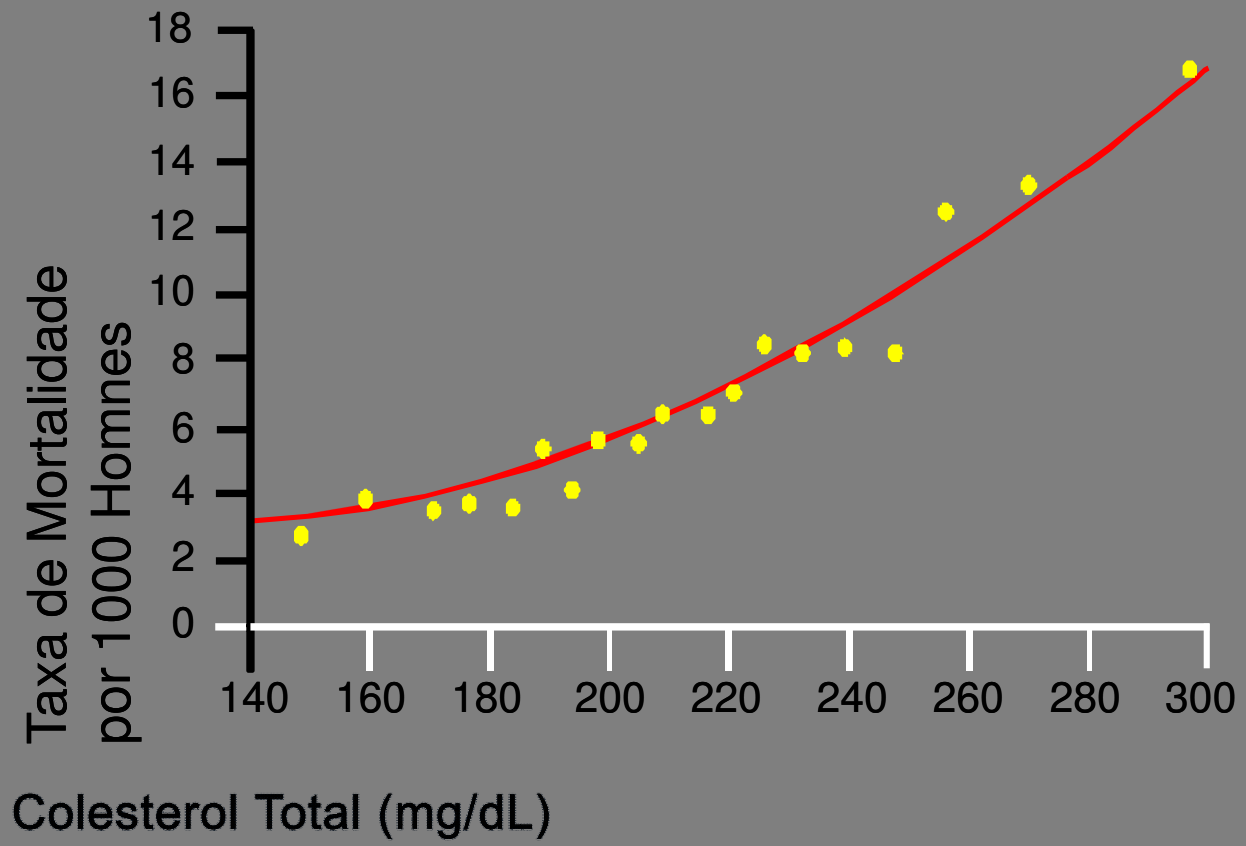
Atualizações em Dislipidemia

Qual o real papel do ezetimibe?

*Declaro não possuir conflito de Interesses com a minha apresentação

Quanto Mais Alto o Nível do Colesterol Maior a Taxa de Mortalidade

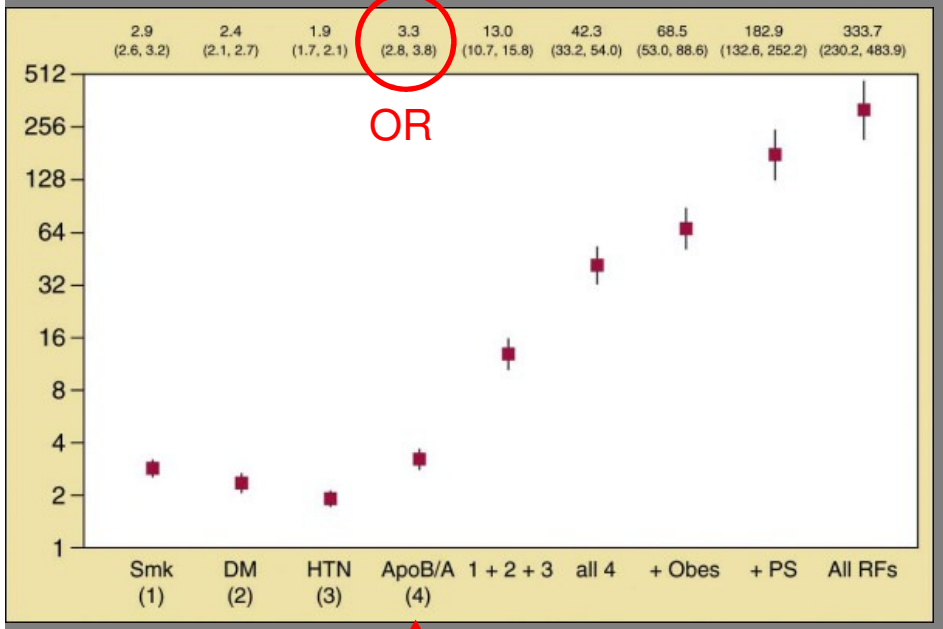


MRFIT study JAMA. 1986; 256:2.823-8

Relação entre Dislipidemia e o risco de Eventos Cardiovasculares (INTERHEART e INTERSTROKE)

