

I farmaci ipocolesterolemizzanti nel diabete

Relatore

Dott. Roberto Scicali

Conflitto di interessi

Il dott. Scicali Roberto dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Agenda

- Dislipidemia diabetica
- Efficacia delle terapia ipolipemizzanti convenzionali nel paziente diabetico
- Efficacia degli Inibitori di PCSK9 nel paziente diabetico

Agenda

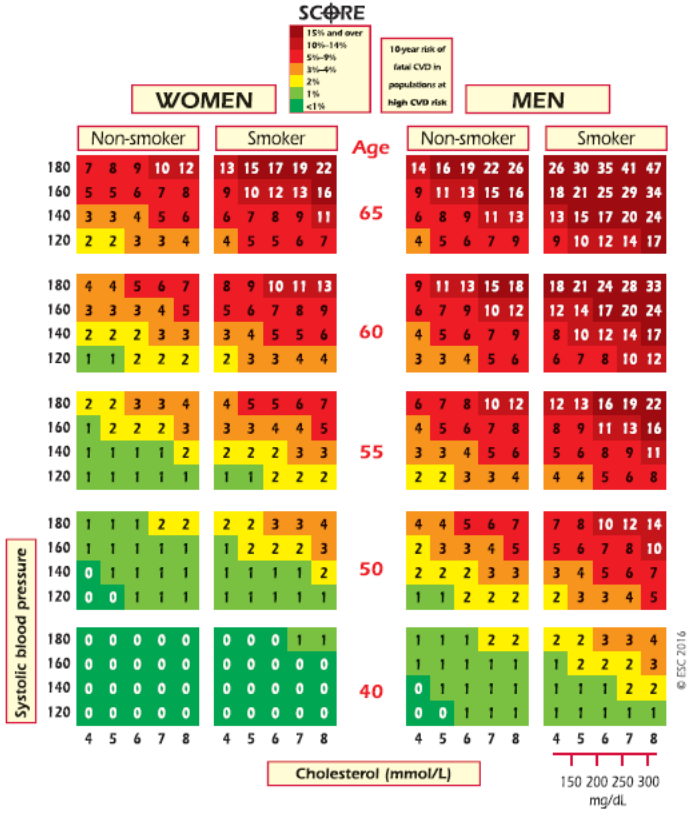
- Dislipidemia diabetica
- Efficacia delle terapia ipolipemizzanti convenzionali nel paziente diabetico
- Efficacia degli Inibitori di PCSK9 nel paziente diabetico

European Heart Journal (2003) 24, 987–1003

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project



Score 5-9% →

High-risk

Subjects with:

- Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.
- Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).
- Moderate CKD (GFR 30–59 mL/min/1.73 m²).
- A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

Score ≥ 10% →

Very high-risk

Subjects with any of the following:

- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.

I farmaci ipocolesterolemizzanti nel diabete

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

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)

DT2 + complicanze → LDL < 70 mg/dL

DT2 → LDL < 100 mg/dL

Table 4 Risk categories

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m²). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.

Venerdì 30 novembre 2018

Ore 11.30-13.30 • Sesta sessione

IL PROGRESSO DIABETOLOGICO

– Moderatori –

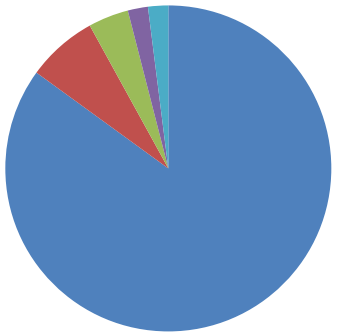
Antonino Belfiore (Catania) • Gabriele Lettina (Messina)

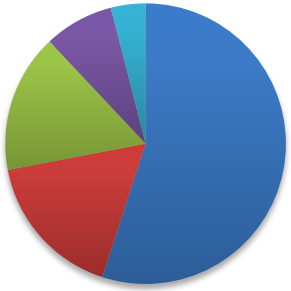
11.30 **I farmaci ipocolesterolemizzanti nel diabete**

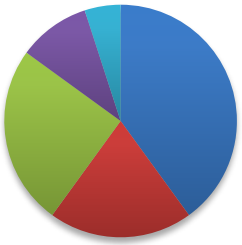
Roberto Scicali (Catania)

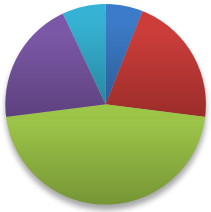


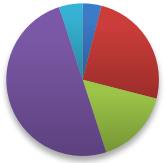
Chilomicroni - VLDL - IDL - LDL (Lpa) - HDL

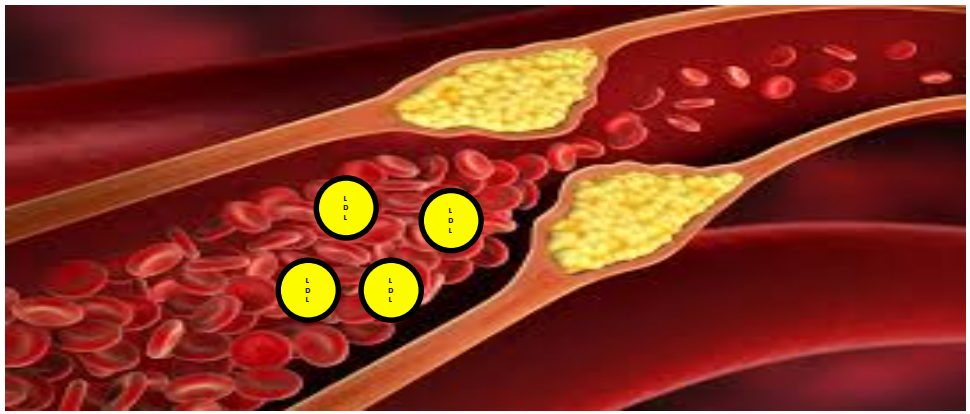












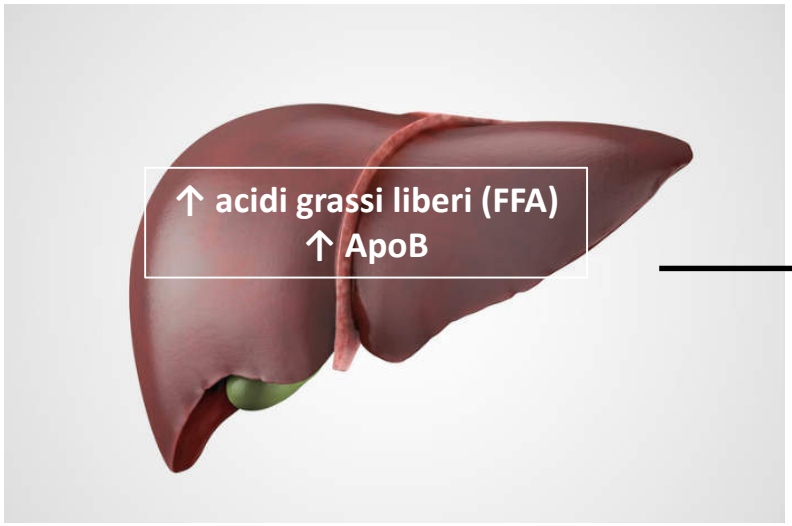
- Low-density lipoprotein subclass patterns and risk of myocardial infarction.
Austin MA *et al*, JAMA 1988

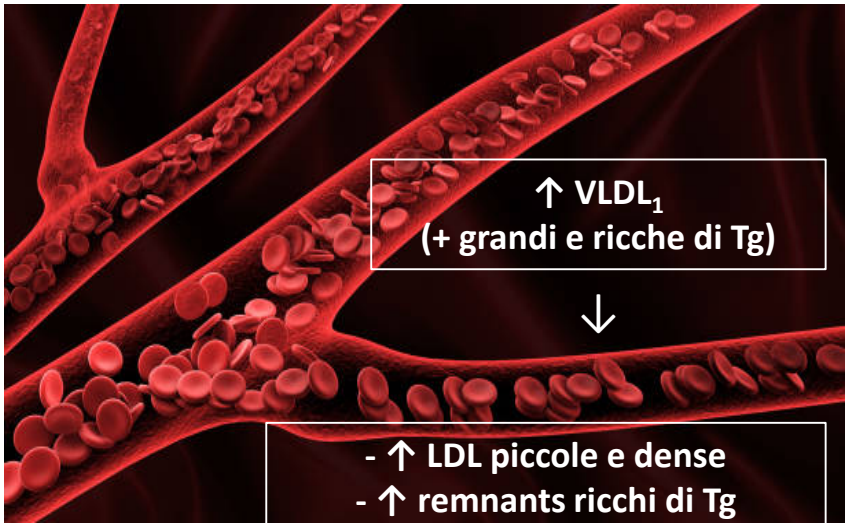
- Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women.
Gardner CD, Fortmann SP, Krauss RM, JAMA. 1996

Fisiopatologia della dislipidemia diabetica



Insulino-resistenza





Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes.
Vergès B. Atherosclerosis 2010.

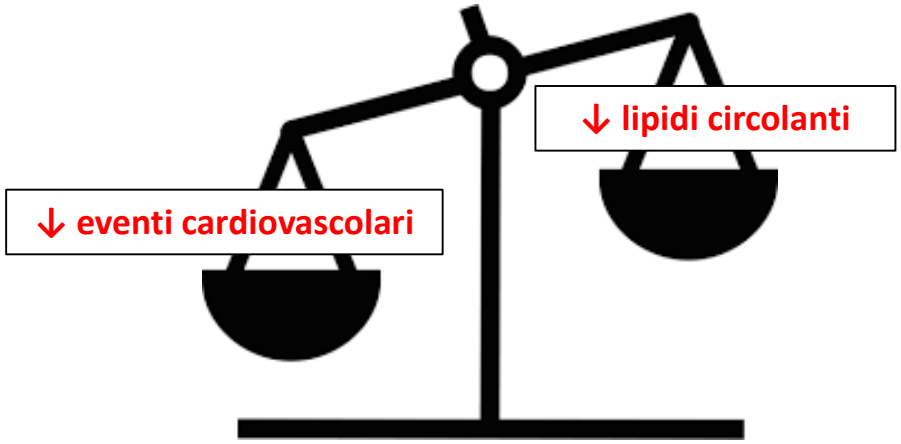
Agenda

- Dislipidemia diabetica

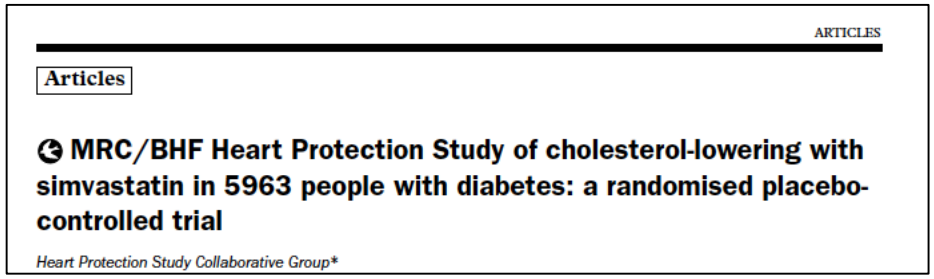
- Efficacia delle terapie ipolipemizzanti convenzionali nel paziente diabetico

