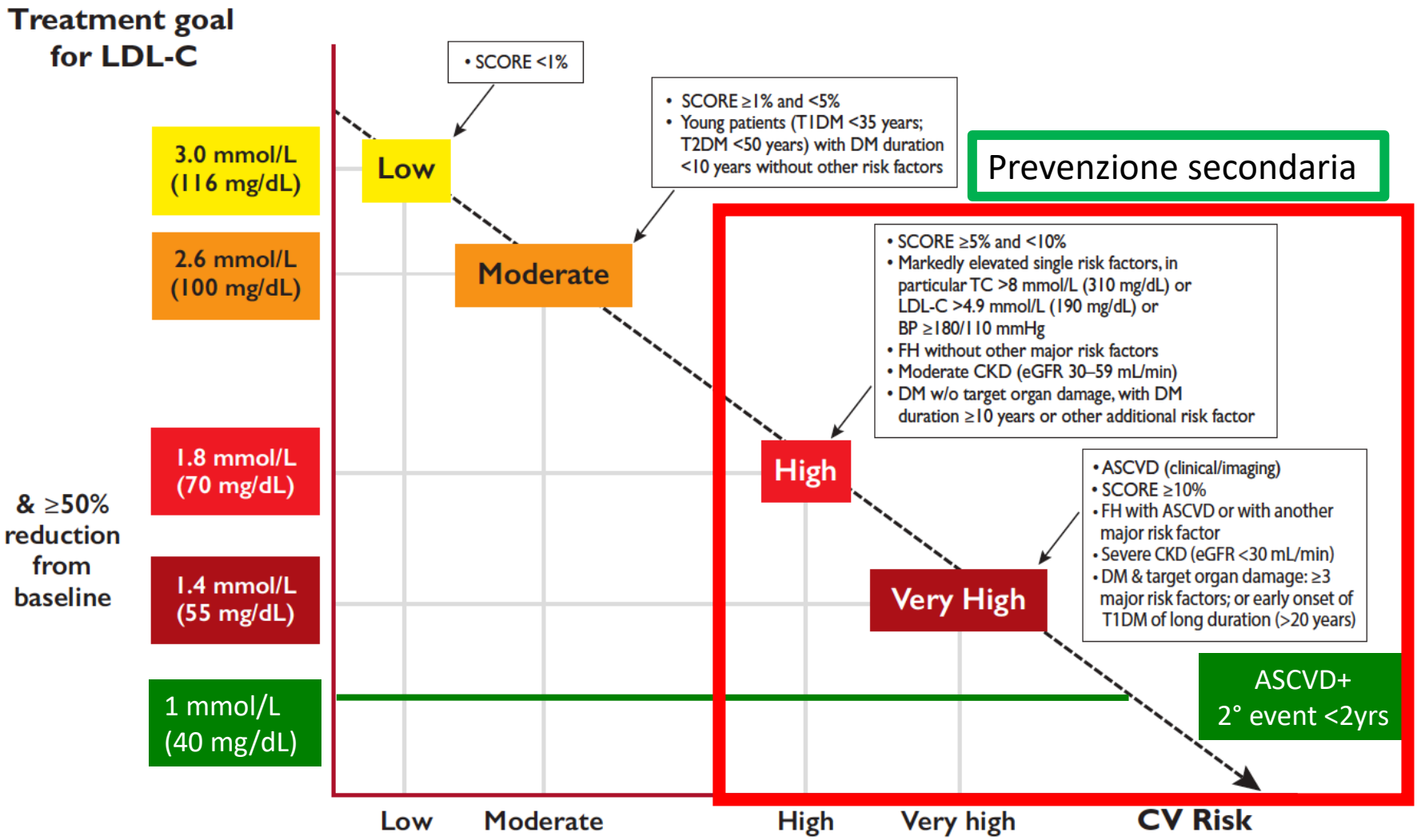
Pathogenesis of diabetic dyslipidemia



Progress in Cardiovascular Diseases 62 (2019) 334–341

Treatment algorithm for diabetic dyslipidemia




Treatment goal for LDL-C
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
1 mmol/L (40 mg/dL)
& ≥50% reduction from baseline
• SCORE <1%
Low
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
Moderate
Prevenzione secondaria
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
High
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Very High
ASCVD+ 2° event <2yrs
Low
Moderate
High
Very high
CV Risk

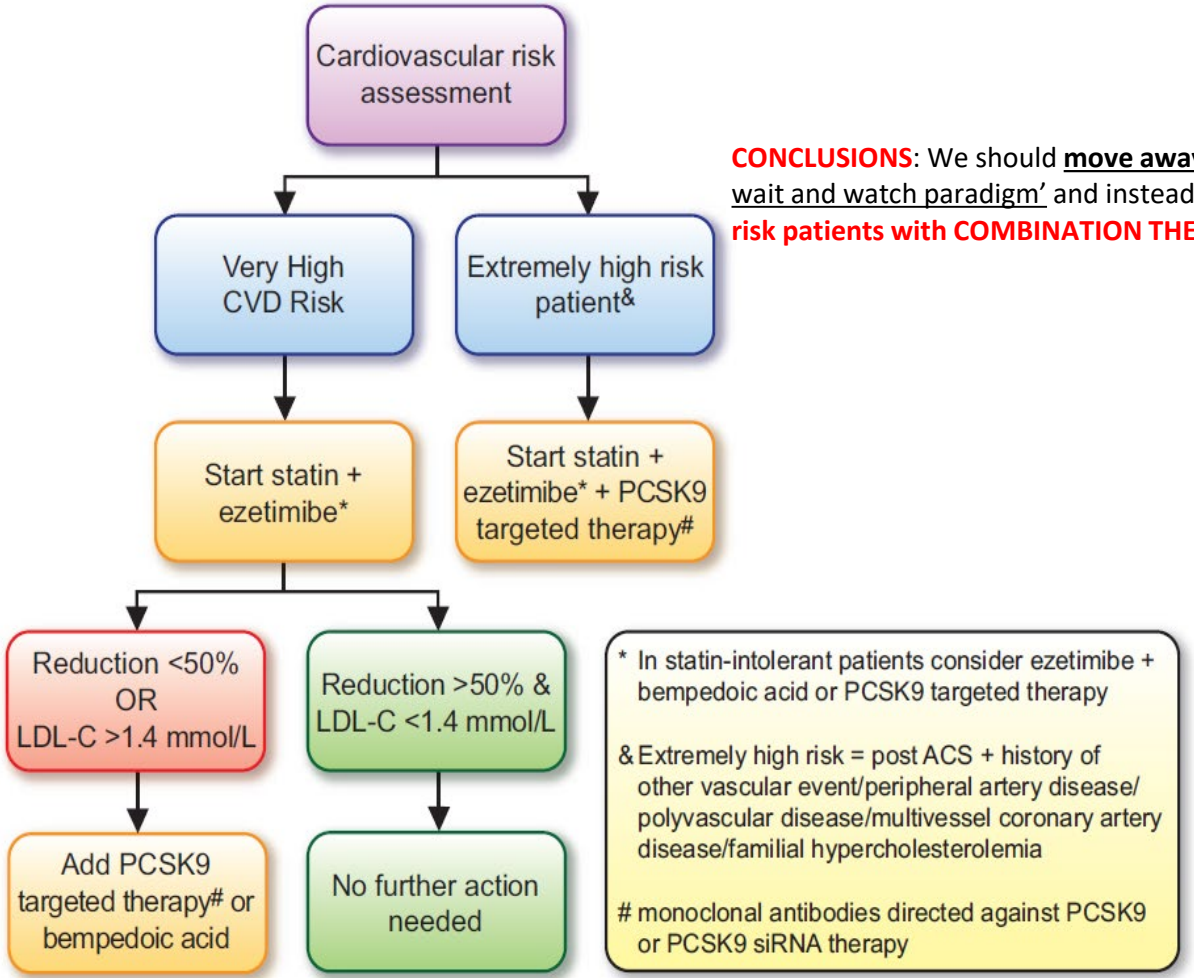
Combination lipid-lowering therapy as first-line strategy in very high-risk patients

Kausik K. Ray[1]*, Laurens F. Reeskamp [2], Ulrich Laufs [3], Maciej Banach [4], François Mach [5], Lale S. Tokgözoğlu [6], Derek L. Connolly[7], Anja J. Gerrits[8], Erik S. G. Stroes [2], Luis Masana [9], and John J. P. Kastelein [2]

VIEWPOINT
Epidemiology and prevention

Combination lipid-lowering therapy as first line strategy in very high-risk patients

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718



CONCLUSIONS: We should **move away** from 'high-intensity statin treatment' and 'the wait and watch paradigm' and instead **start treating all very high- and extremely high-risk patients with COMBINATION THERAPY as the basic standard of care**.

Efficacy of cholesterol-lowering therapy in 18 686 peop with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Proportional eff ects on major vascular events per mmol/L reduction in LDL cholesterol by baseline prognostic factors in participants with diabetes

Groups	Events (%) Treatment	Control	RR (CI)	Test for heterogenity or trend
Type of diabetes:				
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)	χ^2_1=0·0; p=1·0
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)	
Sex:				
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)	
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)	χ^2_1=0·1; p=0·7
Age (years):				
≤65	701 (13·1%)	898 (17·1%)	0·77 (0·68–0·87)	
>65	764 (18·9%)	884 (21·8%)	0·81 (0·71–0·92)	χ^2_1=0·5; p=0·5
Currently treated hypertension:				
Yes	1030 (16·3%)	1196 (19·1%)	0·82 (0·74–0·91)	
No	435 (14·2%)	586 (19·3%)	0·73 (0·63–0·85)	χ^2_1=2·7; p=0·1
Body-mass index:				
<25·0	276 (15·7%)	362 (20·4%)	0·78 (0·64–0·95)	
≥25·0–<30·0	639 (15·9%)	774 (19·8%)	0·77 (0·68–0·88)	
≥30·0	532 (15·1%)	628 (17·6%)	0·82 (0·71–0·95)	χ^2_1=0·5; p=0·5
Systolic blood pressure (mm Hg):				
<160	993 (15·0%)	1276 (19·1%)	0·76 (0·69–0·85)	
≥160	472 (17·1%)	505 (19·2%)	0·83 (0·71–0·96)	χ^2_1=1·3; p=0·3
Diastolic blood pressure (mm Hg):				
≤90	1176 (16·5%)	1417 (19·8%)	0·81 (0·73–0·89)	
>90	288 (12·9%)	364 (17·1%)	0·73 (0·61–0·87)	χ^2_1=1·7; p=0·2
Smoking status:				
Current smokers	266 (17·5%)	347 (22·5%)	0·78 (0·64–0·96)	
Non-smokers	1199 (15·2%)	1435 (18·5%)	0·79 (0·72–0·87)	χ^2_1=0·0; p=0·9
Estimated GFR (mL/min/1·73m²):				
<60	415 (20·6%)	477 (24·0%)	0·83 (0·71–0·97)	
≥60–<90	816 (15·5%)	961 (18·4%)	0·81 (0·72–0·91)	
≥90	194 (12·5%)	286 (18·7%)	0·65 (0·50–0·84)	χ^2_1=2·9; p=0·09
Predicted risk of major vascular event (per year):				
<4·5%	474 (8·4%)	631 (11·2%)	0·74 (0·64–0·85)	
≥4·5–<8·0%	472 (23·2%)	540 (27·3%)	0·80 (0·66–0·96)	
≥8·0%	519 (30·5%)	611 (35·8%)	0·82 (0·70–0·95)	χ^2_1=1·8; p=0·2
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

Global test for heterogeneity within subtotals: χ^2_{13}=13·9: p=0·4

RR (99% CI)