1º IAM

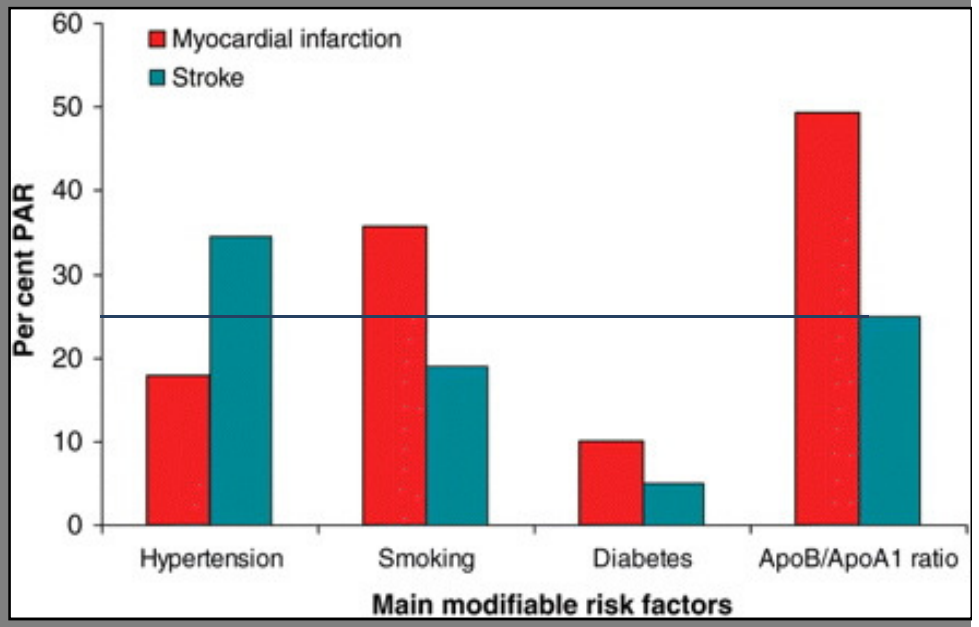
*1



PAR= 54,1

1º AVC

*2



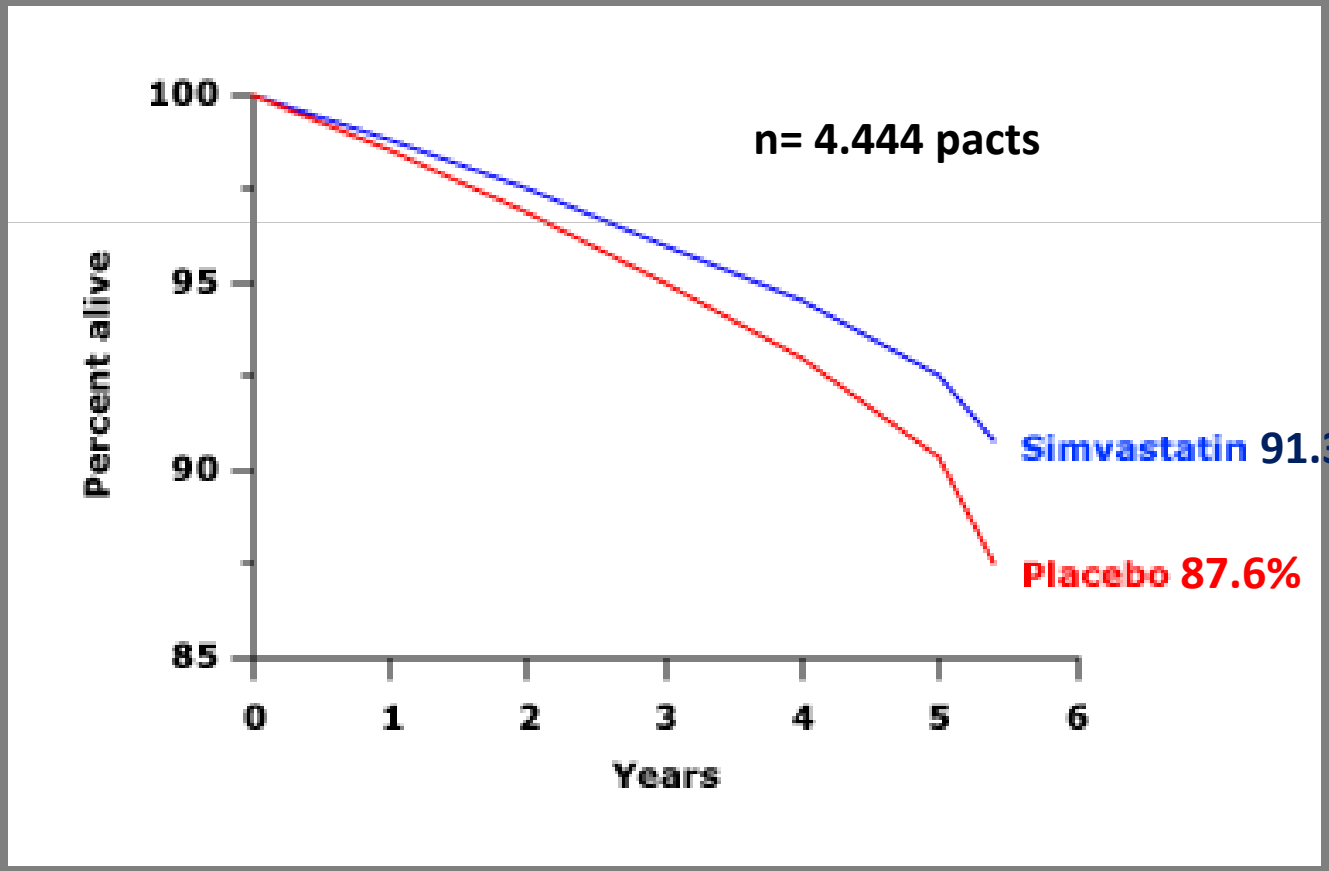
*1. Lancet 2004; 364: 937-952

*2. Lancet. 2010;376:112–123

Redução de Mortalidade em pacientes com DAC
Scandinavian Simvastatin Survival Study (4S)

Mortalidade coronária reduzida em 42%

*__Mortalidade total reduzida em 30% (IC=0.58-0.85 p=0.0003)__



Lancet 1994; 344:1383-89

A Importância do LDL-Colesterol
Metanálise dos Trialistas

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

Lancet 2010; 376: 1670–81
Published Online November 9, 2010
DOI:10.1016/S0140-6736(10)61350-5