- Efficacia degli Inibitori di PCSK9 nel paziente diabetico

Efficacia terapia ipolipemizzante



Statine

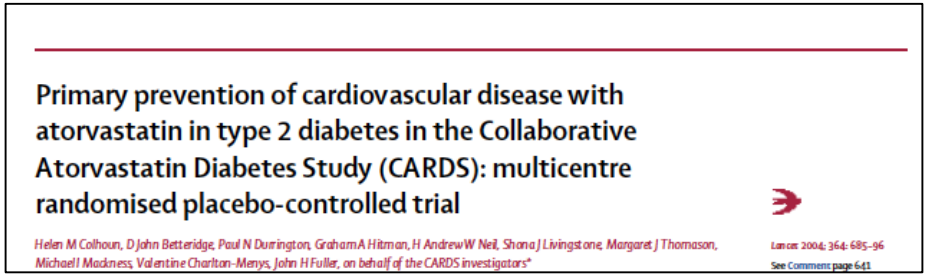


ARTICLES

Articles

MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial

*Heart Protection Study Collaborative Group**

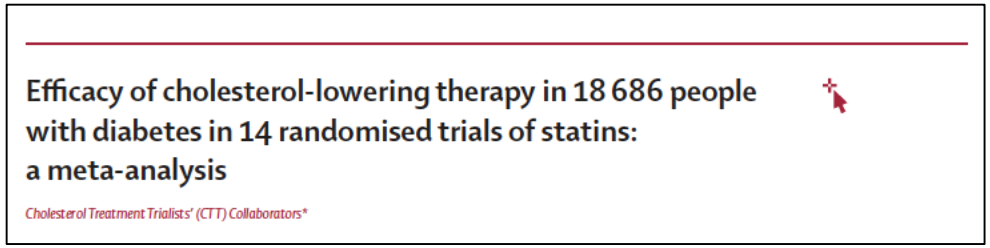


Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

*Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingstone, Margaret J Thomason, Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators**

Lancet 2004; 364: 685–96

See Comment page 641



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

*Cholesterol Treatment Trialists' (CTT) Collaborators**

	Statine → ↓ LDL 39 mg/dL
Mortalità per tutte le cause	↓ 9%
eventi coronarici fatali e non – rivascolarizzazione coronarica e ictus	↓ 21%

Statine

S86 **Diabetes Care** Volume 41, Supplement 1, January 2018



9. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

Diabetes Care 2018;41(Suppl. 1):S86–S104 | https://doi.org/10.2337/dc18-S009

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Table 9.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Ezetimibe

Circulation

ORIGINAL RESEARCH ARTICLE

Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus

Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

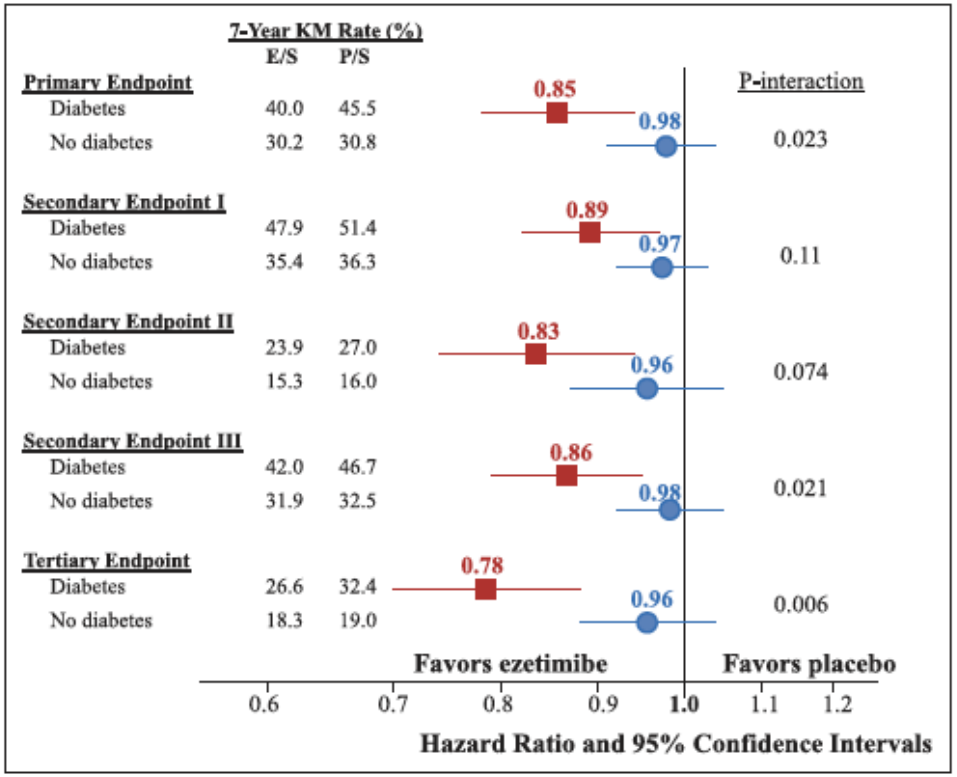


Figure 2. Composite efficacy outcomes stratified by treatment and diabetes mellitus status. Hazard ratios and 95% confidence intervals are shown for the comparison of ezetimibe/simvastatin (E/S) versus placebo/simvastatin (P/S) in patients with (red) and without (blue) diabetes mellitus. See text and the footnotes to Table 2 for definitions of the composite endpoints.

Sequestranti acidi biliari



Fibrati

OPEN ACCESS Freely available online PLOS ONE

Variants Identified in a GWAS Meta-Analysis for Blood Lipids Are Associated with the Lipid Response to Fenofibrate

Stella Aslibekyan[1*], Mark O. Goodarzi[3,4], Alexis C. Frazier-Wood[1,2], Xiaofei Yan[4], Marguerite R. Irvin[1], Eric Kim[4], Hemant K. Tiwari[2], Xiuqing Guo[4], Robert J. Straka[5], Kent D. Taylor[4], Michael Y. Tsai[6], Paul N. Hopkins[8], Stanley G. Korenman[9], Ingrid B. Borecki[7], Yii-Der I. Chen[4], Jose M. Ordovas[10,11,12], Jerome I. Rotter[4], Donna K. Arnett[13]

ARTICLES

Genetic Variants in *HSD17B3*, *SMAD3*, and *IPO11* Impact Circulating Lipids in Response to Fenofibrate in Individuals With Type 2 Diabetes

Daniel M. Rotroff[1,2], Sonja S. Pijut[3], Skylar W. Marvel[1], John R. Jack[1], Tammy M. Havener[4], Aurora Pujol[5,6], Agatha Schluter[5], Gregory A. Graf[3,7,8], Henry N. Ginsberg[9], Hetal S. Shah[10], He Gao[10], Mario-Luca Morieri[10], Alessandro Doria[10], Josyf C. Mychaleckyj[11], Howard L. McLeod[12], John B. Buse[13], Michael J. Wagner[4], Alison A. Motsinger-Reif[1,2] and the ACCORD/ACCORDion Investigators

A genome-wide study of lipid response to fenofibrate in Caucasians: a combined analysis of the GOLDN and ACCORD studies

Marguerite R. Irvin[a,*], Daniel M. Rotroff[c,*], Stella Aslibekyan[a,*], Degui Zhi[b,*], Bertha Hidalgo[a], Alison Motsinger-Reif[c], Skylar Marvel[c], Vinodh Srinivasasainagendra[b], Steven A. Claas[a], John B. Buse[d], Robert J. Straka[f], Jose M. Ordovas[g], Ingrid B. Borecki[h], Xiuqing Guo[i], Ida Y.D. Chen[j], Jerome I. Rotter[k], Michael J. Wagner[e,*] and Donna K. Arnett[a,*]

Medicina di precisione

polimorfismi genetici → ↓ Tg e ↓ LDL (↓ VLDL)

Agenda

- Dislipidemia diabetica
- Efficacia delle terapia ipolipemizzanti convenzionali nel paziente diabetico
- Efficacia degli Inibitori di PCSK9 nel paziente diabetico

Farmaci ipocolesterolemizzanti

↓

Ieri: Statine - ezetimibe - sequestranti acidi biliari - fibrati

↓

Oggi: Statine - ezetimibe - sequestranti acidi biliari - fibrati

\+

Inibitori di PCSK9 🤔

Step di trattamento

Caso clinico

DT2 - M - aa 61
- STEMI
- Assetto lipidico:
CT 298 - HDL 31 - TG 220 - LDL 223

1°

Statine ad alta intensità (riduzione LDL 50-55%)
- Atorvastatina 40-80 mg
- Rosuvastatina 20-40 mg

Assetto lipidico:
CT 209 - HDL 38 - TG 170 - LDL 137

2°

- Ezetimibe (riduzione 15-20%)
- Fibrati
- Resine

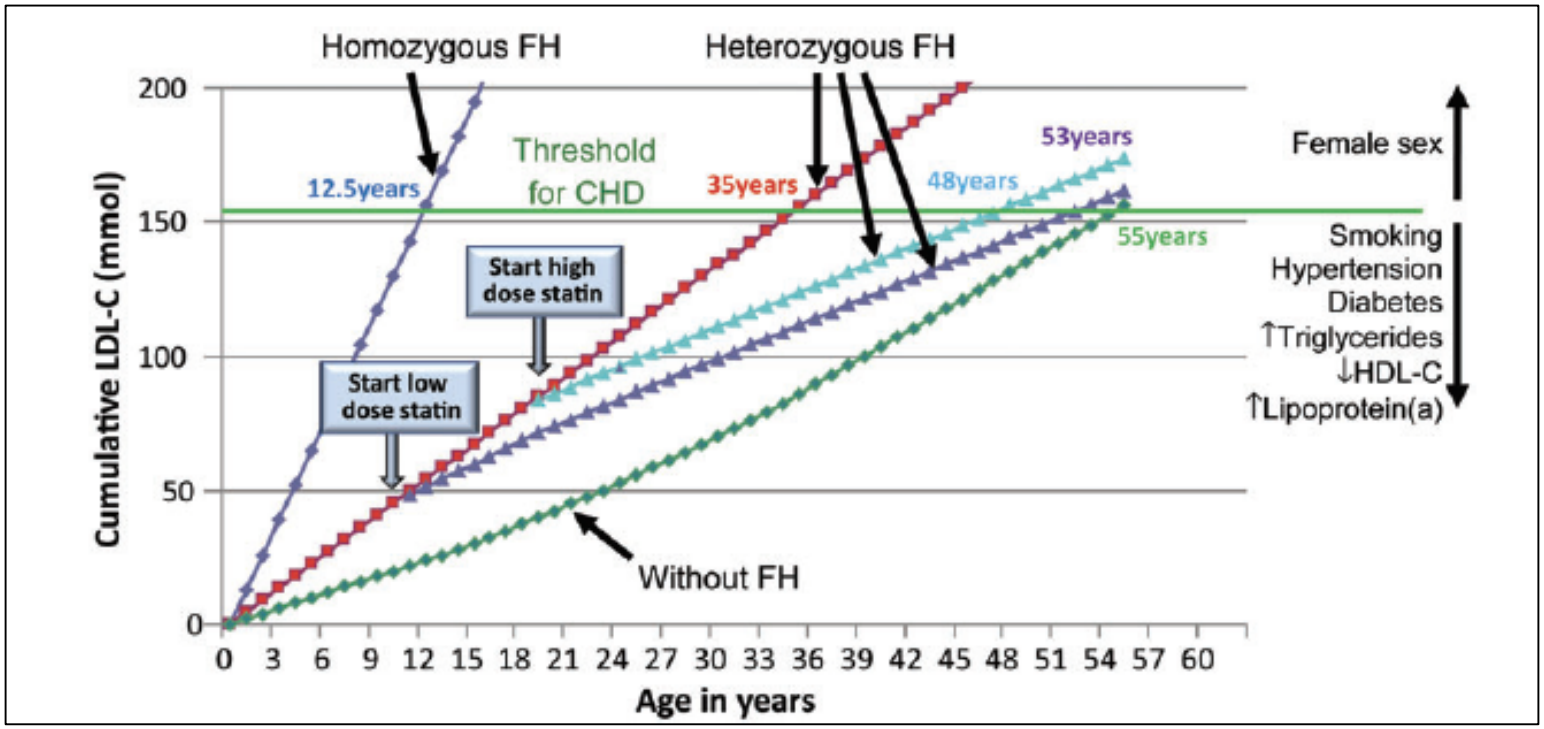
Assetto lipidico:
CT 186 - HDL 38 - TG 170 - LDL 114