RR (95% CI)

0·5 Treatment better

1·0

1·5 Control better

Lancet 2008; 371: 117–25

Summary of principal RCTs with PCSK9 inhibitors

	DT2 subjects, *n* (%)	LDL cholesterol reduction from baseline, %	Cardiovascular events, hazard ratio (95% CI)
RCTs with alirocumab			
ODYSSEY LONG TERM	818 (34.9)	– 61.0	0.52 (0.31-0.90)[a]
ODYSSEY COMBO II	221 (30.7)	– 50.6	–
ODYSSEY ALTERNATIVE	75 (23.9)	– 54.8	–
ODYSSEY DM-INSULIN	441 (85.3)	– 48.2	–
RCTs with evolocumab			
PROFICIO OSLER I–II	599 (13.4)	– 60.9	0.47 (0.28-0.78)[b]
PROFICIO GAUSS III	26 (11.9)	– 52.8	–
PROFICIO GLAGOV	202 (20.9)	– 56.3	–
PROFICIO FOURIER	11,031 (40.0)	– 59.0	0.85 (0.79-0.92)

Acta Diabetologica (2018) 55:209–218

Ray *et al. Cardiovasc Diabetol* (2019) 18:149
https://doi.org/10.1186/s12933-019-0951-9

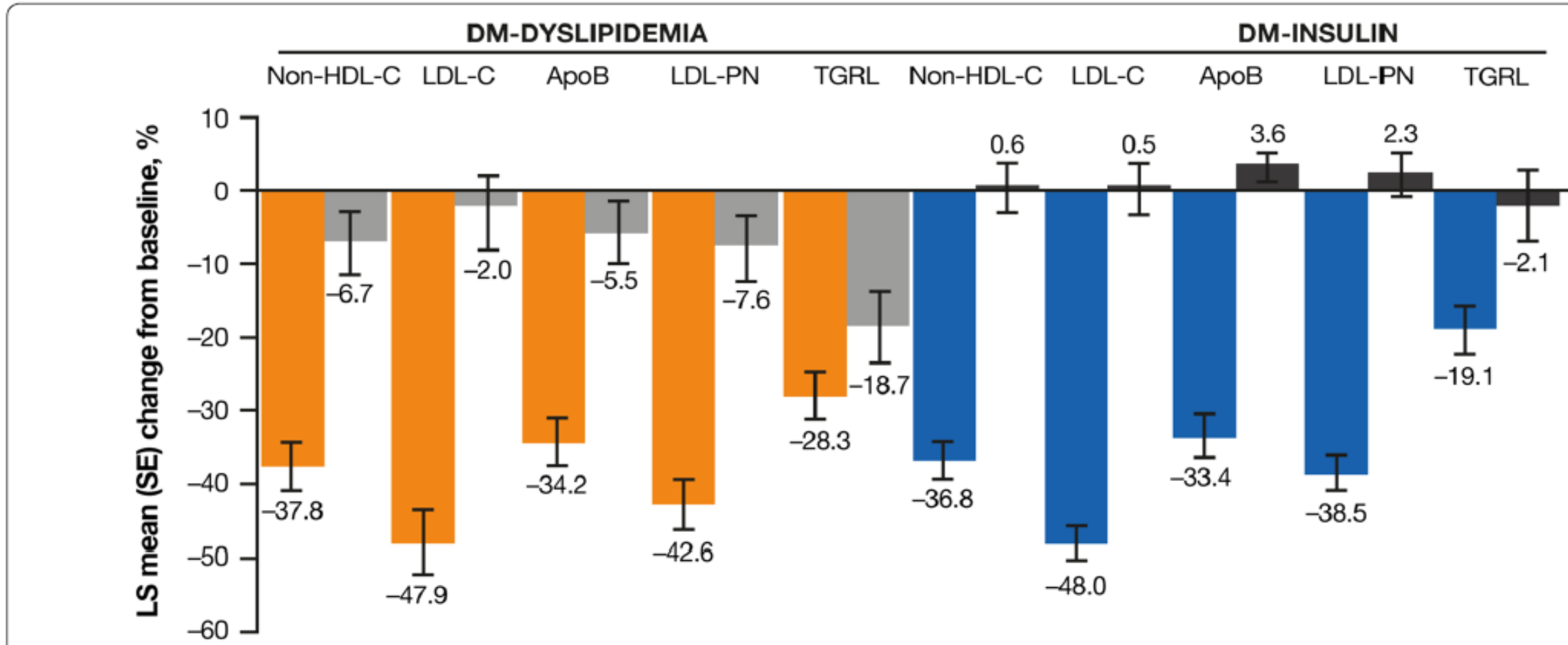
Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Alirocumab therapy in individuals with type 2 diabetes mellitus and atherosclerotic cardiovascular disease: analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies

Kausik K. Ray[1*], Stefano Del Prato[2], Dirk Müller-Wieland[3], Bertrand Cariou[4], Helen M. Colhoun[5], Francisco J. Tinahones[6], Catherine Domenger[7], Alexia Letierce[8], Jonas Mandel[9], Rita Samuel[10], Maja Bujas-Bobanovic[11] and Lawrence A. Leiter[12]

Percentage change from baseline to week 24 in non-HDL-C, LDL-C, ApoB, LDL-PN



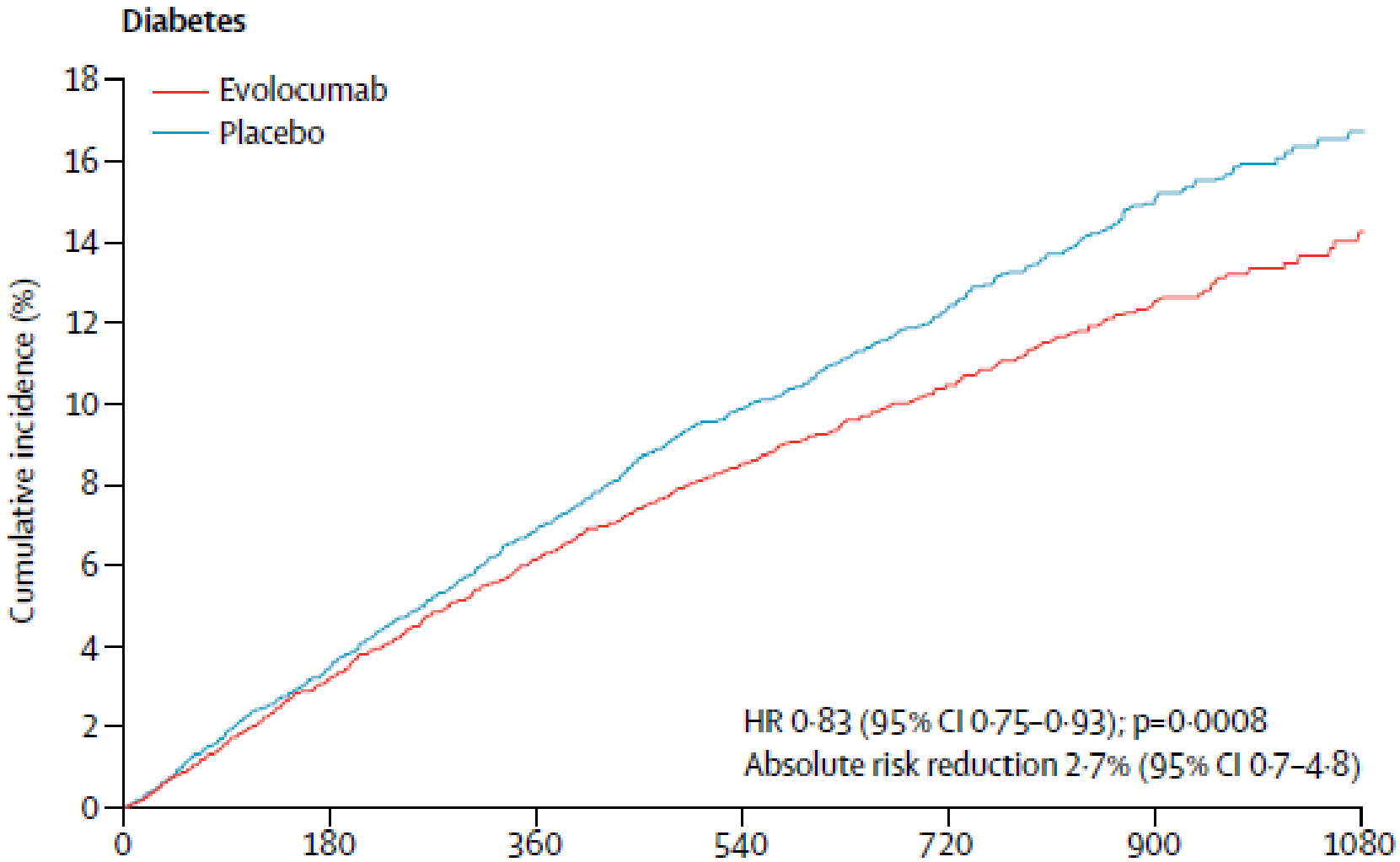
	Non-HDL-C	LDL-C	ApoB	LDL-PN	TGRL	Non-HDL-C	LDL-C	ApoB	LDL-PN	TGRL
LS mean difference (SE) vs control, %	−31.1 (4.3)	−45.9 (5.8)	−28.7 (3.9)	−35.0 (4.4)	−9.6 (6.3)	−37.4 (3.9)	−48.5 (4.4)	−37.1 (3.5)	−40.8 (3.9)	−17.0 (6.2)
95.0% CI	−39.6 to −22.7	−57.2 to −34.6	−36.4 to −21.0	−43.7 to −26.3	−21.9 to −2.7	−45.0 to −29.8	−57.1 to −39.9	−43.9 to −30.2	−48.4 to −33.2	−29.1 to −4.9
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.1266	<0.0001	<0.0001	<0.0001	<0.0001	0.0058

DM-DYSLIPIDEMIA Alirocumab (n=94) UC (n=47)
DM-INSULIN Alirocumab (n=115) Placebo (n=55)

Acta Diabetologica (2018) 55:209–218

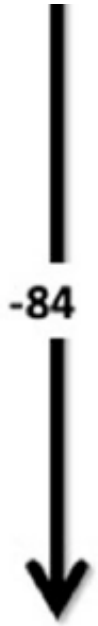
Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen