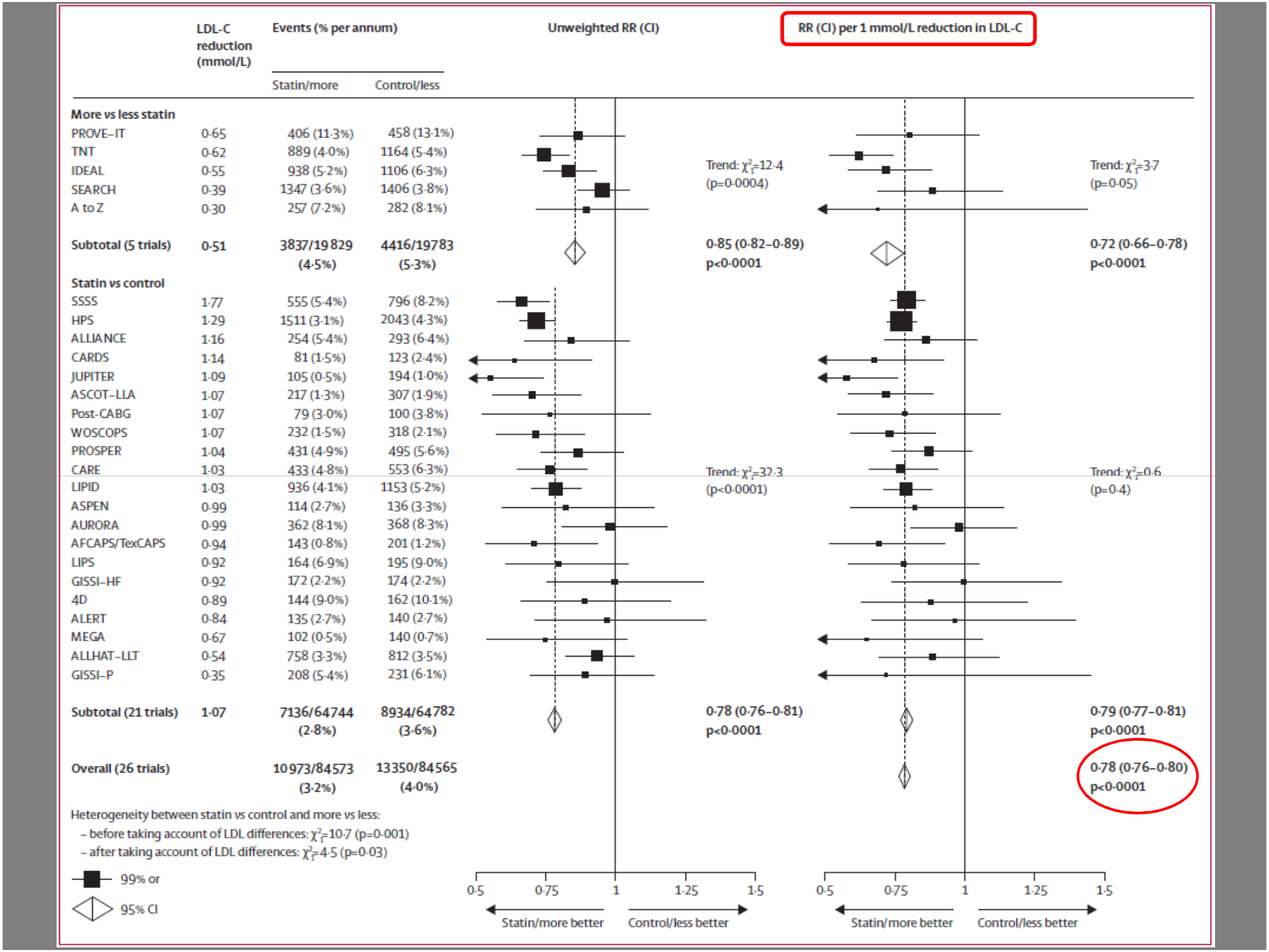
See Comment page 1622
See Articles page 1658

*Collaborators are listed at the end of the paper
Correspondence to:

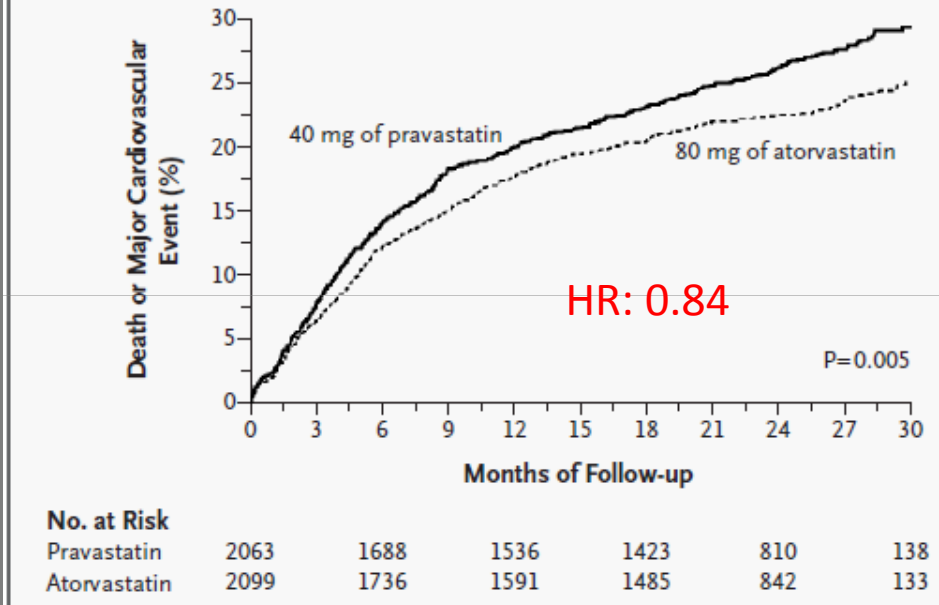
Summary

Background Lowering of LDL cholesterol with standard statin regimens reduces the risk of occlusive vascular events in a wide range of individuals. We aimed to assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy.

Methods We undertook meta-analyses of individual participant data from randomised trials involving at least 1000 participants and at least 2 years' treatment duration of more versus less intensive statin regimens (five trials; 39 612 individuals; median follow-up 5·1 years) and of statin versus control (21 trials; 129 526 individuals; median follow-up 4·8 years). For each type of trial, we calculated not only the average risk reduction, but also the average risk reduction per 1·0 mmol/L LDL cholesterol reduction at 1 year after randomisation.