3°

Lipoaferesi

LDL < 70 ← **LDL 114**

accumulo di colesterolo LDL (*LDL cholesterol burden*) ed eventi cardiovascolari



- *Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society.*
Nordestgaard BG *et al*; European Atherosclerosis Society Consensus Panel. Eur Heart J. 2013

Farmaci ipocolesterolemizzanti

↓

Ieri: Statine - ezetimibe - sequestranti acidi biliari - fibrati

↓

Oggi: Statine - ezetimibe - sequestranti acidi biliari - fibrati

+

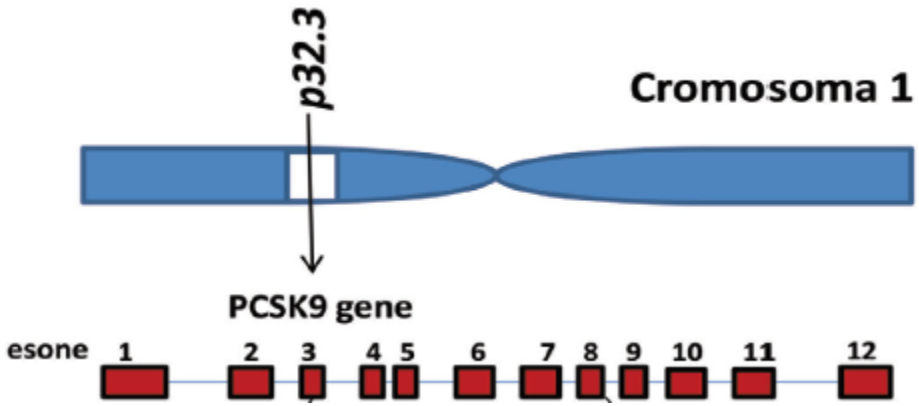
Inibitori di PCSK9 

PCSK9

↓

proproteina convertasi subtilisina/kexina tipo 9

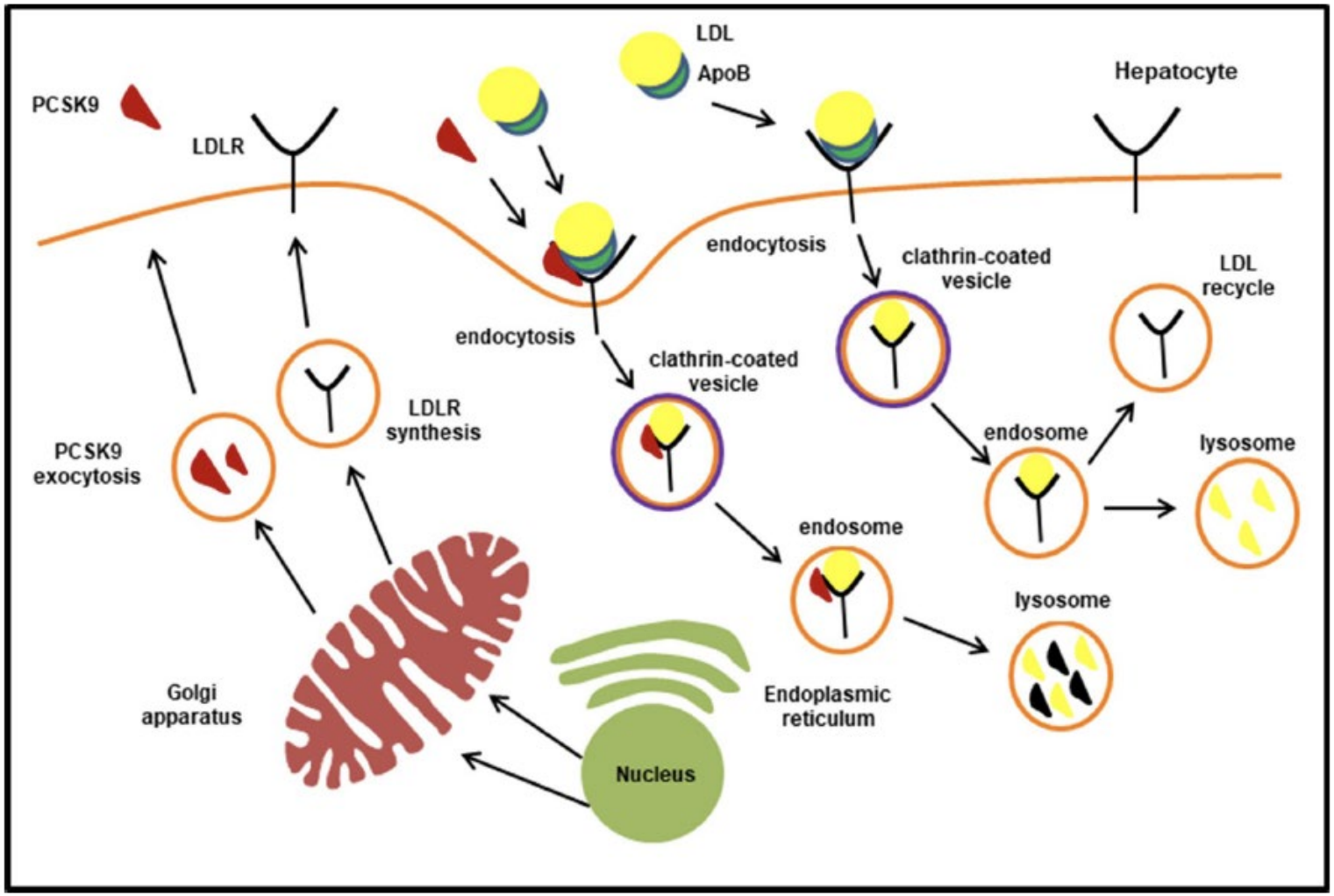
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693 AA

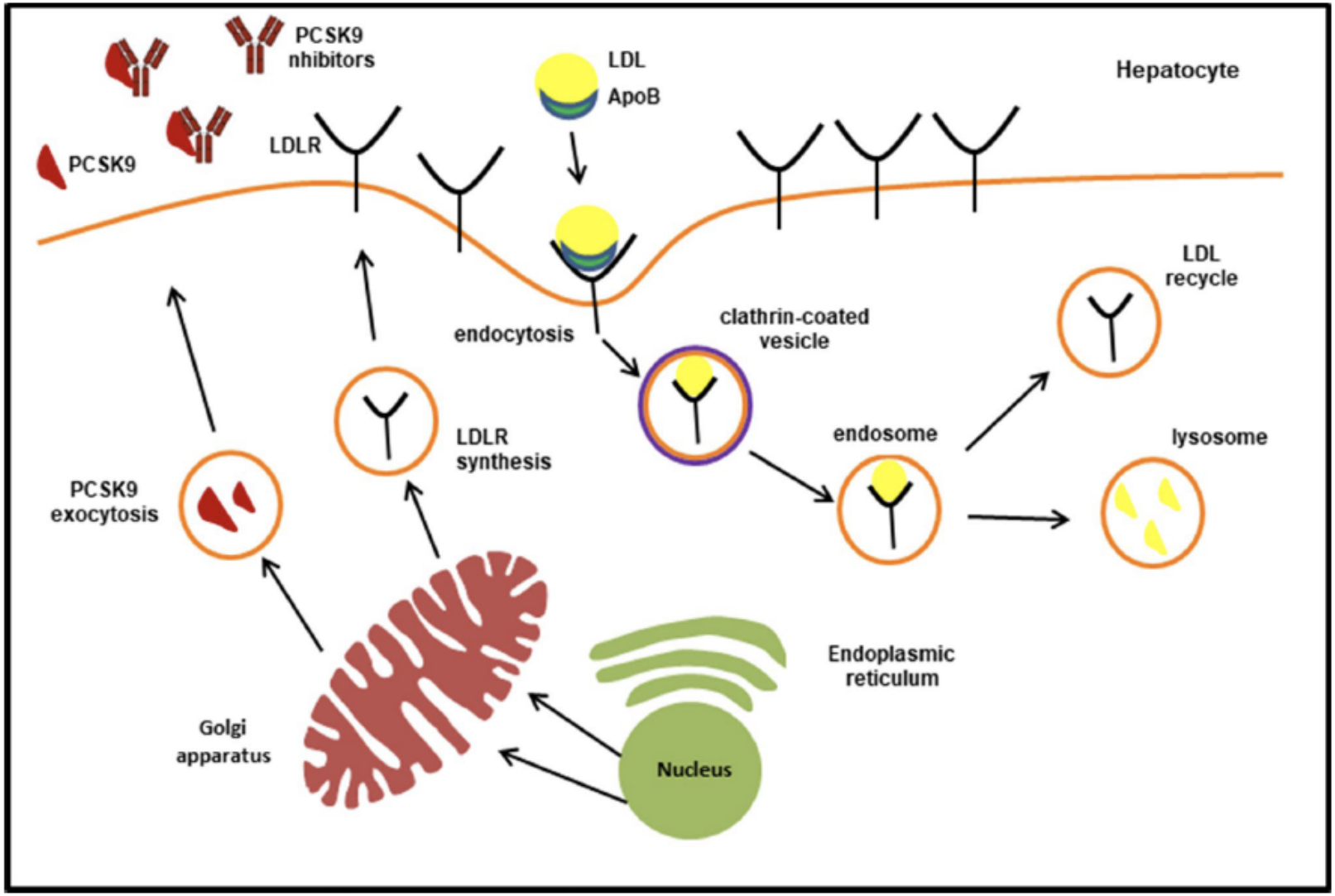
The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation.
Seidah NG et al, Proc Natl Acad Sci U S A. 2003