Il raggiungimento degli obiettivi terapeutici nell' era degli inibitori di PCSK9

Statina ad alta intensità+
Ezetimibe+
PCSK9i



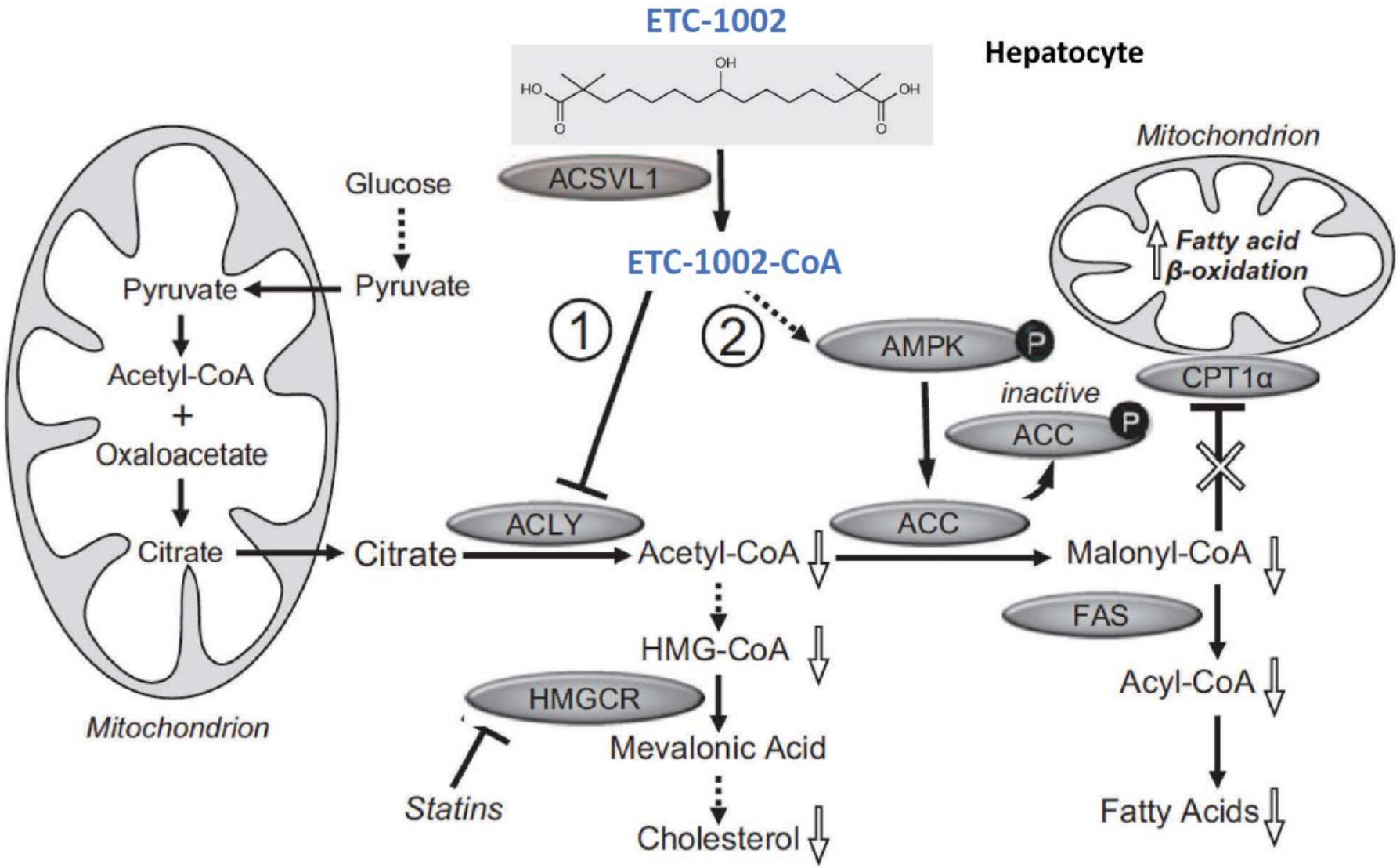
Current Cardiology Reports 2020

Agenda

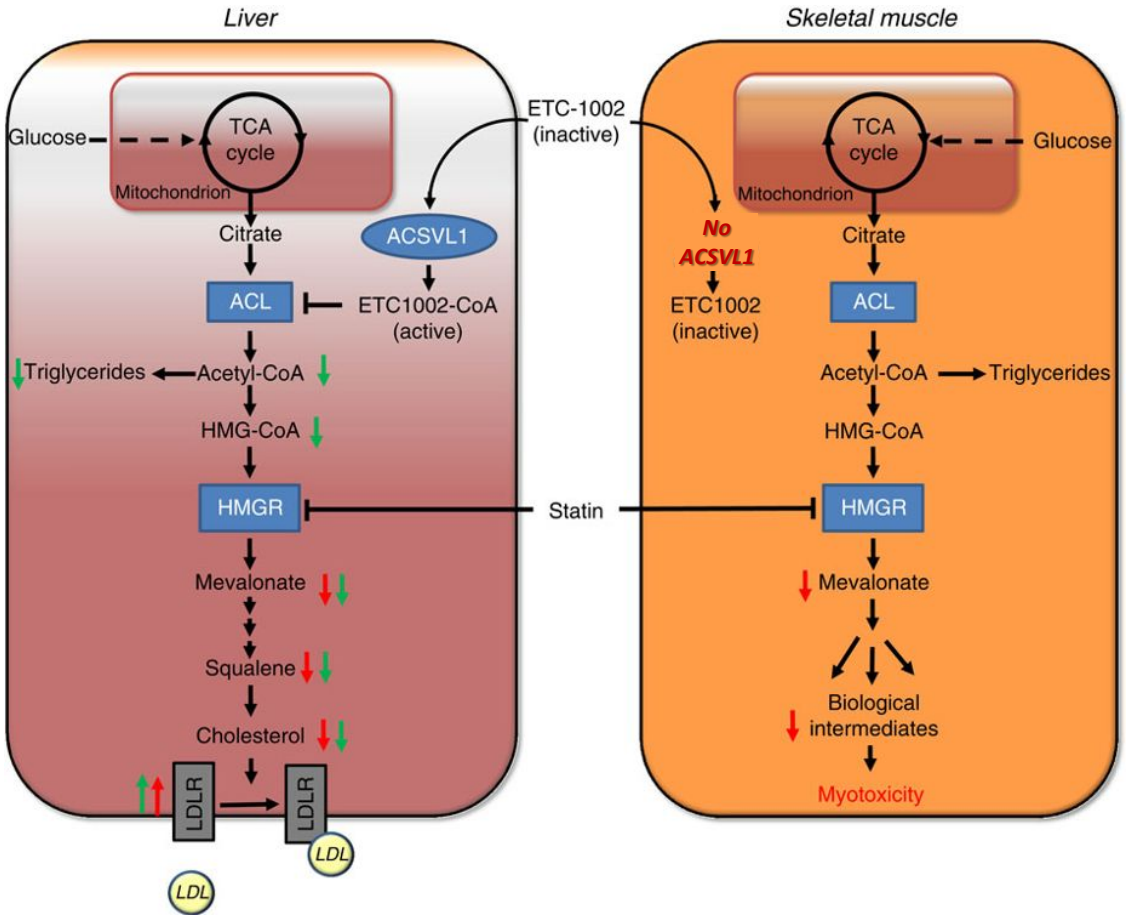
✓ *Il futuro della terapia di riduzione di LDL-C*

- ❑ ***Bempedoic acid***
- ❑ ***PCSK9 sirans***

ATP-citrate lyase (ACLY) is an enzyme possessing the unique feature to be positioned at the intersection of nutrient catabolism, cholesterol and fatty acid biosynthesis, thus connecting glucose metabolism to lipogenesis

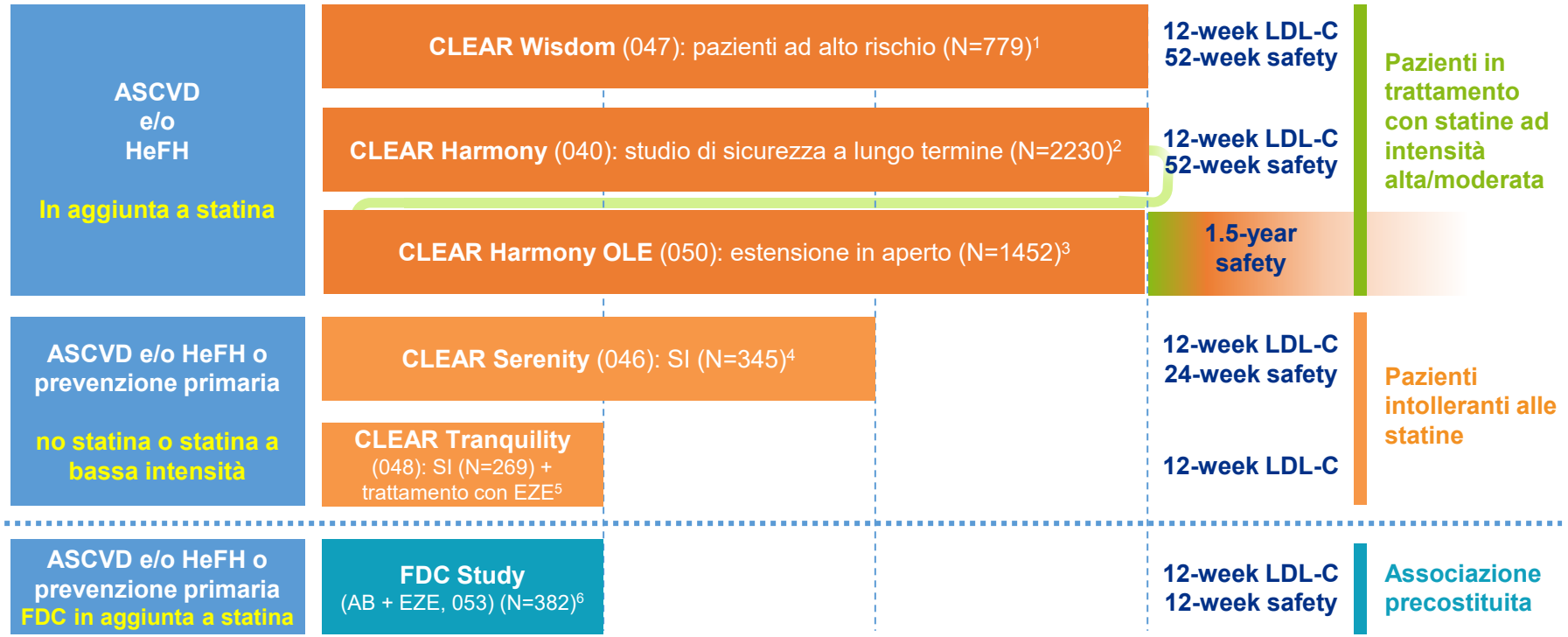


L’Acido Bempedoico non è attivato nel muscolo scheletrico



Pinkosky S et al. *Nat Commun*. 2016;7:13457.

L'Acido Bempedoico è stato valutato in un solido programma clinico che ha incluso un ampio spettro di pazienti

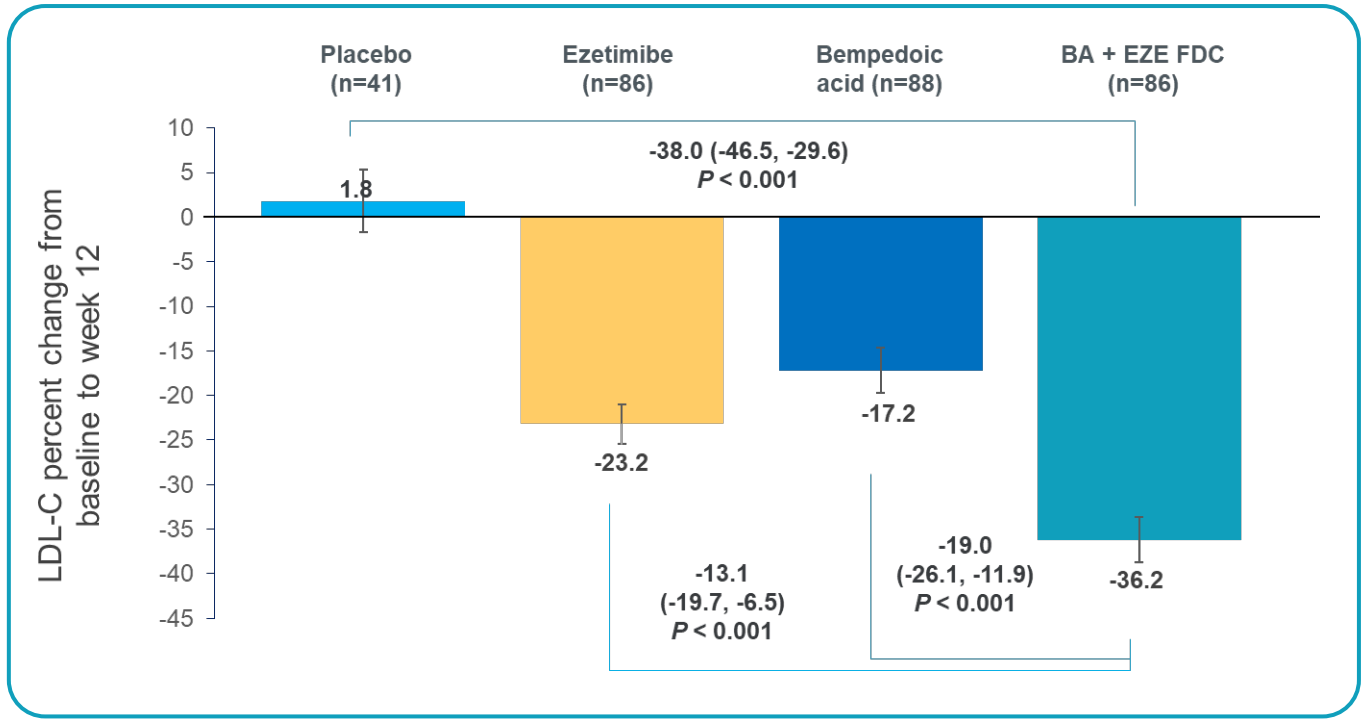


- ASCVD = malattia cardiovascolare su base aterosclerotica; AB = acido bempedoico; EZE = ezetimibe; HeFH = iperholesterolemia familare eterozigote; LDL-C Colesterolo LDL; OLE = open-label extension; SI = statino-intolleranti