LDL-C reduction (mmol/L)
Events (% per annum)
Statin/more
Control/less
Unweighted RR (CI)
RR (CI) per 1 mmol/L reduction in LDL-C
More vs less statin
PROVE-IT 0·65 406 (11·3%) 458 (13·1%)
TNT 0·62 889 (4·0%) 1164 (5·4%)
IDEAL 0·55 938 (5·2%) 1106 (6·3%)
SEARCH 0·39 1347 (3·6%) 1406 (3·8%)
A to Z 0·30 257 (7·2%) 282 (8·1%)
Subtotal (5 trials) 0·51 3837/19829 (4·5%) 4416/19783 (5·3%)
0·85 (0·82–0·89) p<0·0001
0·72 (0·66–0·78) p<0·0001
Trend: χ²1=12·4 (p=0·0004)
Trend: χ²1=3·7 (p=0·05)
Statin vs control
SSSS 1·77 555 (5·4%) 796 (8·2%)
HPS 1·29 1511 (3·1%) 2043 (4·3%)
ALLIANCE 1·16 254 (5·4%) 293 (6·4%)
CARDS 1·14 81 (1·5%) 123 (2·4%)
JUPITER 1·09 105 (0·5%) 194 (1·0%)
ASCOT-LLA 1·07 217 (1·3%) 307 (1·9%)
Post-CABG 1·07 79 (3·0%) 100 (3·8%)
WOSCOPS 1·07 232 (1·5%) 318 (2·1%)
PROSPER 1·04 431 (4·9%) 495 (5·6%)
CARE 1·03 433 (4·8%) 553 (6·3%)
LIPID 1·03 936 (4·1%) 1153 (5·2%)
ASPEN 0·99 114 (2·7%) 136 (3·3%)
AURORA 0·99 362 (8·1%) 368 (8·3%)
AFCAPS/TexCAPS 0·94 143 (0·8%) 201 (1·2%)
LIPS 0·92 164 (6·9%) 195 (9·0%)
GISSI-HF 0·92 172 (2·2%) 174 (2·2%)
4D 0·89 144 (9·0%) 162 (10·1%)
ALERT 0·84 135 (2·7%) 140 (2·7%)
MEGA 0·67 102 (0·5%) 140 (0·7%)
ALLHAT-LLT 0·54 758 (3·3%) 812 (3·5%)
GISSI-P 0·35 208 (5·4%) 231 (6·1%)
Subtotal (21 trials) 1·07 7136/64744 (2·8%) 8934/64782 (3·6%)
0·78 (0·76–0·81) p<0·0001
0·79 (0·77–0·81) p<0·0001
Trend: χ²1=32·3 (p<0·0001)
Trend: χ²1=0·6 (p=0·4)
Overall (26 trials) 10973/84573 (3·2%) 13350/84565 (4·0%)
0·78 (0·76–0·80) p<0·0001
Heterogeneity between statin vs control and more vs less:
– before taking account of LDL differences: χ²1=10·7 (p=0·001)
– after taking account of LDL differences: χ²1=4·5 (p=0·03)
99% or
95% CI
0·5
0·75
1
1·25
1·5
Statin/more better
Control/less better

Estatinas Pós-SCA (Prove IT)
Risco Residual Elevado



26.3%

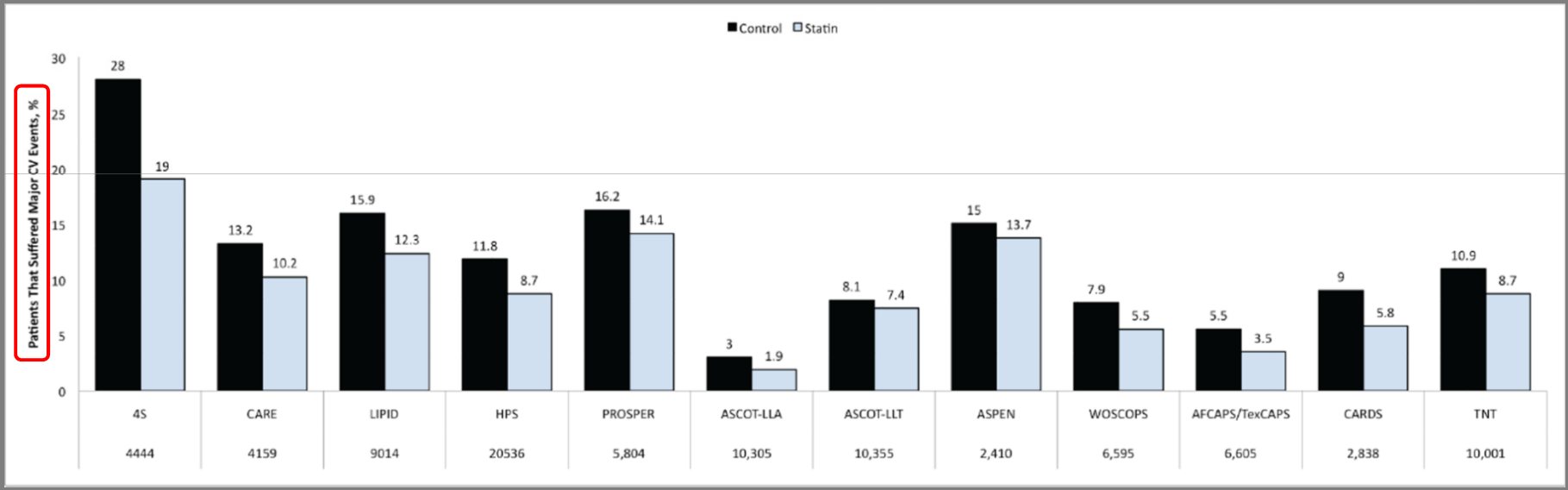
22.4%

Figure 2. Kaplan–Meier Estimates of the Incidence of the Primary End Point of Death from Any Cause or a Major Cardiovascular Event.

Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16 percent.

N Engl J Med 2004;350:1495-504

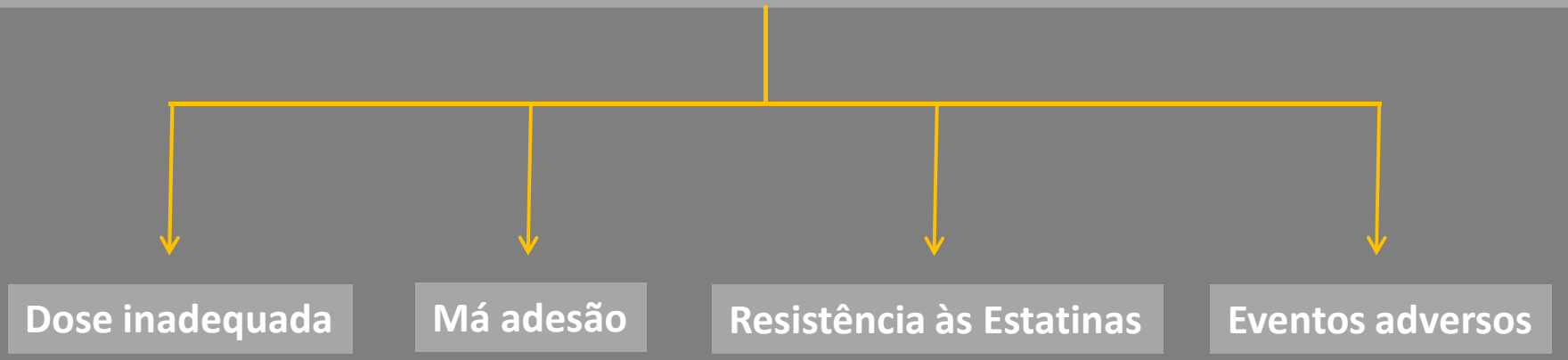
Estudos Prospectivos com Estatinas
Risco Residual Elevado