Funzione recettore LDL (LDLR) e ciclo vitale



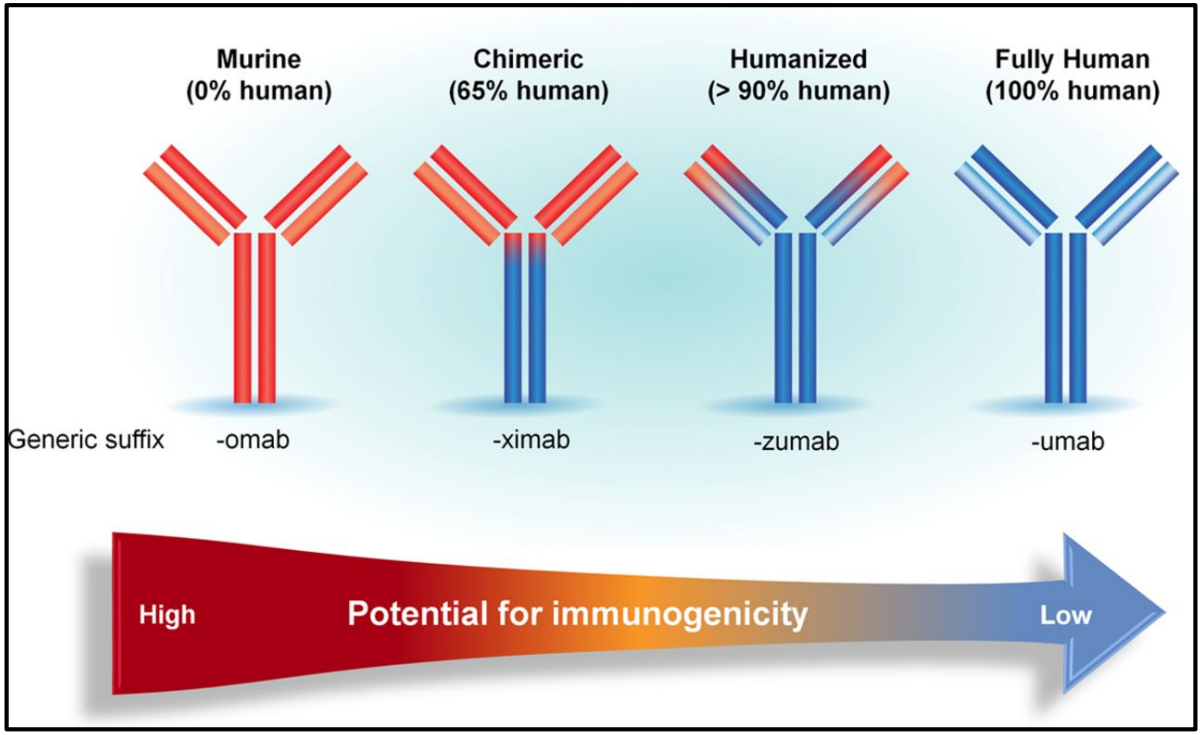
New treatment options for lipid-lowering therapy in subjects with type 2 diabetes.
Scicali R, Di Pino A, Ferrara V, Urbano F, Piro S, Rabuazzo AM, Purrello F. Acta Diabetol. 2018

Anticorpi monoclonali contro PCSK9



New treatment options for lipid-lowering therapy in subjects with type 2 diabetes.
Scicali R, Di Pino A, Ferrara V, Urbano F, Piro S, Rabuazzo AM, Purrello F. Acta Diabetol. 2018

Anticorpi monoclonali contro PCSK9



Alirocumab - Evolocumab - Bococizumab



Studi fase III

Ottobre 2016



Evolution and emergence of therapeutic monoclonal antibodies: what cardiologists need to know.
Foltz IN, Karow M, Wasserman SM, Circulation. 2013

I farmaci ipocolesterolemizzanti nel diabete

Anticorpi monoclonali contro PCSK9

Alirocumab

Studi clinici del programma ODYSSEY

Forme di ipercolesterolemia	Trial clinico	Popolazione/confronto	Risultati alla 24ª settimana
Familiare eterozigote	**FH I** multicentrico, controllato, in doppio cieco, della durata di 78 settimane	485 pazienti alirocumab (75-150 mg/2 settimane) + terapia ipolipemizzante vs placebo + terapia ipolipemizzante	Riduzione del 58% del C-LDL
	FH II multicentrico, controllato, in doppio cieco, della durata di 78 settimane	247 pazienti alirocumab (75-150 mg/2 settimane) + terapia ipolipemizzante vs placebo + terapia ipolipemizzante	Riduzione del 51% del C-LDL
	HIGH FH	106 pazienti	Riduzione del 39%
	multicentrico, in doppio cieco, controllato, della durata di 104 settimane	Alirocumab (75-150 mg/2 settimane) + statine vs ezetimibe + statine	del C-LDL
	OPTIONS I randomizzato, in doppio cieco, controllato, della durata di 24 settimane	355 pazienti Alirocumab (75-150 mg/2 settimane) + atorvastatina (20-40 mg) vs ezetimibe + atorvastatina vs atorvastatina ad alto dosaggio vs rosuvastatina	Alirocumab + atorvastatina (20 mg) ha ridotto C-LDL: del 24% vs ezetimibe del 39% vs statine Alirocumab + atorvastatina (40 mg) ha ridotto C-LDL: del 31% vs ezetimibe del 49% vs statine del 33% vs rosuvastatina
	OPTIONS II randomizzato, in doppio cieco, controllato, della durata di 24 settimane	300 pazienti Alirocumab (75-150 mg/2 settimane) + rosuvastatina vs ezetimibe + rosuvastatina vs rosuvastatina ad alto dosaggio	Alirocumab + rosuvastatina (10 mg) ha ridotto C-LDL: del 36% vs ezetimibe del 34% vs statine Alirocumab + rosuvastatina (20 mg) ha ridotto C-LDL: del 25% vs ezetimibe del 20% vs statine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

Evolocumab

Studi clinici del programma PROFICIO

Forme di ipercolesterolemia	Trial clinico	Popolazione/confronto	Risultati
Familiare omozigote	**TESLA** multicentrico, randomizzato, in doppio cieco, controllato, della durata di 12 settimane	49 pazienti evolocumab (420 mg/mese) + terapia ipolipemizzante vs placebo + terapia ipolipemizzante	Alla 12ª settimane riduzione del 32% del C-LDL
Familiare eterozigote	**RUTHERFORD-2** multicentrico, randomizzato, in doppio cieco, controllato, della durata di 12 settimane	329 pazienti evolocumab (140 mg/2 settimane e 420 mg/mese) + terapia ipolipemizzante	Alla media delle settimane 10 e 12 evolocumab 140 mg/2 settimane e 420 mg/mese hanno ridotto rispettivamente il C-LDL del 61%
Ipercolest primaria mista			10 e 12 ttimane idotto el 72% o imibe
			10 e 12 ttimane idotto el 40% alla 12ª acebo one
	THOMAS-1 multicentrico, randomizzato, in aperto, della durata di 4 settimane	149 pazienti evolocumab (140 mg/2 settimane) siringa preriempita + terapia ipolipemizzante vs evolocumab (140 mg/2 settimane) penna preriempita + terapia ipolipemizzante	Alla 6ª settimana evolocumab siringa preriempita e evolocumab penna preriempita hanno ridotto rispettivamente il C-LDL del 61% e del 64%
	THOMAS-2 multicentrico, randomizzato, in aperto, della durata di 8 settimane	164 pazienti evolocumab (420 mg/mese) microinfusore automatico + terapia ipolipemizzante vs evolocumab (420 mg/mese) penna preriempita + terapia ipolipemizzante	Alla media delle settimane 10 e 12 evolocumab microinfusore automatico e evolocumab penna preriempita hanno ridotto rispettivamente il C-LDL del 69% e del 67%
Pazienti intolleranti alle statine	**GAUSS-2** multicentrico, randomizzato, in doppio cieco, controllato, della durata di 12 settimane	307 pazienti evolocumab (140 mg/2 settimane e 420 mg/mese) vs ezetimibe	Alla media delle settimane 10 e 12 evolocumab 140 mg/2 settimane e 420 mg/mese hanno ridotto rispettivamente il C-LDL del 38% e del 39%

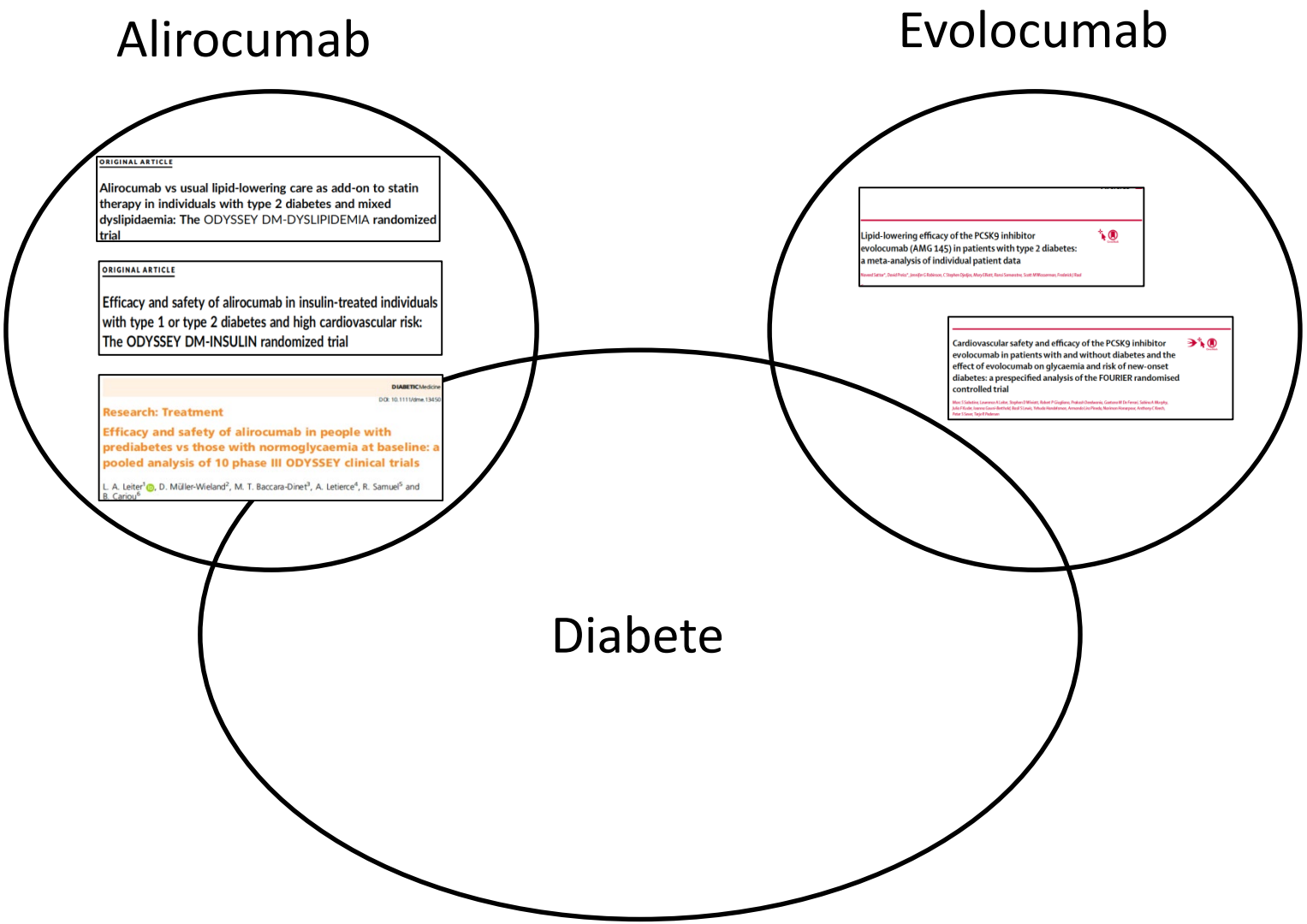
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