- **1**.Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585; **2.** Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; **3.** ClinicalTrials.gov identifier NCT03067441; **4.** Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662; **5.** Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-2036. **6.** Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Acido Bempedoico + Ezetimibe fixed dose combination-FDC

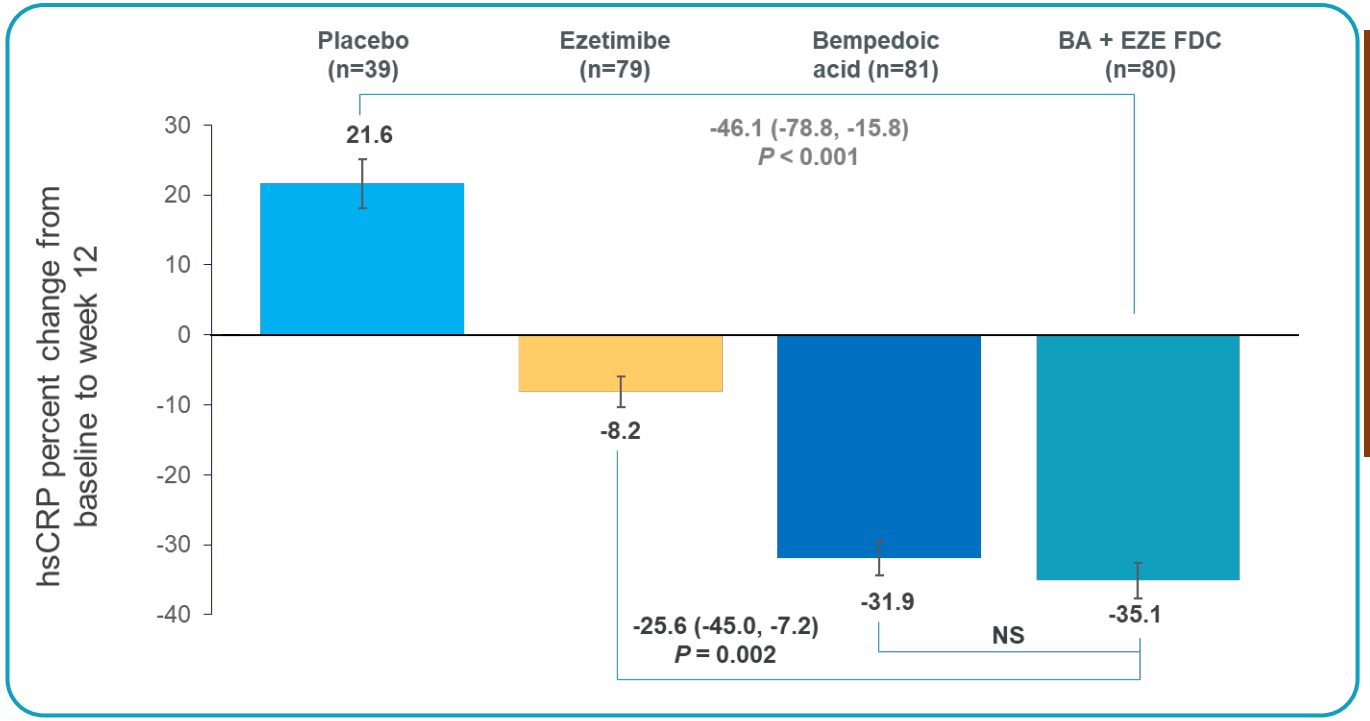
Studio FDC



Riduzione di LDL-C del 38%

Acido Bempedoico + Ezetimibe FDC

Studio FDC: l'acido bempedoico riduce hsCRP sia da solo che in associazione fissa con ezetimibe



L'acido bempedoico riduce hsCRP nei pazienti con ipercolesterolemia, indipendentemente dalla presenza o dall'intensità di una terapia statinica sottostante.

- Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.
- Erik S. G. Stroes, Presented at the American College of Cardiology/World Congress of Cardiology , Chicago, March 28 2020

Post hoc population

BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-Reactive Protein; NS, non-significant.

Un’analisi combinata di sicurezza condotta su più di 3.600 pazienti ha confermato che l’acido bempedoico è ben tollerato

Eventi avversi durante il trattamento	Acido Bempedoico N=2424, % (n)	Placebo N=1197, % (n)	Eventi avversi di speciale interesse
Debolezza muscolare	0.5 (13)	0.6 (7)	0.82
Nuova insorgenza di diabete/iperglicemia	4.0 (96)	5.6 (67)	0.03
Aumento di acido urico nel sangue	2.1 (51)	0.5 (6)	< 0.001
Iperuricemia	1.7 (40)	0.6 (7)	0.007
Gotta	1.4 (33)	0.4 (5)	0.008
Aumento di creatinina nel sangue	0.8 (19)	0.3 (4)	0.12
Diminuzione della velocità di filtrazione glomerulare	0.7 (16)	<0.1 (1)	0.02
Aumento degli enzimi epatici	2.8 (67)	1.3 (15)	0.004
> 3 volte rispetto ai limiti superiori di riferimento	0.7 (18)	0.3 (3)	0.10
> 5 volte rispetto ai limiti superiori di riferimento	0.2 (6)	0.2 (2)	> 0.99
Disordini neurocognitivi	0.7 (16)	0.8 (9)	0.83

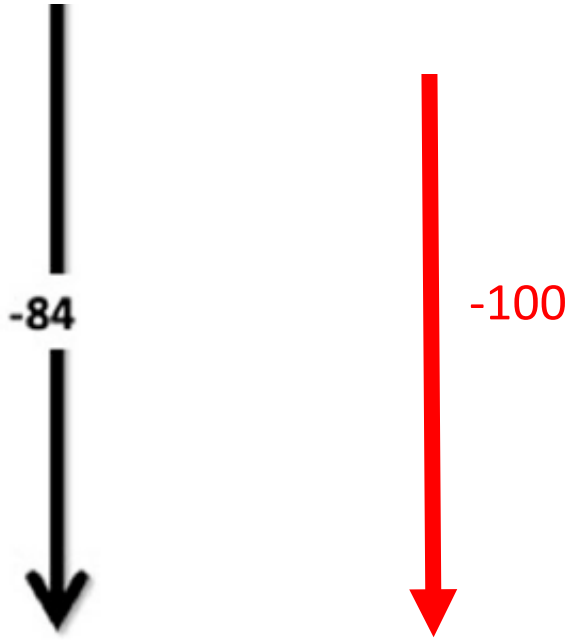
- L’incidenza di mialgia e debolezza muscolare è risultata simile tra i gruppi di trattamento anche in pazienti con sottostante terapia statinica ad elevata intensità.
- Modeste variazioni dei livelli ematici di creatinina e acido urico si sono verificate precocemente, sono risultate stabili nel tempo e reversibili dopo l’interruzione del farmaco.
- Episodi di gotta sono stati riportati più frequentemente nel gruppo di pazienti trattati con l’acido bempedoico rispetto al placebo, ma l’incidenza è stata comunque bassa in entrambi i gruppi di trattamento e gli eventi si sono verificati soprattutto in pazienti con una precedente diagnosi di gotta.

Banach M. et al., JAMA Cardiology, published online July 1, 2020.

Il raggiungimento degli obiettivi terapeutici nell' era degli inibitori di PCSK9 E DI ACIDO BEMPEDOICO