Curr Atheroscler Rep. 2012 February ; 14(1): 1–10

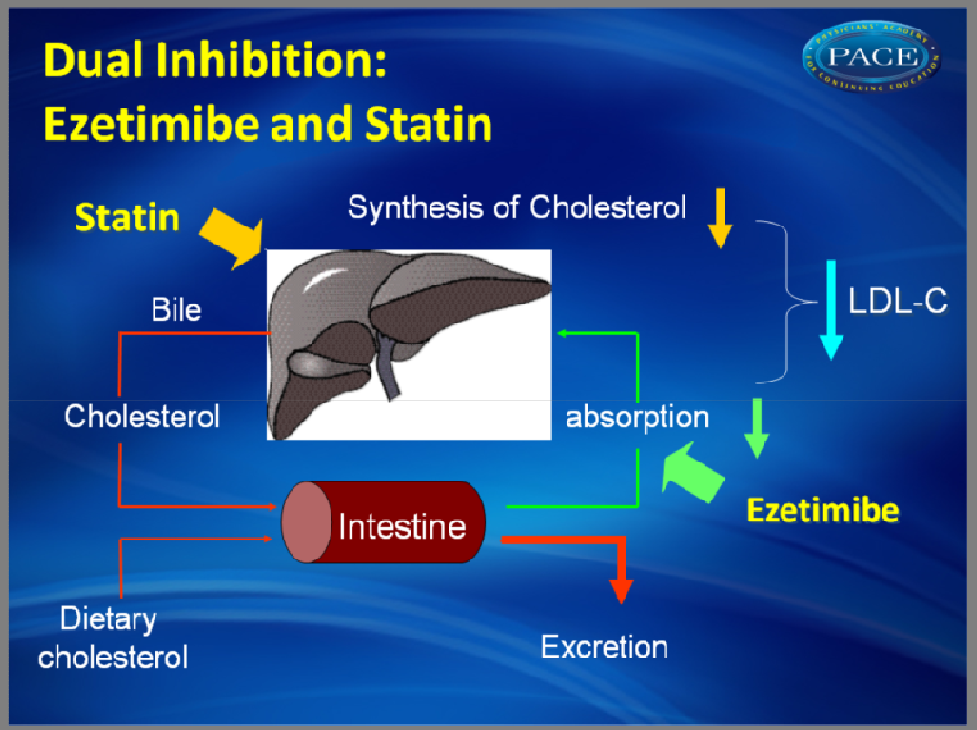
Risco residual elevado
Necessidade de novas terapias

1. **A despeito da redução significativa da tx de eventos com Estatinas (30-40%), o risco residual permanece elevado.**
2. **Número marcante de pacientes com hipercolesterolemia não alcança níveis adequados de colesterol com Estatinas.**
3. **Estima-se que na Europa e Canadá 50% dos pacientes com hipercolesterolemia não estão com LDL-C dentro das "metas".**



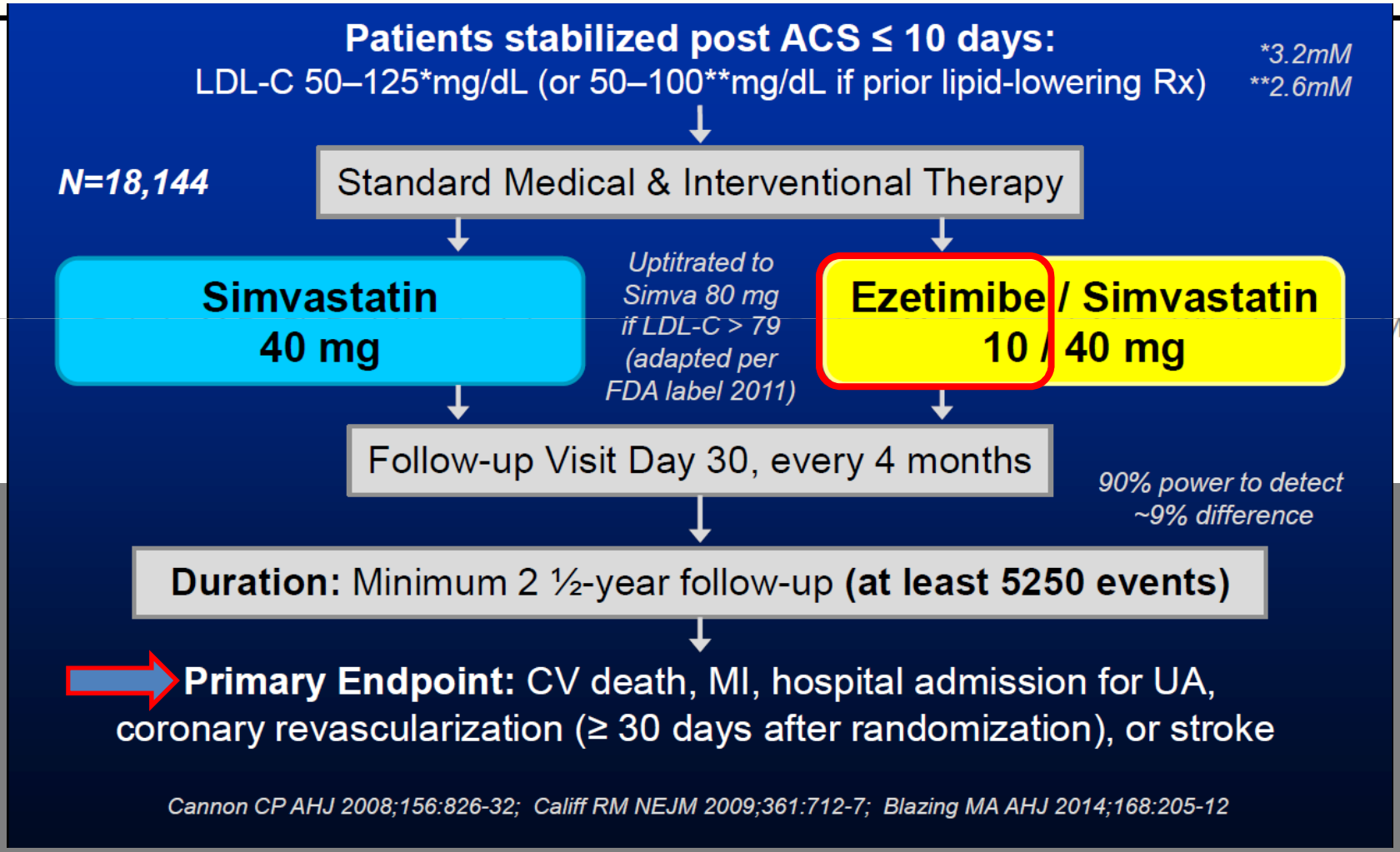
JACC Vol. 62, No. 16, 2013

Qual o real papel do ezetimibe?