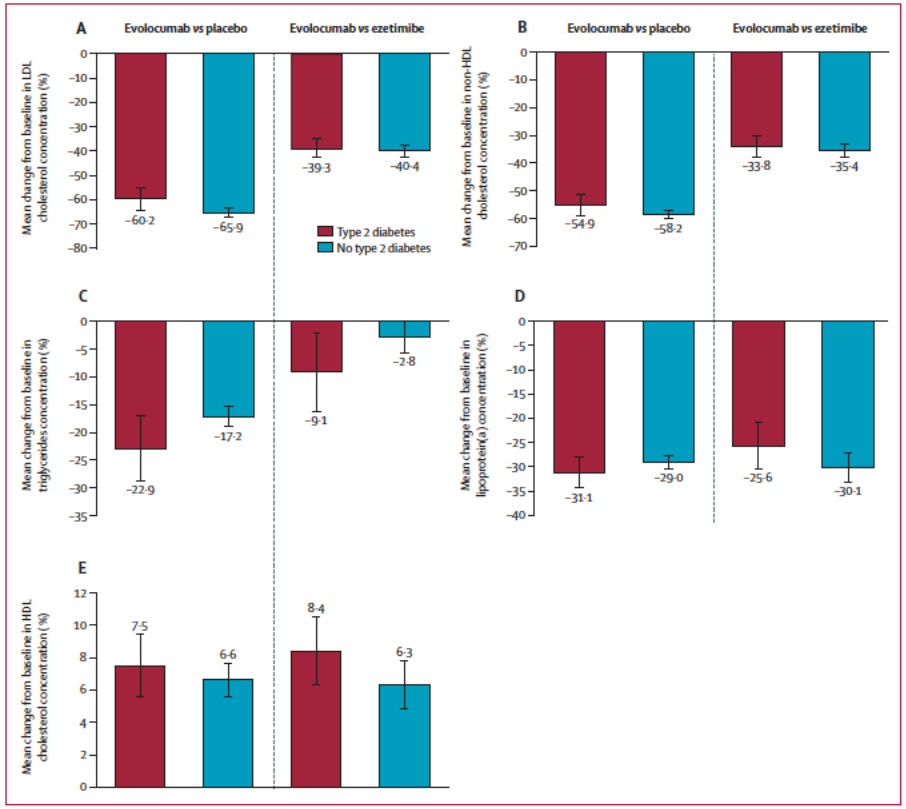
I farmaci ipocolesterolemizzanti nel diabete



Evolocumab

Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data

Naveed Sattar*, David Preiss*, Jennifer G Robinson, C Stephen Djedjos, Mary Elliott, Ransi Somaratne, Scott M Wasserman, Frederick J Raal



Evolocumab

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

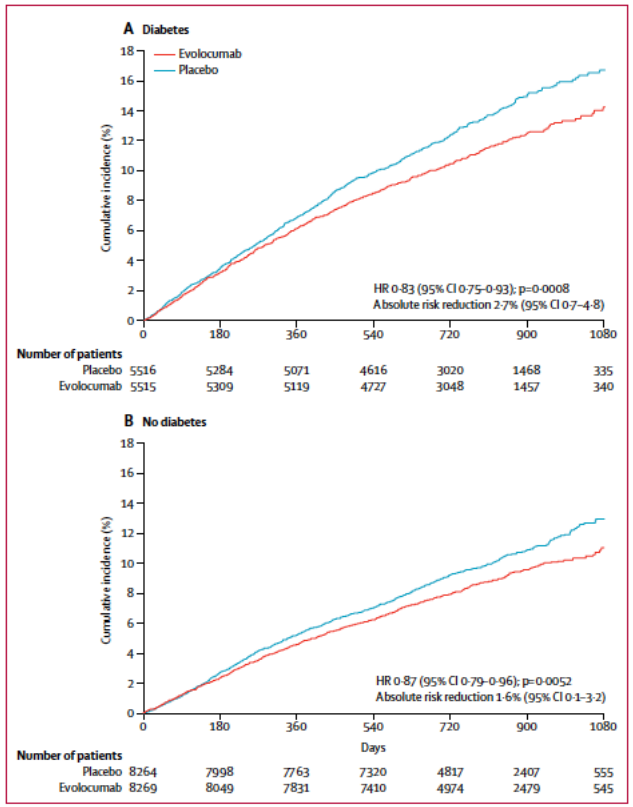


Figure 2: **Primary endpoint**
Data are the cumulative event rates for the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation) in the evolocumab and placebo treatment groups, for patients with and without diabetes at baseline. p values were calculated with log-rank tests. Hazard ratios (HRs) and 95% CI are from a Cox model. The $p_{interaction}$ value between baseline diabetes status and efficacy of evolocumab was 0·60.

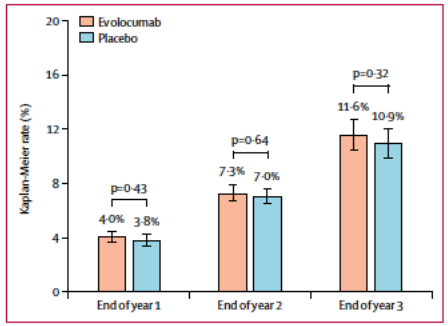


Figure 4: **New-onset diabetes**
Data are the cumulative incidence of new-onset diabetes at the end of 1, 2, and 3 years of follow-up in the evolocumab and placebo treatment groups, among patients without diabetes at baseline. Error bars are 95% CIs.

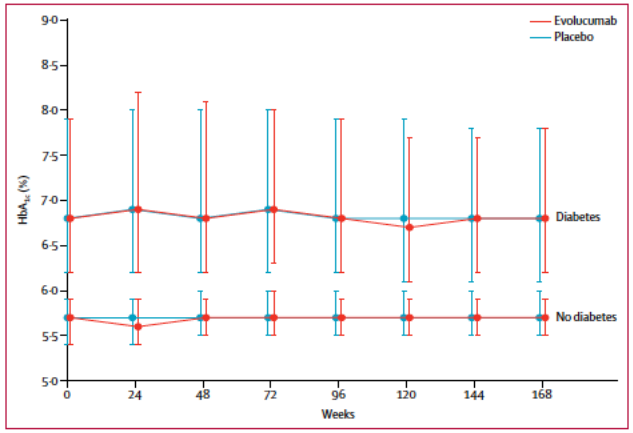


Figure 5: **HbA_{1c} over time**
Data are median values in the evolocumab and placebo treatment groups, for patients with and without diabetes. Error bars are IQRs.

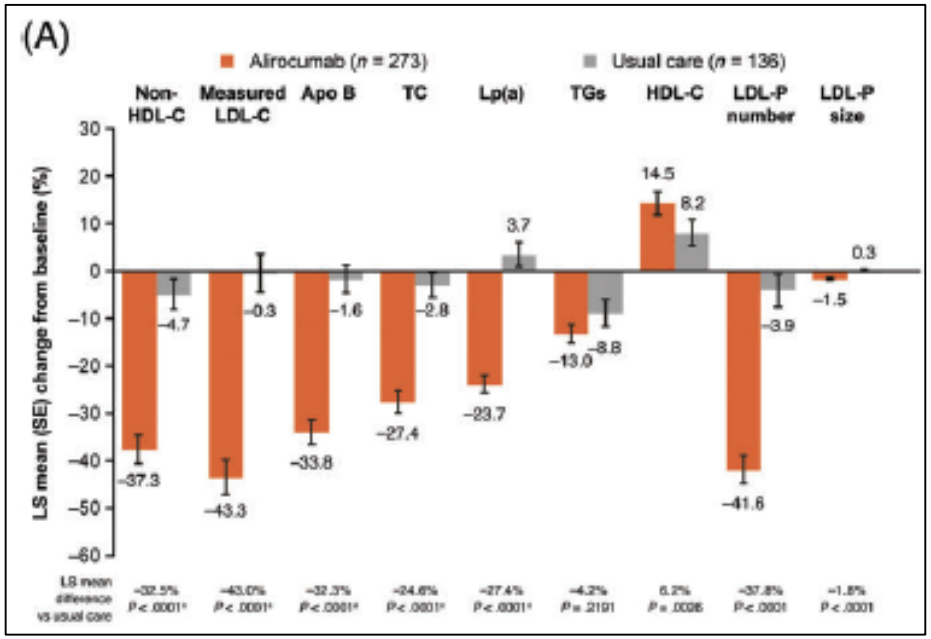
Alirocumab

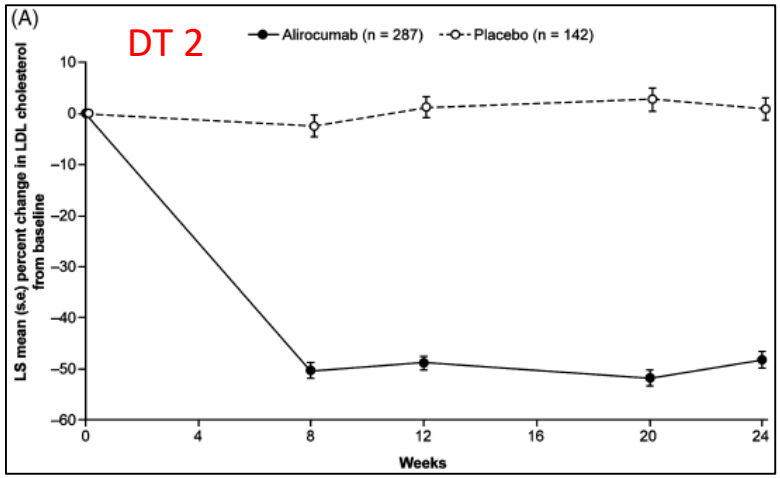
ORIGINAL ARTICLE

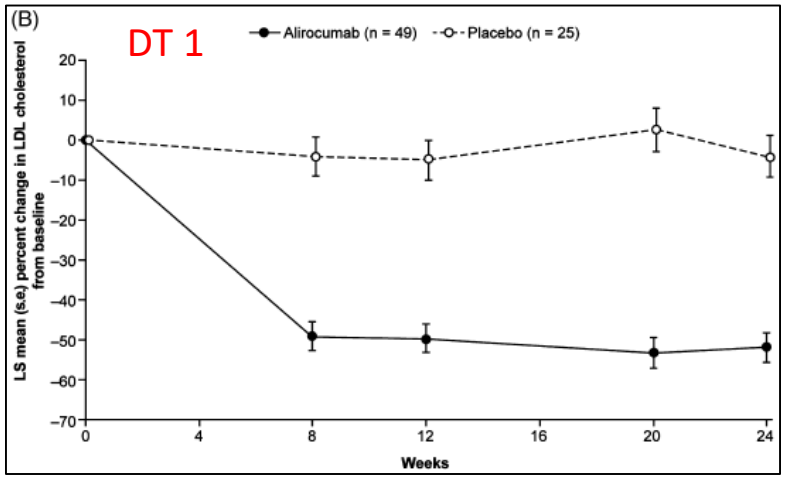
Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: The ODYSSEY DM-DYSLIPIDEMIA randomized trial