Statina ad alta intensità+
Ezetimibe+
PCSK9i

Statina ad alta intensità+
Ezetimibe+
PCSK9i+
Acido Bempedoico



Aspettando Clear Outcomes 2022

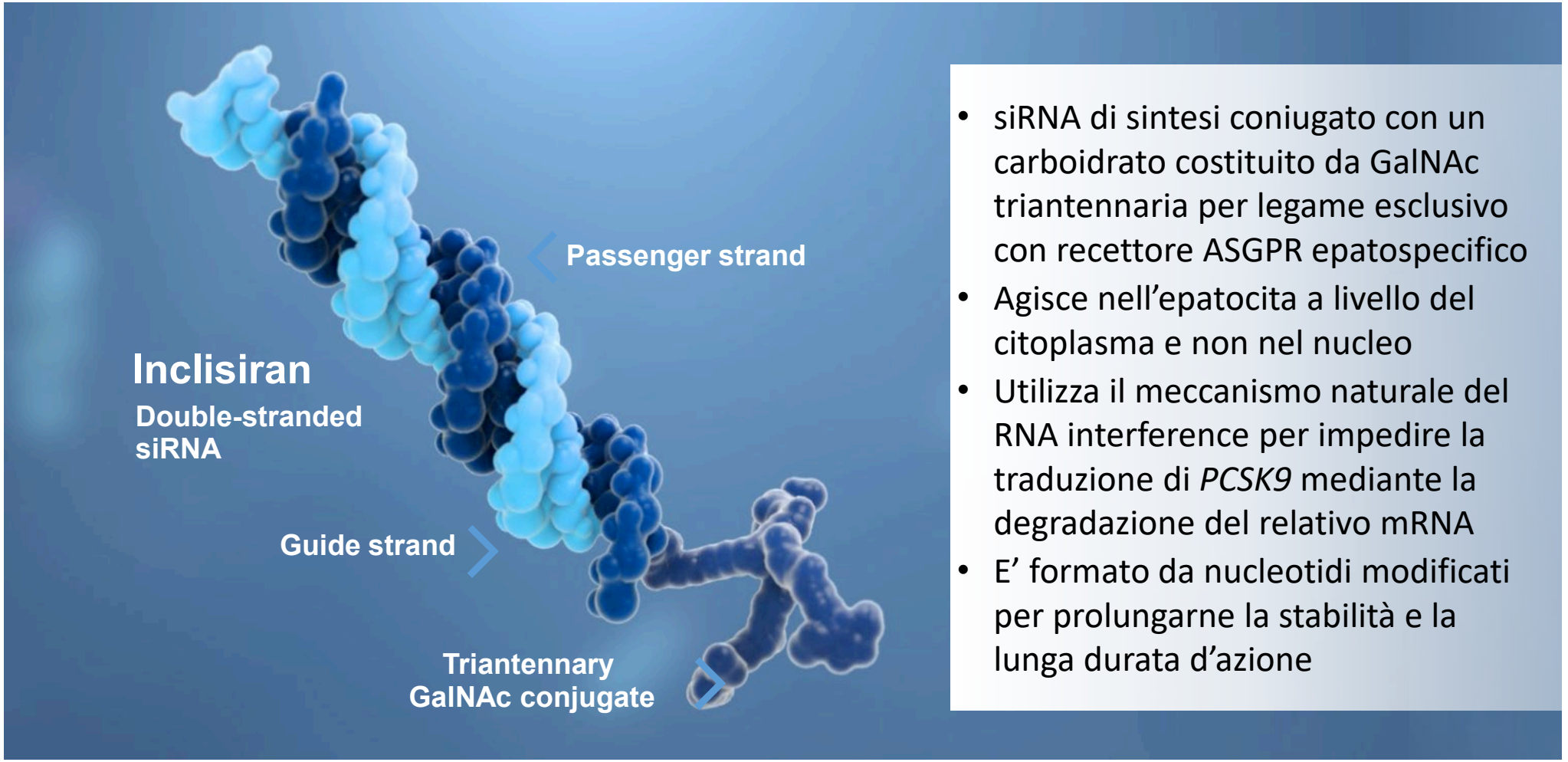
Current Cardiology Reports 2020

Agenda

✓ *Il futuro della terapia di riduzione di LDL-C*

- ❑ ***Bempedoic acid***
- ❑ ***PCSK9 sirans***

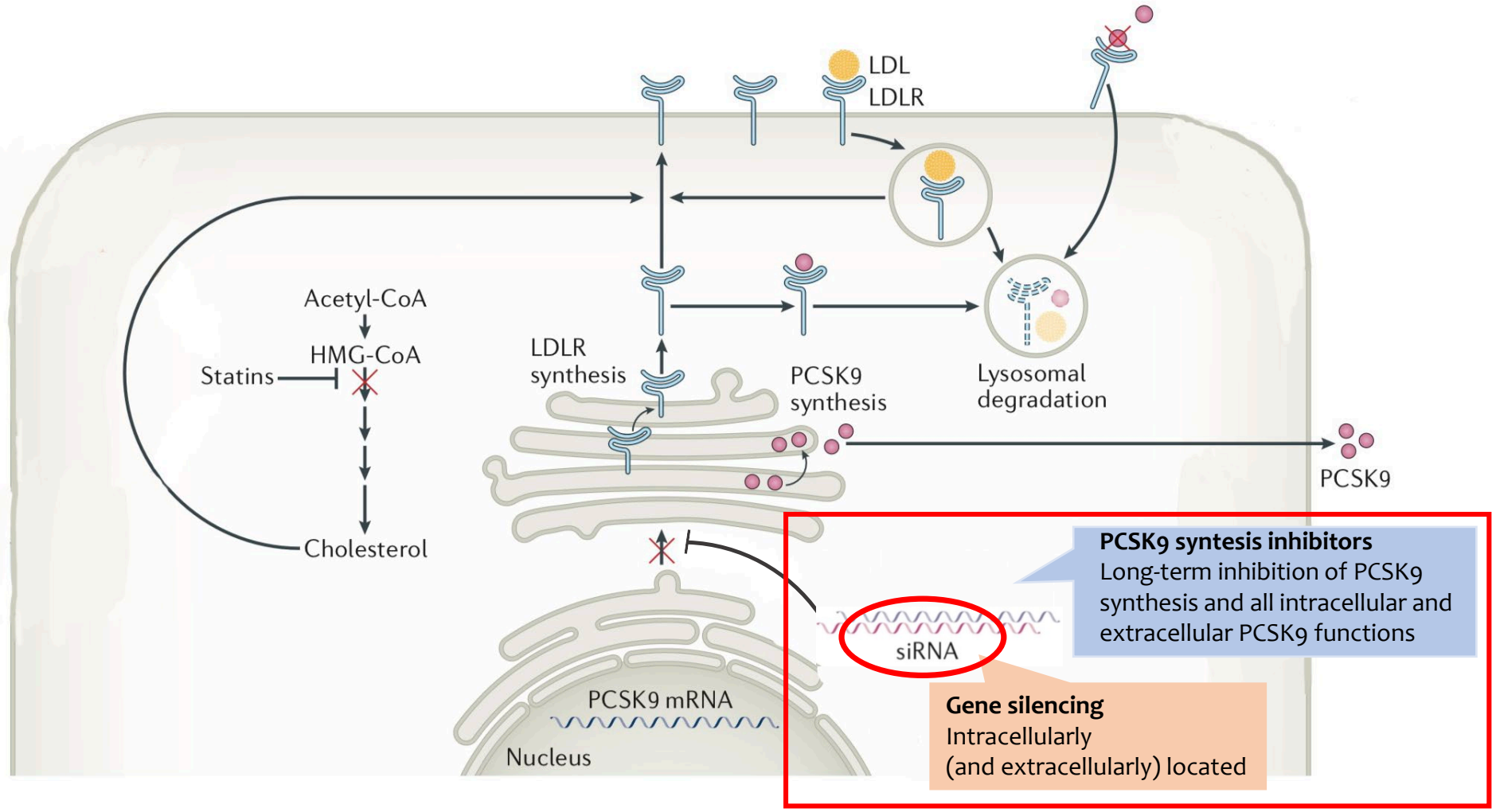
Inclisiran è un siRNA che mima il processo fisiologico di RNA interference. Aumenta l'espressione dei recettori LDL sulla superficie dell'epatocita grazie al blocco della produzione di PCSK9.



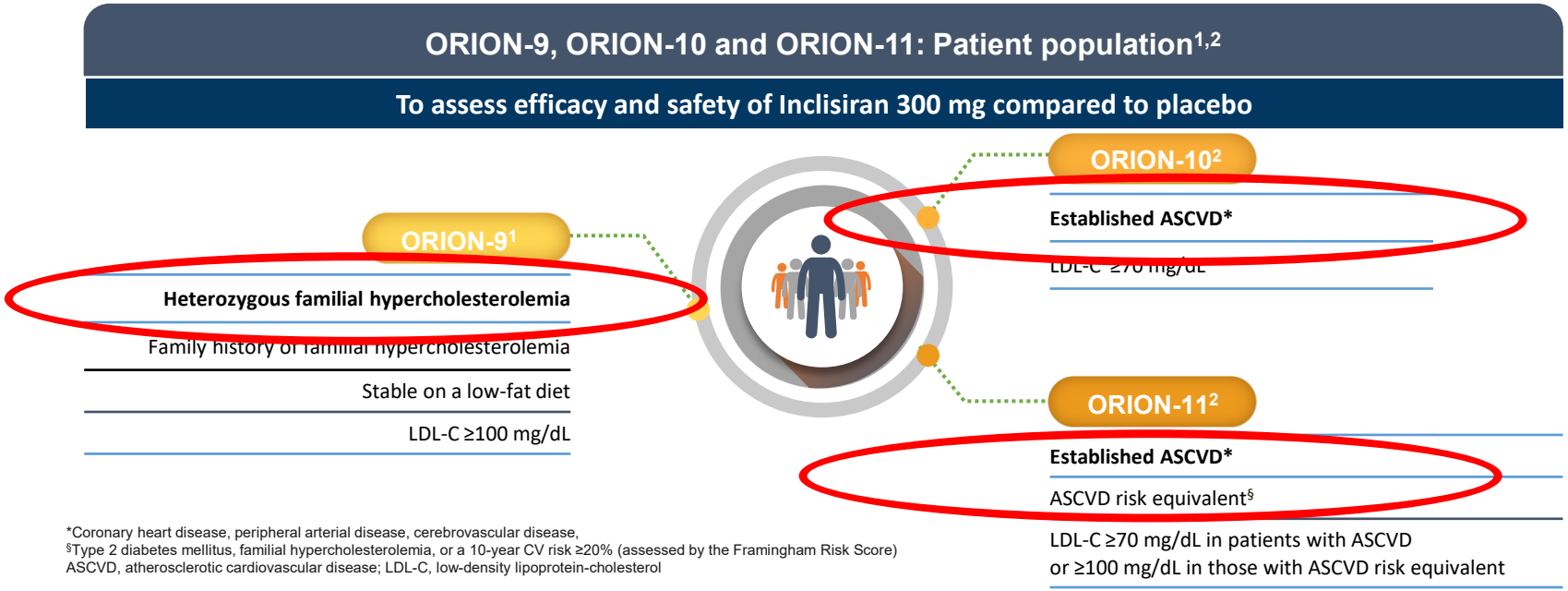
- siRNA di sintesi coniugato con un carboidrato costituito da GalNAc triantennaria per legame esclusivo con recettore ASGPR epatospecifico
- Agisce nell'epatocita a livello del citoplasma e non nel nucleo
- Utilizza il meccanismo naturale del RNA interference per impedire la traduzione di *PCSK9* mediante la degradazione del relativo mRNA
- E' formato da nucleotidi modificati per prolungarne la stabilità e la lunga durata d'azione

Khvorova A, et al. *N Engl J Med*. 2017;376:4-7.
Fitzgerald K, et al. *N Engl J Med*. 2017;376:41-51.
Wang N, et al. Circ Res. 2017;120:1063-1065; 2. Fitzgerald K, et al. N Engl J Med. 2017;376:41-51

Approcci terapeutici per ridurre LDL-C attraverso il recettore per le LDL: siRNA



Caratteristiche studi di fase 3 ORION 9-10-11: 18 mesi durata, doppio-cieco, randomizzati, vs placebo



Common key inclusion criteria:

≥18 years of age; fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening; had received statin treatment at the maximally tolerated dose or demonstrated documented intolerance. Ezetimibe therapy was allowed.

Common key exclusion criteria:

Prior or planned use of a PCSK9 mAb; MACE within 3 months of randomization; had prior/planned use of other investigational drugs; NYHA class IV heart failure or LVEF <25%; uncontrolled severe hypertension; severe concomitant non CV disease; fasting TG ≥4.52 mmol/L (400 mg/dL).

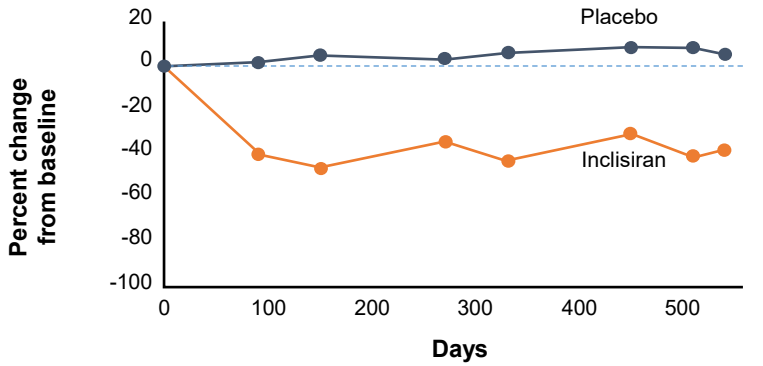
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530. **2.** Raal FJ, et al. [supplementary appendix]. *N Engl J Med.* 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. **3.** Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519. **4.** Ray KK, et al. [supplementary appendix]. *N Engl J Med.* doi: 10.1056/NEJMoa1912387.