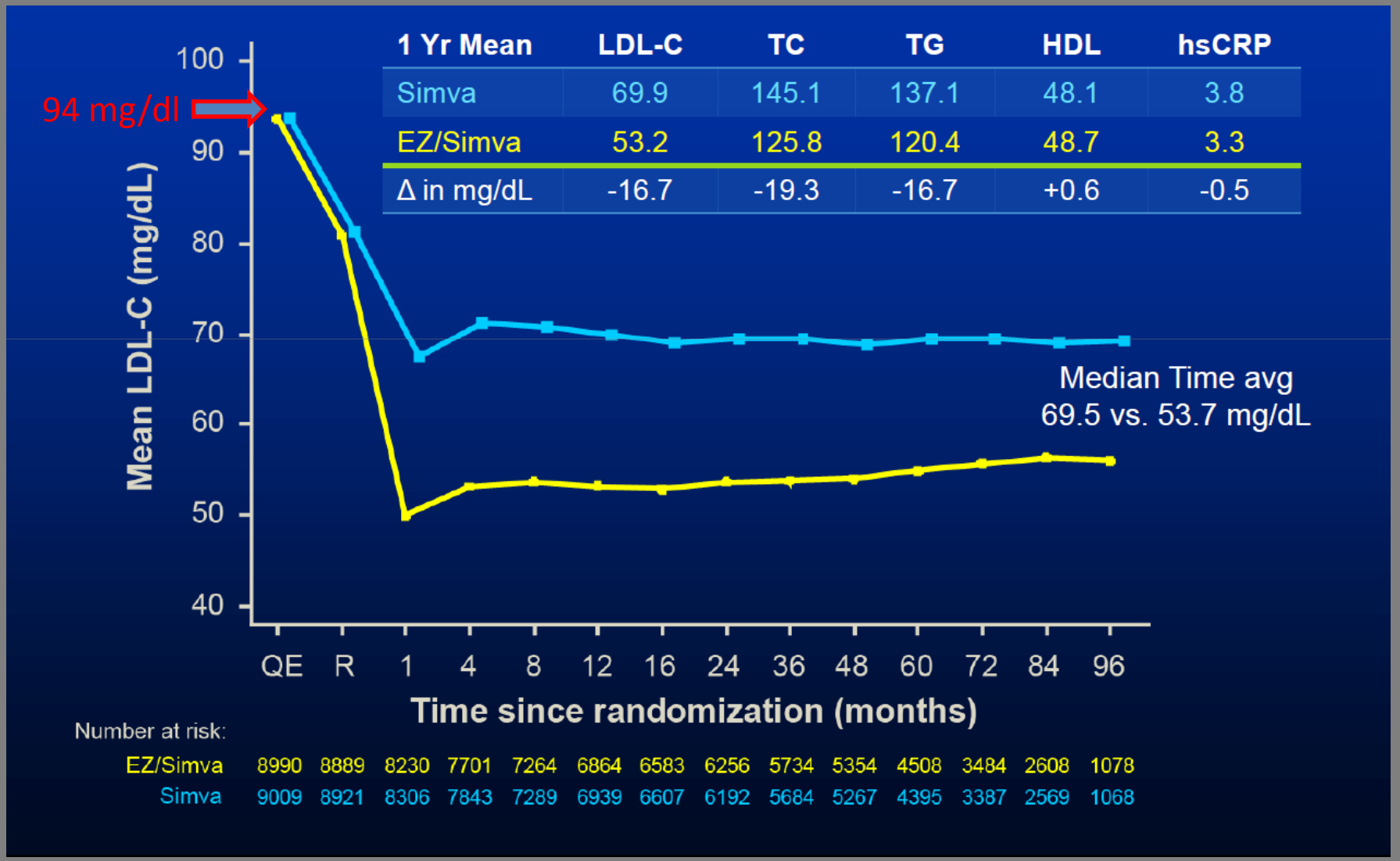


- Seletivamente, redução a absorção de colesterol na luz intestinal-Inibe a enzima NPC1L1
- Reduz a oferta de colesterol no fígado
- Aumenta a expressão de LDL-R na superfície dos hepatócitos
- Reduz colesterol sérico em 18-20%