ORIGINAL ARTICLE

Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial







Alirocumab

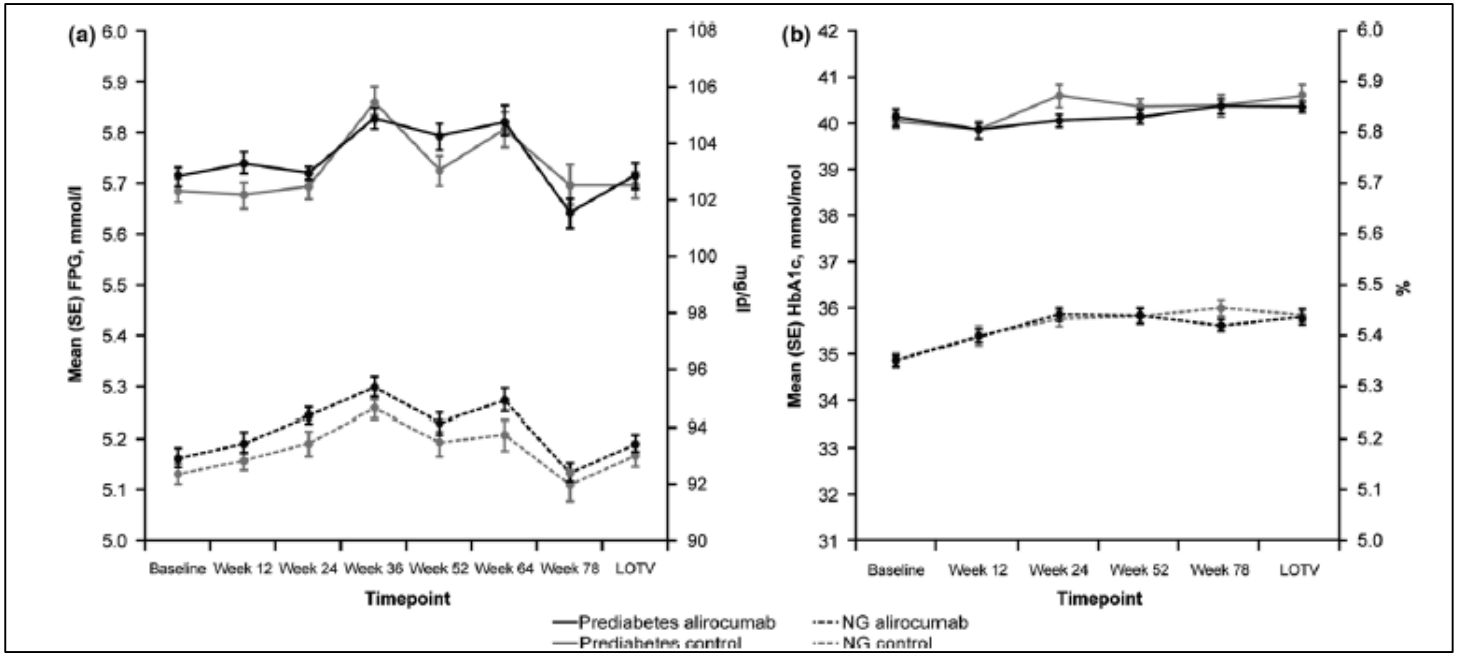
DIABETICMedicine

DOI: 10.1111/dme.13450

Research: Treatment

Efficacy and safety of alirocumab in people with prediabetes vs those with normoglycaemia at baseline: a pooled analysis of 10 phase III ODYSSEY clinical trials

L. A. Leiter[1], D. Müller-Wieland[2], M. T. Baccara-Dinet[3], A. Letierce[4], R. Samuel[5] and B. Cariou[6]



PCSK9 loss of function e DT2

PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study

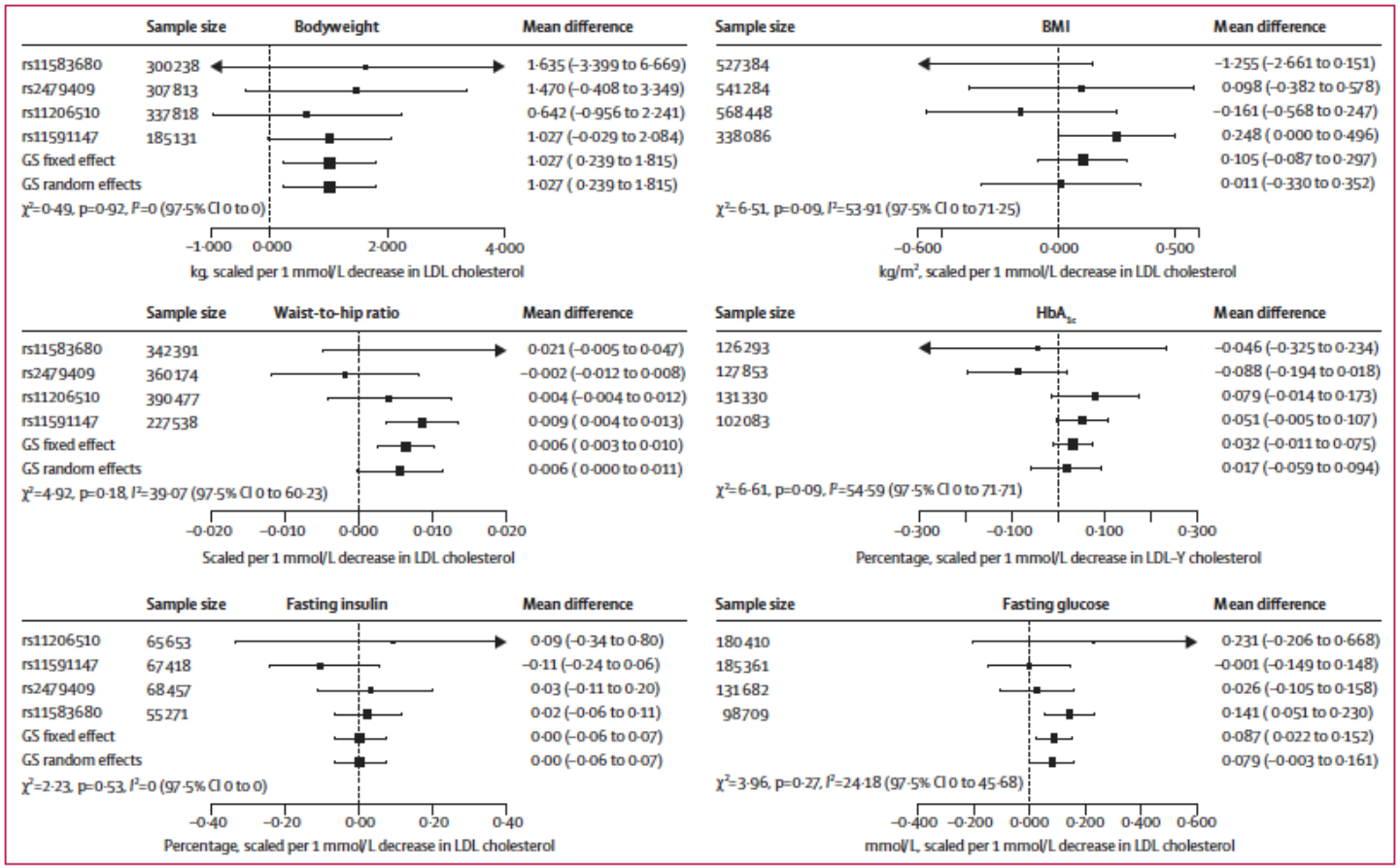


Figure 2: **Association of genetic variants in PCSK9 with glycaemic and anthropometric biomarkers**
Effect estimates are presented as mean difference with 95% CIs. Associations were scaled to a 1 mmol/L reduction in LDL cholesterol. SNP-specific results are pooled by use of a fixed-effect model; weighted gene-centric score (GS) models combining all four SNP-specific estimates are presented as fixed-effect and random-effects estimates. The size of the black dots representing the point estimates is proportional to the inverse of the variance. Between-SNP heterogeneity was measured as a two-sided Q-test (χ^2) and an I^2 with one-sided 97·5% CI. Note that results from individual participant data are supplemented by repository data from the Global Lipids Genetics Consortium, the Meta-Analyses of Glucose and Insulin-related traits Consortium, and the Genetic Investigation of Anthropometric Traits consortium.

PCSK9 loss of function e DT2

***PCSK9* genetic variants and risk of type 2 diabetes: a mendelian randomisation study**

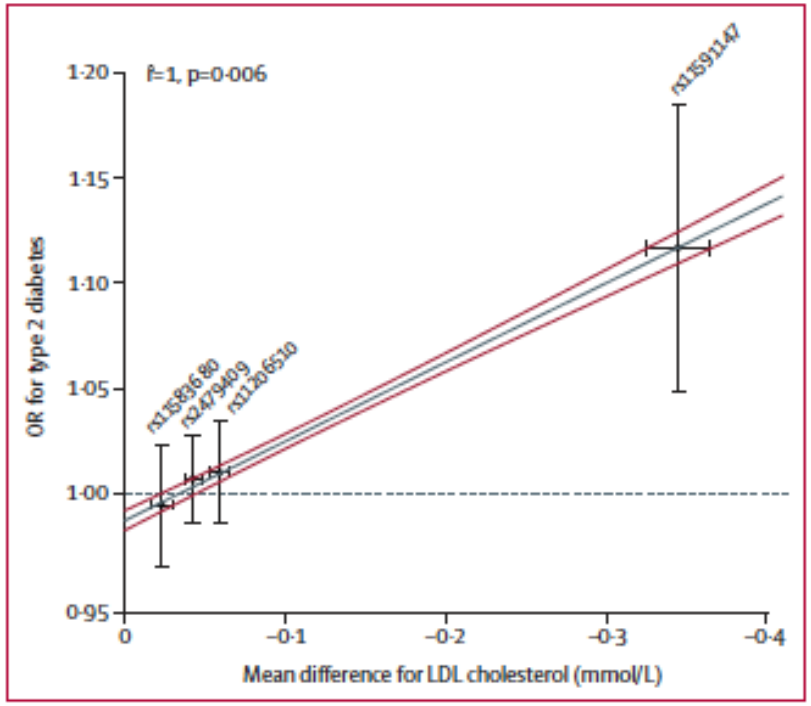


***Figure 4*: Correlation between *PCSK9* associations with LDL cholesterol concentration and type 2 diabetes**

Effect estimates are presented as mean difference in LDL cholesterol concentration (mmol/L) and odds ratios (ORs) for the incidence or prevalence of type 2 diabetes, with 95% CIs. Associations are presented per LDL cholesterol-decreasing allele. The Pearson correlation coefficient, regression line (grey), and its 95% CI (red) were calculated by weighting the SNPs for the inverse of the variance in the type 2 diabetes association. Excluding the SNP with the largest effect on LDL cholesterol (rs11591147) resulted in a correlation coefficient of 0·993 and a p value of 0·437.