Studi ORION 9-10-11: endpoint primario
Inclisiran fornisce un'efficace e prolungata riduzione delle LDL-C per 18 mesi

Variazione percentuale LDL nel tempo (over time)

ORION-9[1]

Change in LDL cholesterol



No. of patients

Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

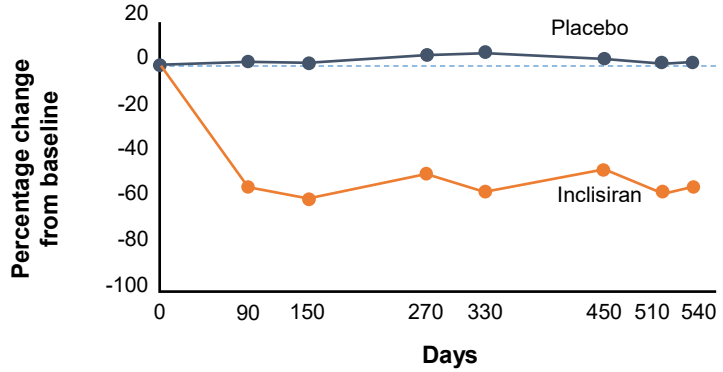
Used with permission. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.

Between group difference

-47.9% (*P*<0.001)

ORION-10[2]

Percentage change in LDL cholesterol



No. of patients

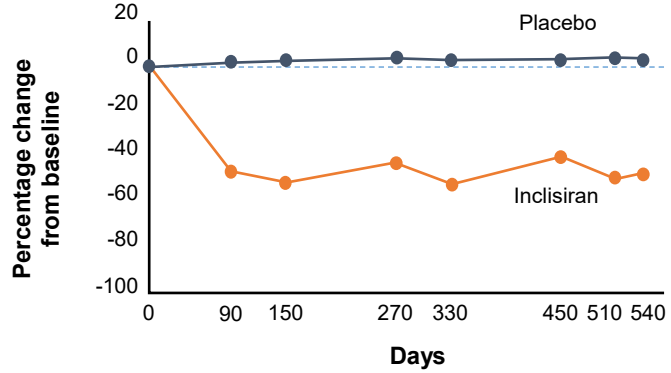
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

Used with permission. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

-52.3% (*P*<0.001)

ORION-11[2]

Percentage change in LDL cholesterol



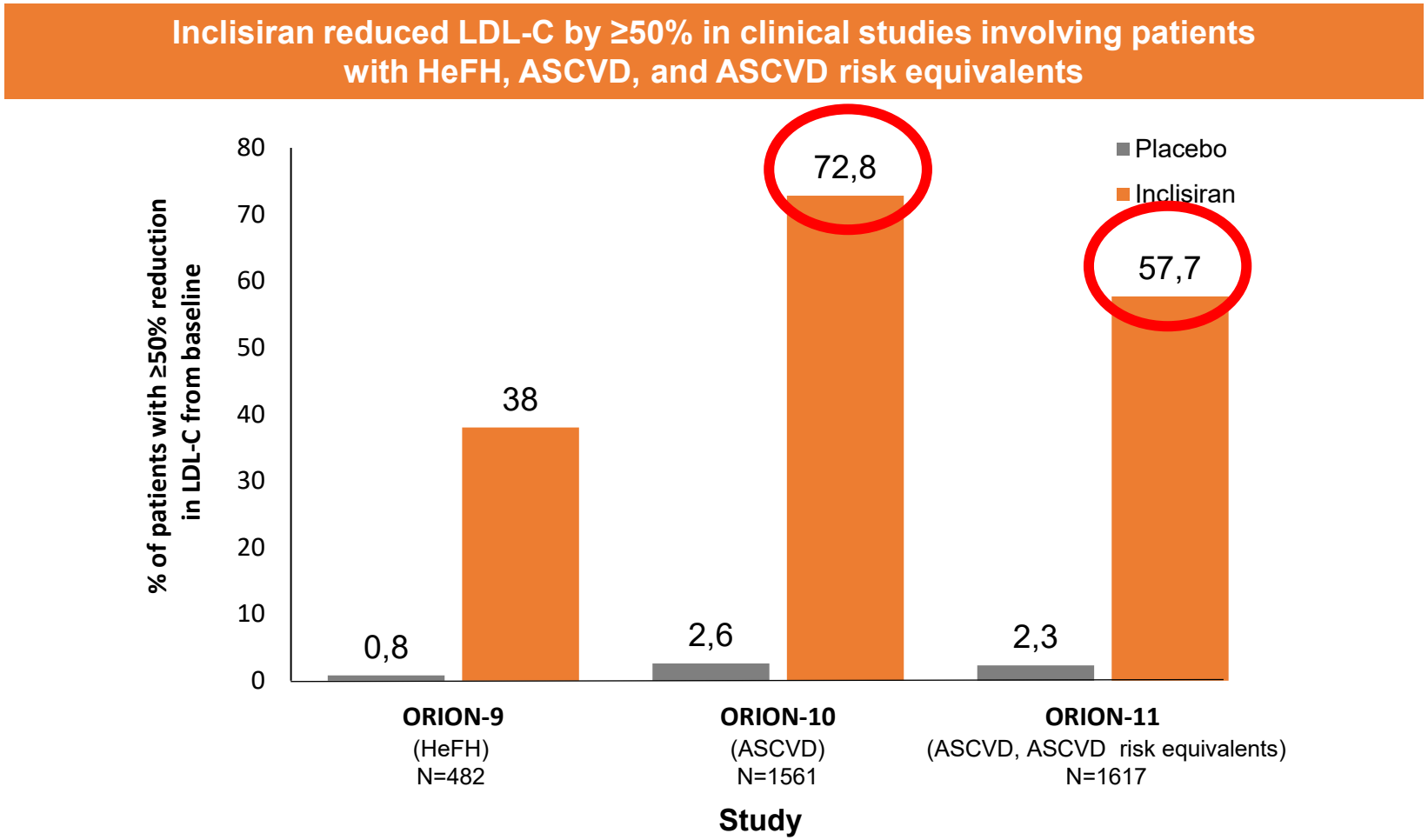
No. of patients

Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

-49.9% (*P*<0.001)

1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.
2. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Studi ORION 9-10-11
Endpoint secondario: Percentuale di pazienti con riduzione ≥50% del colesterolo LDL rispetto al basale al giorno 510



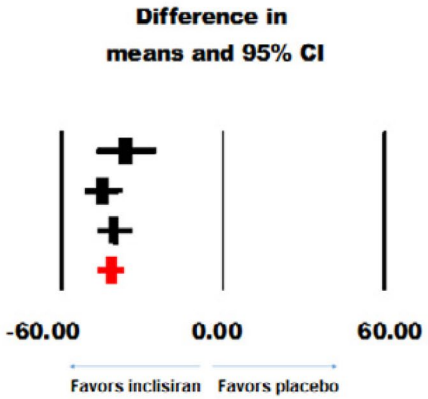
1. Raal FJ, et al. *N Engl J Med*. 2020;382(16):1520-1530.
2. Ray KK, et al. [supplementary appendix*] N Engl J Med*. doi: 10.1056/NEJMoa1912387.

Metanalisi studi Orion 9-10-11
Riduzione delle LDL-C e Major adverse Cardiovascular Event (MACE)

A: LDL cholestrol Level

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
ORION-9	-47.90	-53.39	-42.41	0.000
ORION-10	-52.30	-55.75	-48.85	0.000
ORION-11	-49.90	-53.15	-46.65	0.000
Total	-50.53	-52.73	-48.34	0.000

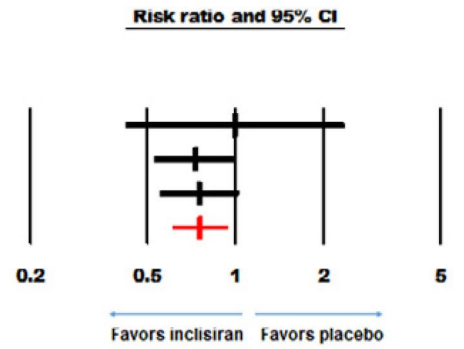
Heterogeneity ($Q = 2.0, P = 0.36; I^2 = 2.0$)



B: MACE

Study name	Statistics for each study			
	Risk ratio	Lower limit	Upper limit	p-Value
ORION-9	1.00	0.42	2.35	0.992
ORION-10	0.73	0.53	1.01	0.058
ORION-11	0.75	0.55	1.03	0.075
Total	0.76	0.61	0.94	0.012

Heterogeneity ($Q = 0.4, P = 0.80; I^2 = 0.0$)



Khan SA et al; AM.J Cardiol; 134:69-73

Profilo di safety. Analisi pooled studi ORION 9-10-11 (2)

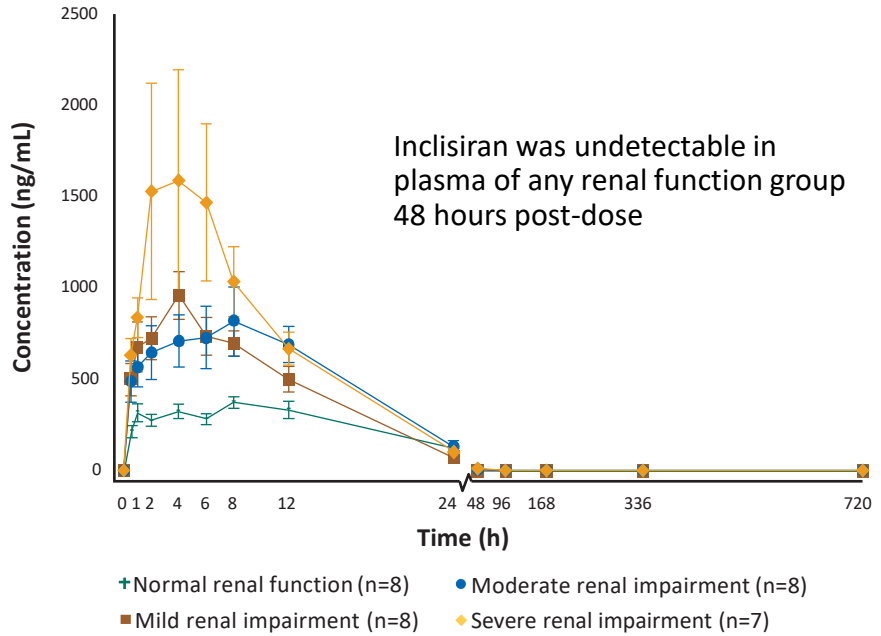
	Inclisiran (n = 1,833)	Placebo (n = 1,822)	Risk Ratio (95% CI)
TEAE			
≥1 TEAE	1,430 (78.0)	1,409 (77.3)	1.01 (0.97-1.04)
≥1 TEAE leading to drug discontinuation	45 (2.5)	35 (1.9)	1.28 (0.83-1.98)
Serious TEAE			
≥1 serious TEAE	374 (20.4)	419 (23.0)	0.89 (0.78-1.00)
Death	27 (1.5)	27 (1.5)	0.99 (0.59-1.69)
New, worsening, or recurrent cancer	44 (2.4)	49 (2.7)	0.89 (0.60-1.33)
Clinically relevant TEAE at the injection site†			
Any reaction	91 (5.0)	12 (0.7)	7.54 (4.14-13.71)
Mild	67 (3.7)	11 (0.6)	6.05 (3.21-11.42)
Moderate	24 (1.3)	1 (0.1)	23.86 (3.23-176.15)
Severe	0 (0.0)	0 (0.0)	–
Persistent	0 (0.0)	0 (0.0)	–
Liver function			
Alanine aminotransferase >3× ULN	9 (0.5)	7 (0.4)	1.28 (0.48-3.42)
Aspartate aminotransferase >3× ULN	8 (0.4)	10 (0.5)	0.80 (0.31-2.01)
Alkaline phosphatase >2× ULN	8 (0.4)	5 (0.3)	1.59 (0.52-4.85)
Bilirubin >2× ULN	14 (0.8)	14 (0.8)	0.99 (0.48-2.08)
Kidney function: creatinine >2 mg/dl	36 (2.0)	42 (2.3)	0.85 (0.55-1.32)
Muscle: creatine kinase >5× ULN	24 (1.3)	22 (1.2)	1.08 (0.61-1.93)
Hematology: platelet count <75 × 10^9/l	1 (0.1)	2 (0.1)	0.50 (0.05-5.48)

ORION-7 studio nella disfunzione renale.
Non sono necessari aggiustamenti di dose in pazienti con problematiche renali.