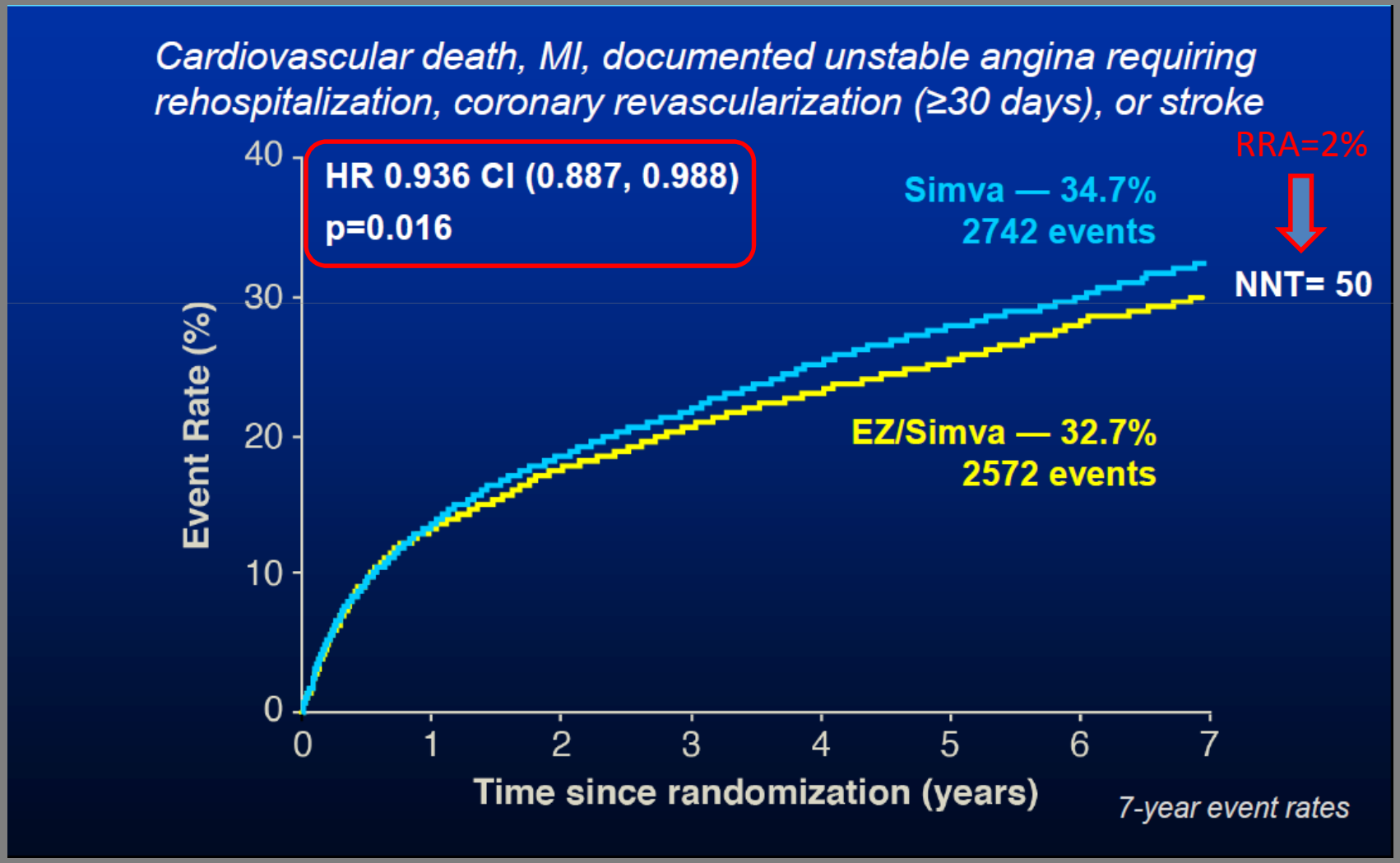
The NEW ENGLAND JOURNAL of MEDICINE



Alterações do LDL-C e Lípides



IMPROVE IT
Desfecho Primário



Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11
Coronary revascularization ≥30 days after randomization	1793 (23.4)	1690 (21.8)	0.95 (0.89–1.01)	0.11
Urgent coronary revascularization ≥30 days after randomization	626 (8.6)	510 (7.0)	0.81 (0.72–0.91)	0.001
Any revascularization ≥30 days after randomization	1962 (25.6)	1871 (24.2)	0.96 (0.90–1.02)	0.18
Hospitalization for unstable angina	148 (1.9)	156 (2.1)	1.06 (0.85–1.33)	0.62
Other prespecified end points				
Death from cardiovascular causes, MI, or stroke	1704 (22.2)	1544 (20.4)	0.90 (0.84–0.96)	0.003
Major vascular events: death from coronary heart disease, MI, stroke, or coronary revascularization ≥30 days after randomization‡	2685 (34.0)	2498 (31.9)	0.928 (0.88–0.98)	0.007

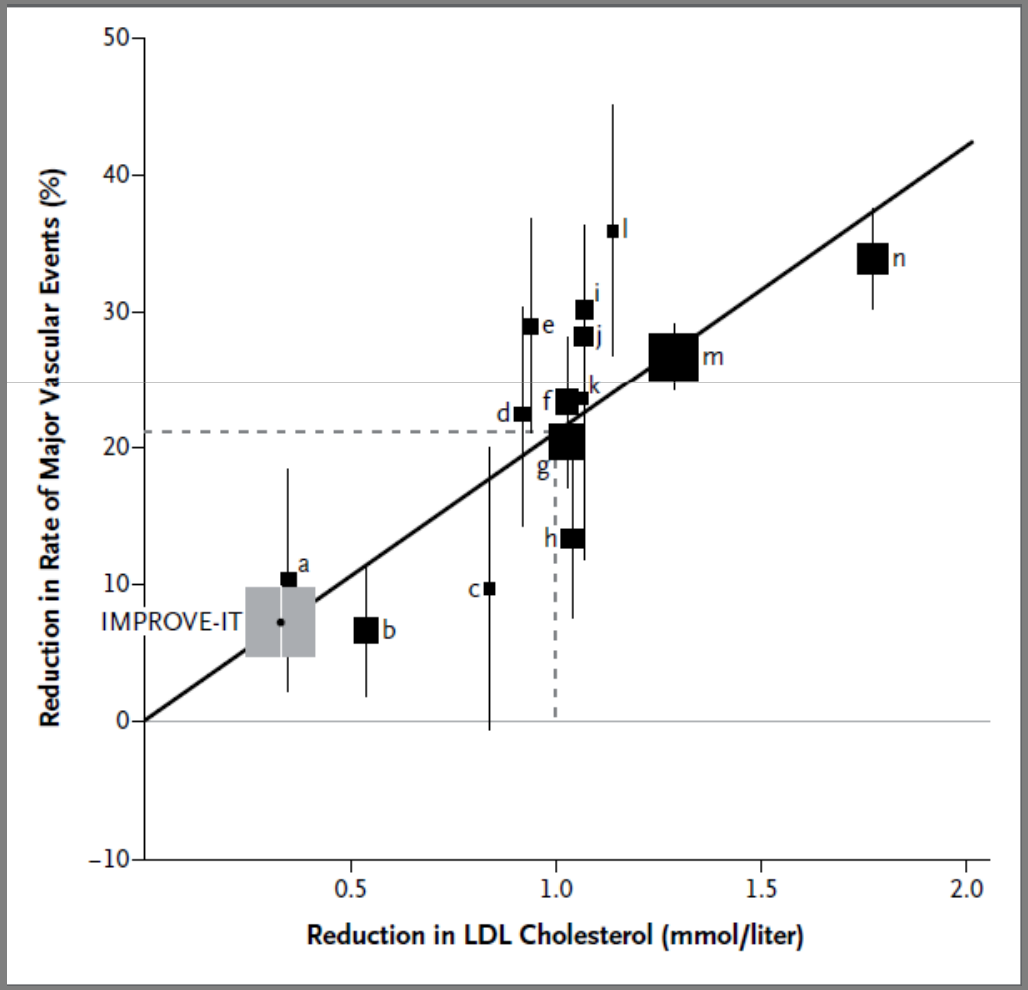
Segurança da Associação Estatina + Ezetimibe

Table 3. Prespecified Safety End Points.*

End Point	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3× ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5× ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