- Terapie senza reale beneficio (sequestranti acidi biliari)



- Terapie efficaci (statine – ezetimibe fibrati – inibitori PCSK9)



- Prospettive future?



Inclisiran → silenziatore di RNA messaggero di PCSK9

Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial

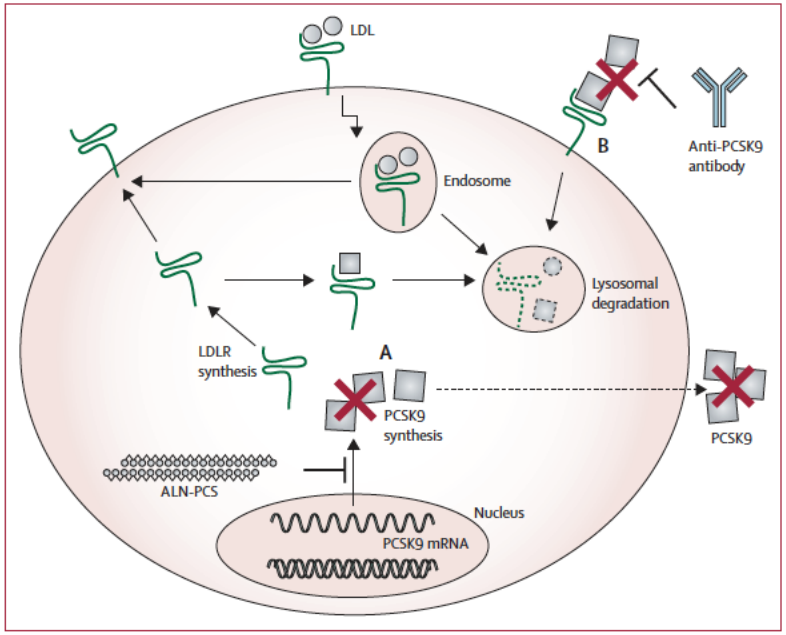


Figure 1: **PCSK9 pathway and RNA interference synthesis-inhibitor approach**
PCSK9 has a role in both intracellular and extracellular degradation of the LDL receptor (LDLR). PCSK9 synthesis inhibitors such as ALN-PCS inhibit PCSK9 synthesis (A) and therefore both intracellular and extracellular functions, whereas PCSK9 blockers (such as anti-PCSK9 antibodies) inhibit only extracellular function (B). mRNA=messenger RNA.

I farmaci ipocolesterolemizzanti nel diabete

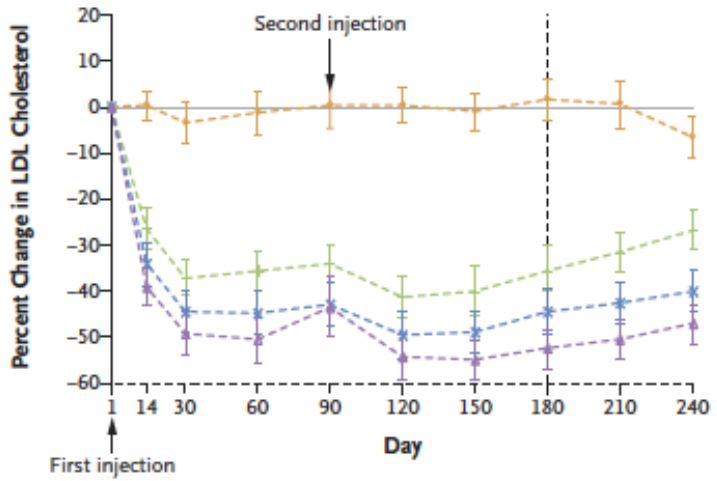
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

Changes in LDL Cholesterol Levels with the Two-Dose Regimen



Two-dose placebo
Two-dose inclisiran, 100 mg
Two-dose inclisiran, 200 mg
Two-dose inclisiran, 300 mg

No. at Risk

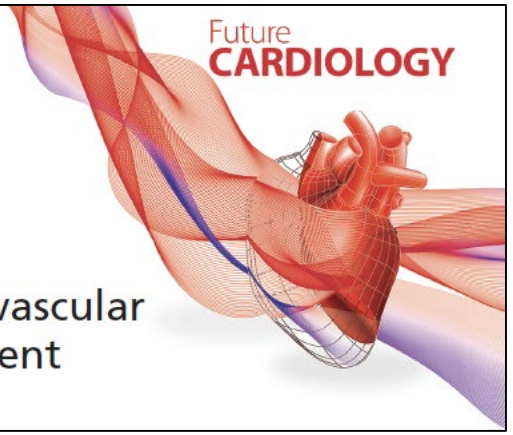
Two-dose placebo	62	62	61	62	60	61	61	61	60	29
Two-dose inclisiran, 100 mg	61	58	60	58	60	58	57	59	59	49
Two-dose inclisiran, 200 mg	62	62	62	62	61	59	58	60	60	56
Two-dose inclisiran, 300 mg	61	61	61	61	60	59	59	59	58	57

I farmaci ipocolesterolemizzanti nel diabete

Clinical Trial Evaluation

For reprint orders, please contact: reprints@futuremedicine.com

Future CARDIOLOGY



Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program

Table 1. Summarizes the current clinical development program for inclisiran.

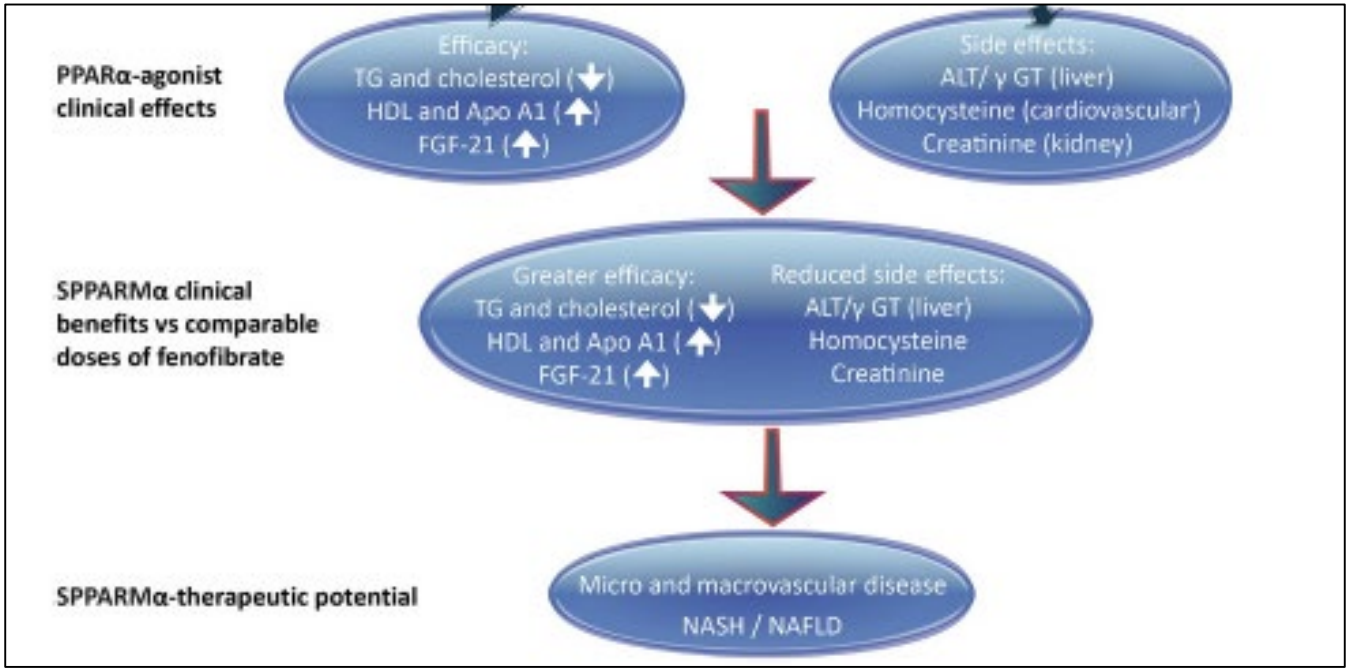
Study	Description	Estimated number of subjects	Duration of follow-up†	Status as on second-half of 2018
ORION-1	Phase II dose finding	501	Up to 360 days	Completed
ORION-2	Homozygous FH pilot study	4	Up to 300 days	Ongoing
ORION-3	Open-label extension study to ORION-1	374	Up to 4 years	Ongoing
ORION-4	Cardiovascular outcomes trial	15,000	Event-driven/median duration ≥5 years	Start-up
ORION-5	Homozygous FH Phase III	45	Up to 2 years	Start-up
ORION-6	Hepatic impairment	24	Up to 180 days	Start-up
ORION-7	Renal Impairment	31	Up to 180 days	Completed
ORION-8	Phase III extension study (ORION-9, -10, -11)	Up to 3600	Up to 3 years	Will start after completion of ORION-9, ORION-10 and ORION-11
ORION-9	Phase III heterozygous FH	482	Up to 540 days	Ongoing
ORION-10	LDL-C lowering in ASCVD (USA)	1561	Up to 540 days	Ongoing
ORION-11	LDL-C lowering in ASCVD and ASCVD risk equivalents (EU)	1617	Up to 540 days	Ongoing
ORION-12	TQTc	Appr. 48	Up to 180 days	Start-up

†The primary trial end point may be before the maximum duration of follow-up; for example in ORION-1, the primary end point was at day 180, whereas follow-up continued until return to >80% of baseline LDL-C with a maximum of 360 days.
ASCVD: Atherosclerotic cardiovascular disease; FH: Familial hypercholesterolemia; LDL-C: Low-density lipoprotein cholesterol.