Phase 1 PK/PD single-dose renal impairment study in patients with normal renal function or mild, moderate, or severe renal impairment* treated with a single 300 mg dose of inclisiran† (N=31)

- Results
  - The $AUC_{0\text{-inf}}$ for inclisiran increased with greater degrees of renal impairment
  - Maximum plasma concentration was increased with greater degrees of renal impairment, with a >4-fold increase in severe renal impairment
  - The safety profile of inclisiran was unaffected by renal impairment

Mean plasma concentration of inclisiran



*Normal renal function: estimated CrCl level, >90 mL/min; mild renal impairment: CrCl level, 60-89 mL/min; moderate renal impairment: CrCl level, 30-59 mL/min; severe renal impairment: CrCl level, 15-29 mL/min.
†300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.

Wright RS, et al. *Mayo Clin Proc*. 2020;95(1):77-89.

Nessuna limitazione per livelli di GFR, per insufficenza epatica lieve e moderata

farmacocinetica

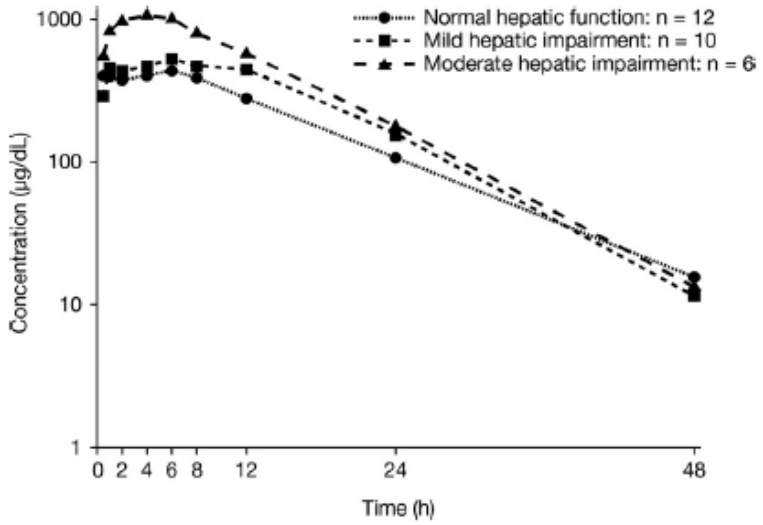


Fig. 1. Mean plasma concentration of inclisiran following a single subcutaneous injection of inclisiran 300 mg to participants with normal hepatic function and patients with hepatic impairment. h, hours.

farmacodinamica

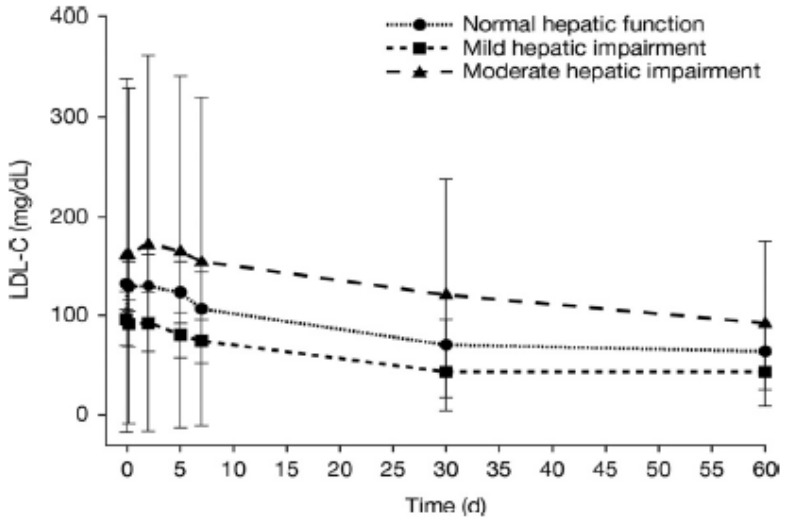


Fig. 2. Mean (standard deviation) LDL-C values over time according to hepatic function (pharmacodynamic population). d, days; LDL-C, low-density lipoprotein cholesterol.

Kallend et al, of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2022.01.001

Studi in corso per valutare i risultati a lungo termine e gli outcome cardiovascolari

Extension trials*

ORION-3[1]

Patients ≥18 years of age
Completion of ORION-1
N=490

ORION-8[2]

Patients ≥18 years of age
Completion of ORION-9, -10, -11, or -5
N=2991

Cardiovascular outcomes trial*

ORION-4[3]

Patients ≥55 years with ASCVD (prior MI, prior stroke or PAD)
N=15,000*

VICTORION-2 PREVENT[4]

Patients ≥40 years with ASCVD
15000 participants

*Please see most recent information available at clinicaltrials.gov for estimated primary completion date.

1. NCT03060577. https://www.clinicaltrials.gov/ct2/show/NCT03060577?term=ORION-3&draw=2&rank=1. Accessed October 20, 2020.
2. NCT03814187. https://clinicaltrials.gov/ct2/show/NCT03814187. Accessed October 20, 2020.
3. NCT03705234. https://www.clinicaltrials.gov/ct2/show/NCT03705234?term=ORION-4&draw=2&rank=1 Accessed October 20, 2020
4. ClinicalTrials.gov Identifier: NCT05030428

Agenda

- ✓ *Il futuro della terapia di riduzione dei TG*

- ❑ ***Icosapentil ethyl***

MILD-TO-MODERATE HTG

names	Tg range	lipoproteins	lipids	mechanism	clinical features	associate condition /stressors	prevalence	disease risk
Primary HTG Type IV Mild-to-Moderate HTG	177– 887 mg/dl	VLDL IDL	↑Tg ↑Col	↕ PR ↕ FCR	Generally asymptomatic	insulin resistance; obesity;diabetes; HTN; uric acid; alchool;drugs	1:20	CVD

EAS

The NEW ENGLAND JOURNAL of MEDICINE

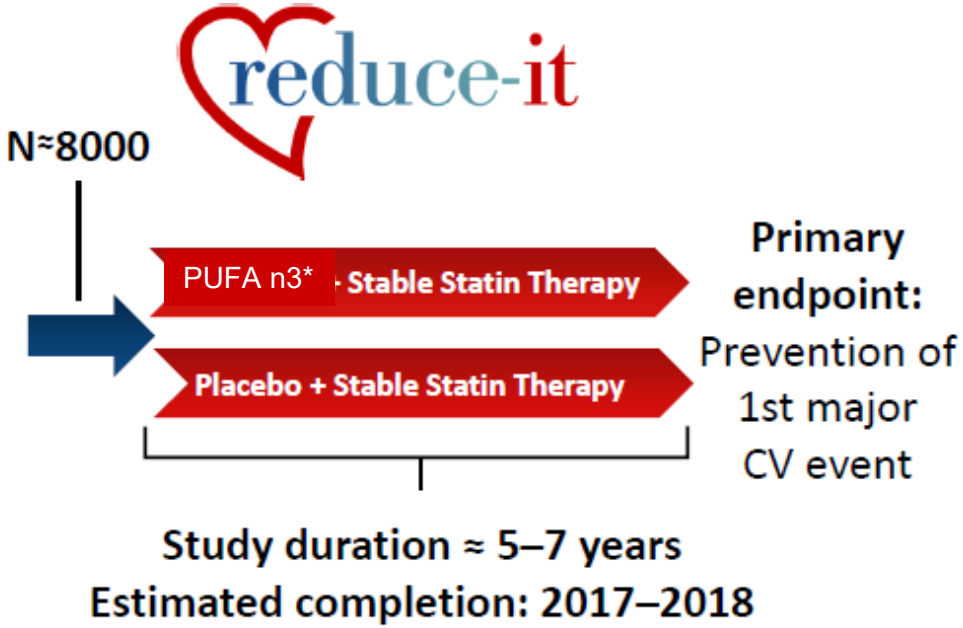
ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Reduction of CV Events with Icosapent Ethyl-Intervention Trial

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
  - TG ≥200 to <500 mg/dL



- Randomized, double-blind, parallel-group design
- International trial; first patient enrolled: November 2011
- Other outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, etc.
- Pre-defined subgroup analyses such as patients with diabetes
- Interim analysis planned for 967th event: Sept–Oct 2016; study expected to continue as planned

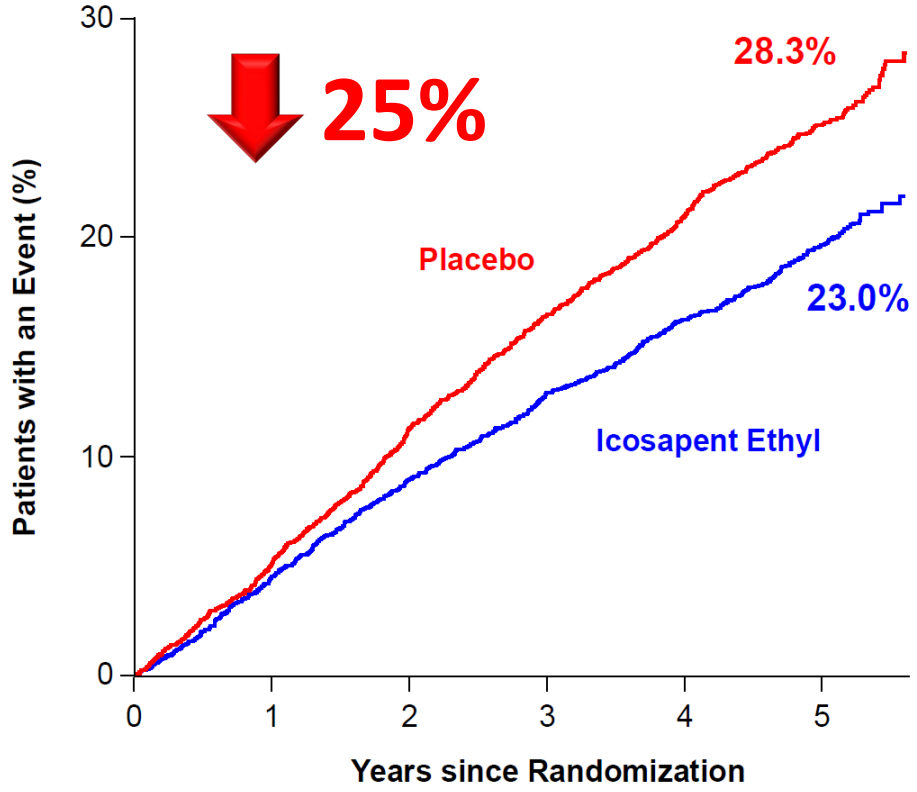
Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