Pemafibrato (modulatore selettivo di PPARα)

REVIEW **Open Access**

Selective peroxisome proliferator-activated receptorα modulators (SPPARMα): The next generation of peroxisome proliferator-activated receptor α-agonists



I farmaci ipocolesterolemizzanti nel diabete

Journal of Clinical Lipidology (2018) 12, 173–184

Journal of Clinical Lipidology

Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor α modulator, in patients with dyslipidemia: Results from a 24-week, randomized, double blind, active-controlled, phase 3 trial

Table 2 Primary efficacy analyses on the percent change from baseline in TG

	Baseline (mmol/L)	% Change from baseline	Difference vs fenofibrate
Treatment group	Mean (SD)	LS mean (SE)	LS mean (SE) [95% CI]
Pemafibrate 0.2 mg/d	2.7 (0.6)	−46.2 (2.0)*	−6.5 (2.8) [−12.0, −1.1]†
Pemafibrate 0.4 mg/d	2.6 (0.7)	−45.9 (1.9)*	−6.2 (2.7) [−11.6, −0.8]†
Fenofibrate 106.6 mg/d	2.7 (0.8)	−39.7 (1.9)*	

ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error ; TG, triglycerides.

LS mean and 95% CI were estimated using a repeated measures ANCOVA model with the baseline as a covariate applied for the percentage changes in TG from baseline to Weeks 8, 12, 16, 20, and 24. The primary efficacy analyses were noninferiority and superiority of pemafibrate 0.2 and 0.4 mg/d to fenofibrate 106.6 mg/d. Predefined noninferiority margin was 10%. Multiplicity in the noninferiority and the superiority testings was adjusted by the closed testing procedure method to test the noninferiority before the superiority.

*$P < .001$ vs baseline.

†$P < .05$ vs fenofibrate.

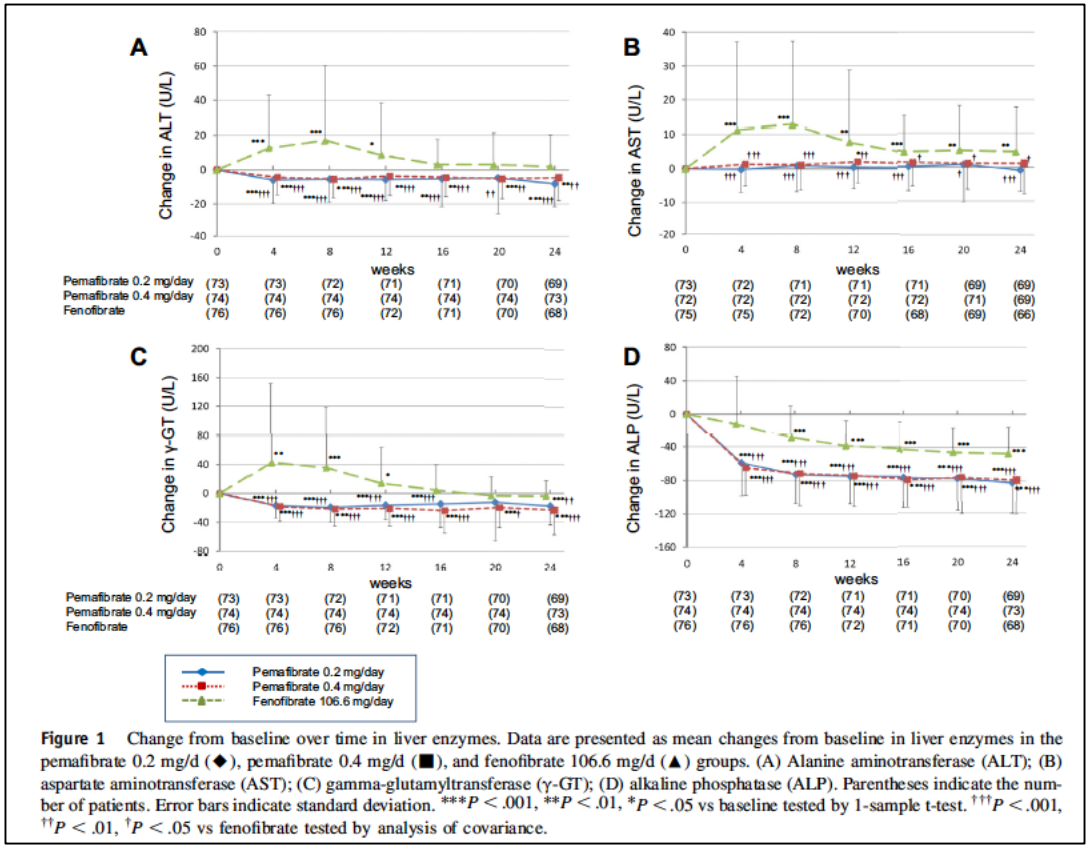


Figure 1 Change from baseline over time in liver enzymes. Data are presented as mean changes from baseline in liver enzymes in the pemafibrate 0.2 mg/d (◆), pemafibrate 0.4 mg/d (■), and fenofibrate 106.6 mg/d (▲) groups. (A) Alanine aminotransferase (ALT); (B) aspartate aminotransferase (AST); (C) gamma-glutamyltransferase (γ-GT); (D) alkaline phosphatase (ALP). Parentheses indicate the number of patients. Error bars indicate standard deviation. ***$P < .001$, **$P < .01$, *$P < .05$ vs baseline tested by 1-sample t-test. †††$P < .001$, ††$P < .01$, †$P < .05$ vs fenofibrate tested by analysis of covariance.

Trial Designs

Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study☆

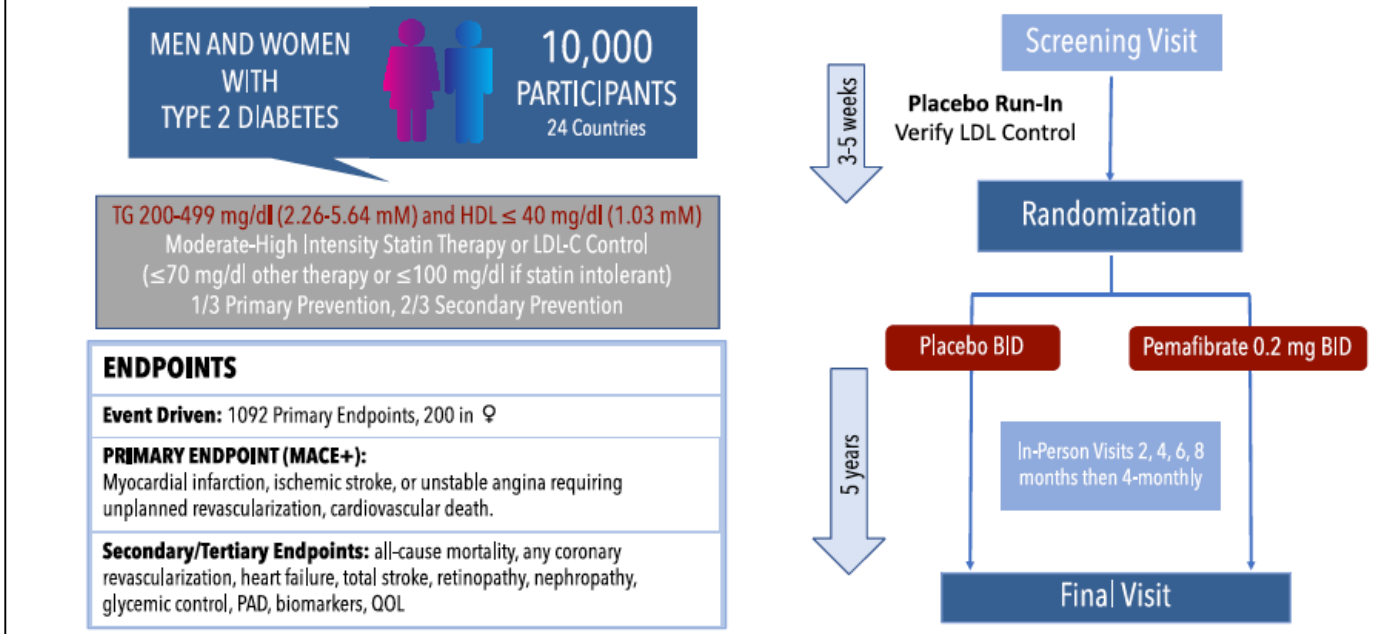


Figure 4

PROMINENT Study Design.

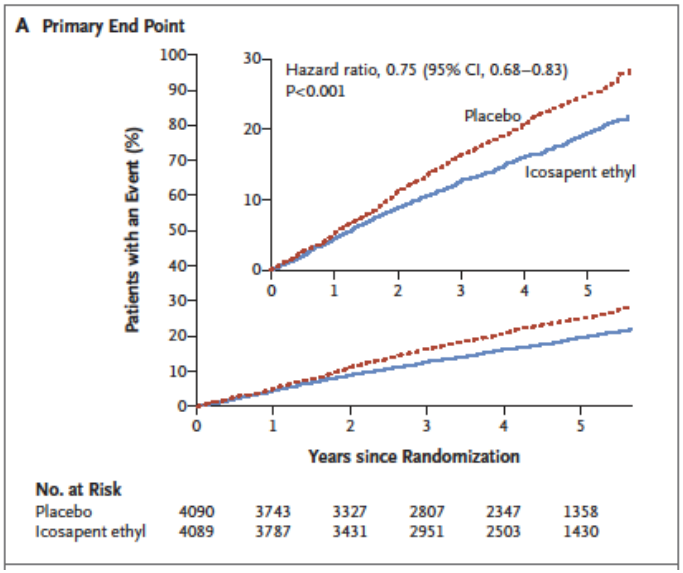
Vascepa (96% EPA)

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ORIGINAL ARTICLE

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*



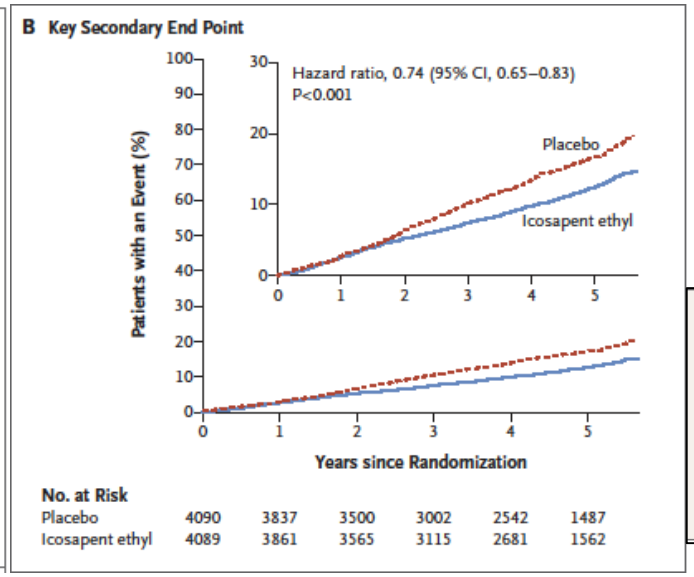


Figure 1. Cumulative Incidence of Cardiovascular Events.
Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan–Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded y axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Supplementary Table 3. Select Prespecified Adjudicated Tertiary Endpoints – ITT Population.

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Primary Endpoint in Patients with Diabetes at Baseline	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68, 0.87)