***96% pure ethyl ester of EPA**
2 X 2gr/day

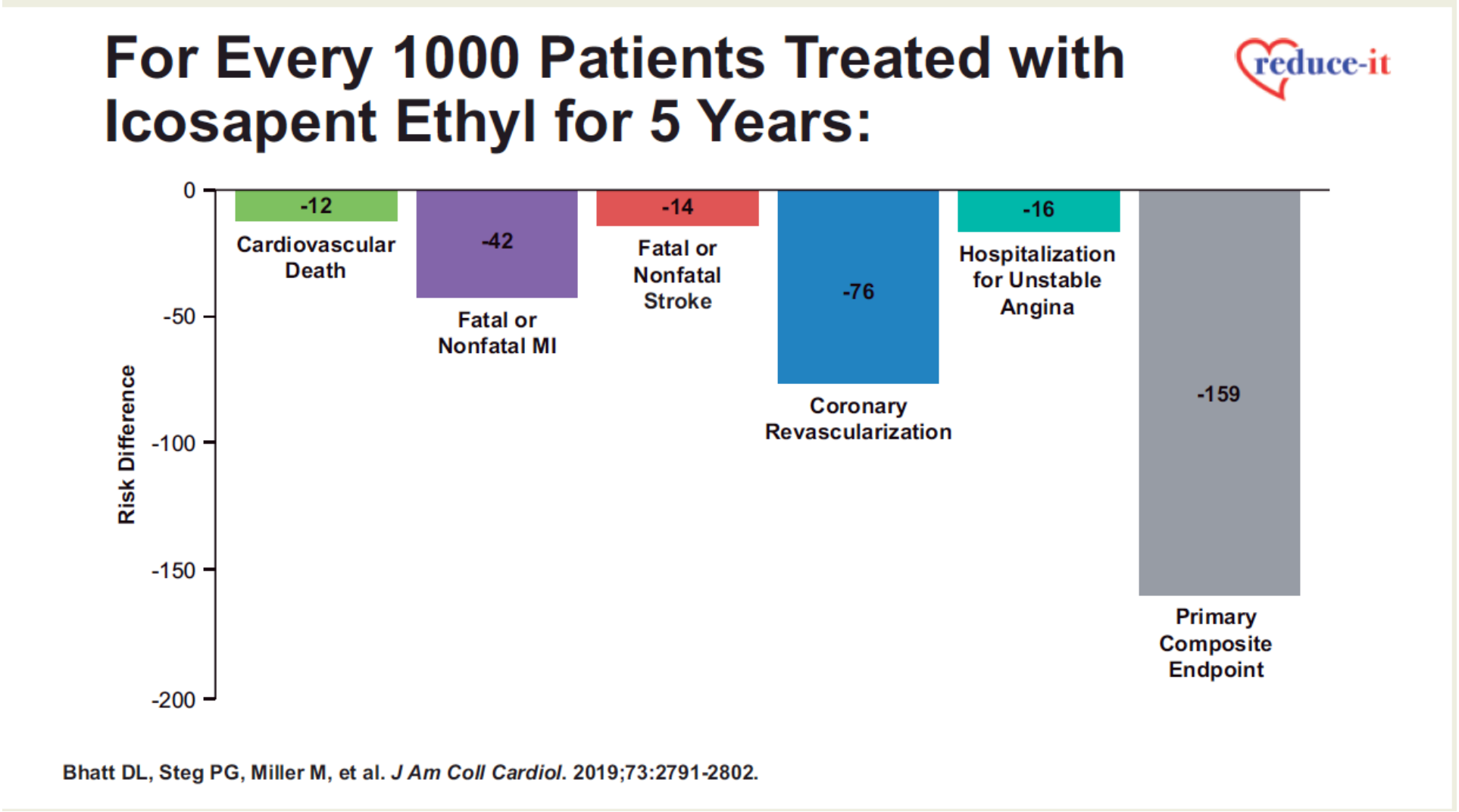
Bhatt DL, Ballantyne CM et al. Clinical Cardiology. 2017;**40:**138–148.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Number of ischaemic events prevented by icosapent ethyl for every 1000 patients treated for 5 years in REDUCE-IT



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

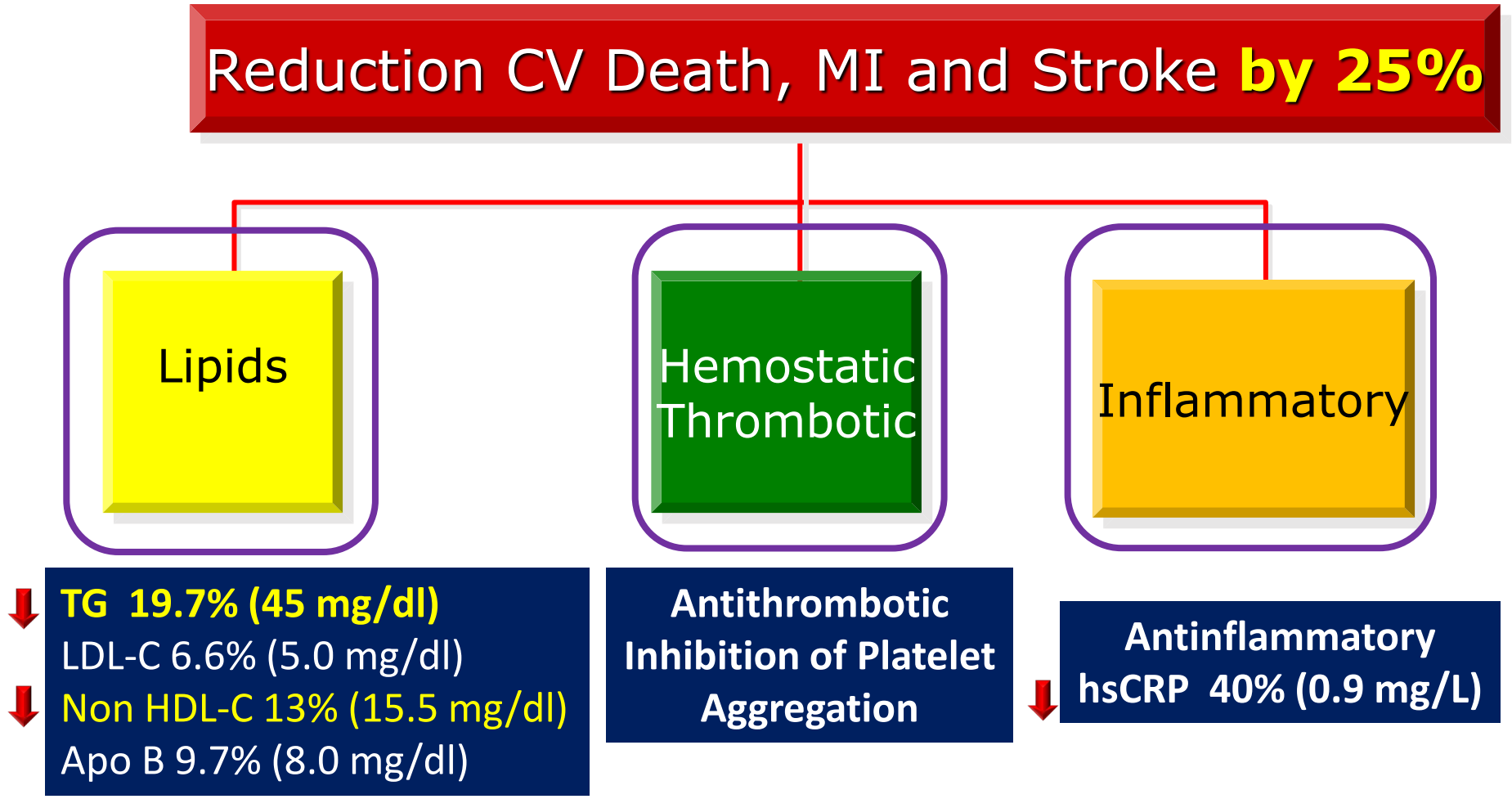
Effects on Biomarkers from Baseline to Year 1

		Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
	Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
2.5	Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
3.1	Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
1.8	LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
	HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
	Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
	hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
	Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
	EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

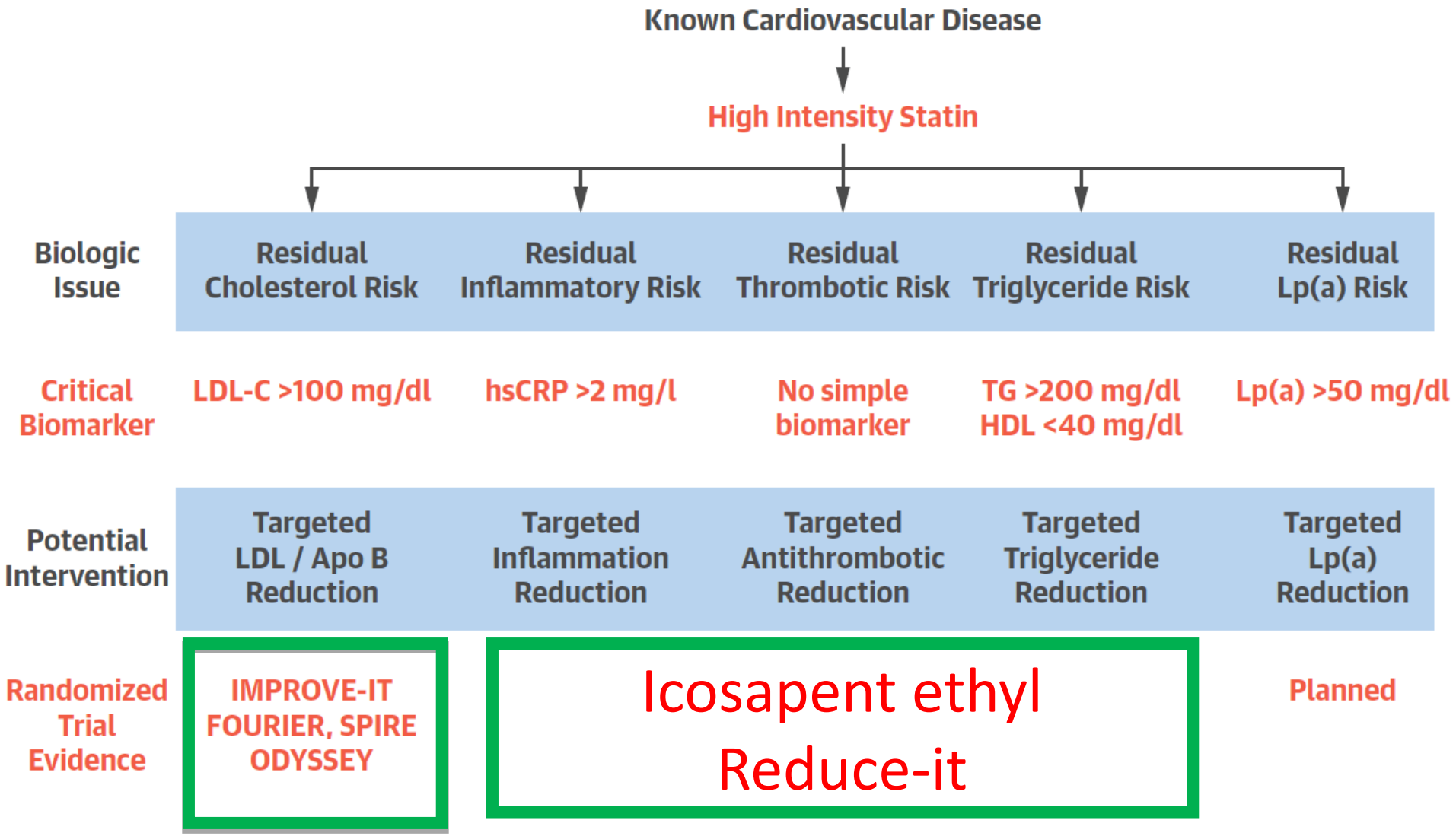
*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

WHAT'S BEHIND THE CV BENEFITS in REDUCE-IT?



Residual Risk and a Movement Toward Personalized Medicine



JACC 2018

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

ESC/EAS GUIDELINES

RECOMMENDATIONS FOR DRUG TREATMENT OF PATIENTS WITH HYPERTRIGLYCERIDAEMIA

High-Risk Patients

N3 PUFA EPA +STATIN

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

- On statin
- High TG

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.

Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.