N Engl J Med 2015;372:2387-97

Redução de Risco CV proporcional à redução do Colesterol



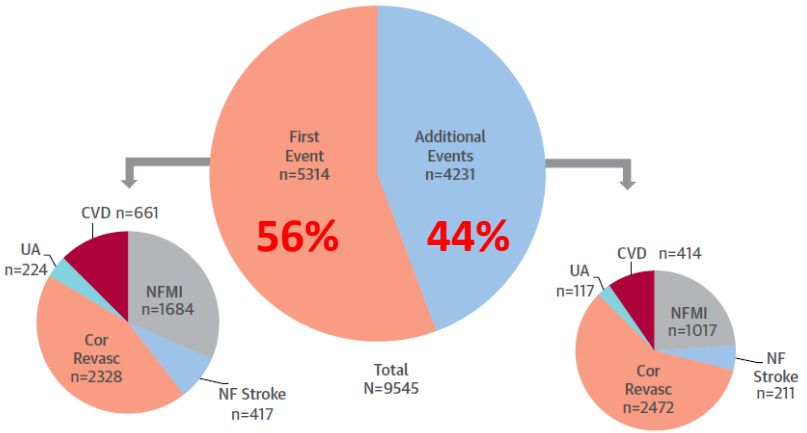
N Engl J Med 2015;372:2387-97

Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome

The IMPROVE-IT Trial

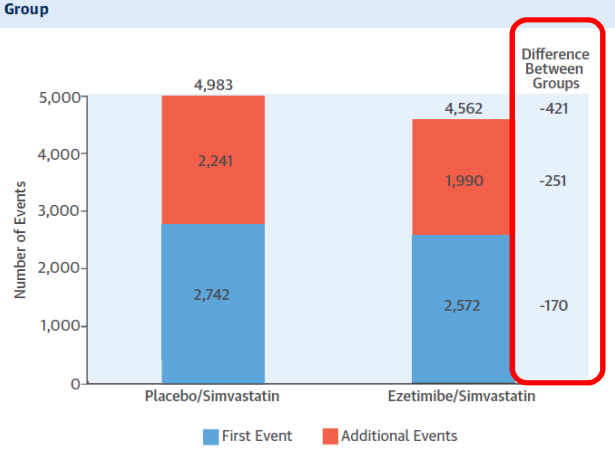
Sabina A. Murphy, MPH,[a] Christopher P. Cannon, MD,[a] Michael A. Blazing, MD,[b] Robert P. Giugliano, MD,[a] Jennifer A. White, MS,[b] Yuliya Lokhnygina, PhD,[b] Craig Reist, PhD,[b] KyungAh Im, PhD,[a] Erin A. Bohula, MD, DPhil,[a] Daniel Isaza, MD,[c] Jose Lopez-Sendon, MD,[d] Mikael Dellborg, MD,[e] Uma Kher, PhD,[f] Andrew M. Tershakovec, MD, MPH,[f] Eugene Braunwald, MD[a]

FIGURE 1 Number of First and Subsequent Primary Endpoint Events, Overall and by Component



Overall, a similar proportion of first and additional events were stroke (7.8% vs. 5.0%, respectively), unstable angina (4.2% vs. 2.8%, respectively), and cardiovascular death (12.4% vs. 9.8%, respectively). There were proportionately fewer MIs (24.0% vs. 31.7%, respectively) and proportionately more revascularizations (58.4% vs. 43.8%, respectively) among the additional events than among the first events. CVD = cardiovascular death; Revasc = revascularization; MI = myocardial infarction; NF = nonfatal; UA = unstable angina.

CENTRAL ILLUSTRATION First, Additional, and Total Primary Endpoint Events During Follow-Up by Randomization Group



Murphy, S.A. et al. J Am Coll Cardiol. 2016; 67(4):353-61.

The first occurrence of the primary endpoint was significantly reduced in the ezetimibe/simvastatin group compared to that in the placebo/simvastatin group (HR: 0.936; 95% CI: 0.887 to 0.988; p = 0.016), as were additional events (RR: 0.88; 95% CI: 0.79 to 0.98) and total events (RR: 0.91; 95% CI: 0.85 to 0.97; p = 0.007).

J Am Coll Cardiol 2016;67:353–61

Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome

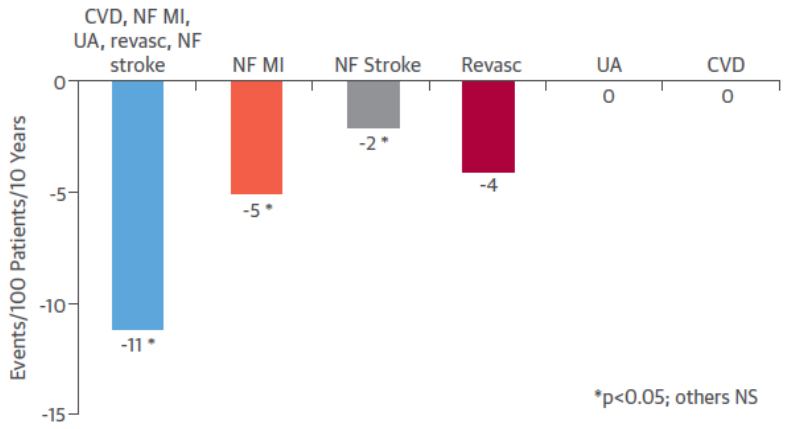
The IMPROVE-IT Trial

Sabina A. Murphy, MPH,[a] Christopher P. Cannon, MD,[a] Michael A. Blazing, MD,[b] Robert P. Giugliano, MD,[a] Jennifer A. White, MS,[b] Yuliya Lokhnygina, PhD,[b] Craig Reist, PhD,[b] KyungAh Im, PhD,[a] Erin A. Bohula, MD, DPhil,[a] Daniel Isaza, MD,[c] Jose Lopez-Sendon, MD,[d] Mikael Dellborg, MD,[e] Uma Kher, PhD,[f] Andrew M. Tershakovec, MD, MPH,[f] Eugene Braunwald, MD[a]

FIGURE 3 Total Events During Follow-Up by Randomization Group for the Primary and 3 Pre-Specified Secondary Endpoints

Total events were consistently lower in the ezetimibe/simvastatin group for the 3 pre-specified secondary endpoints, as well as for the exploratory endpoint of CV death, MI, or stroke. CHD = coronary heart disease death; CV = cardiovascular; other abbreviations as in Figure 1.

FIGURE 5 Risk Differences for 100 Patients Treated for 10 Years With Ezetimibe/Simvastatin for the Components of the Primary Endpoint



For every 100 patients treated for 10 years, 11 total primary endpoint events were prevented with ezetimibe plus simvastatin. Abbreviations as in Figure 1.

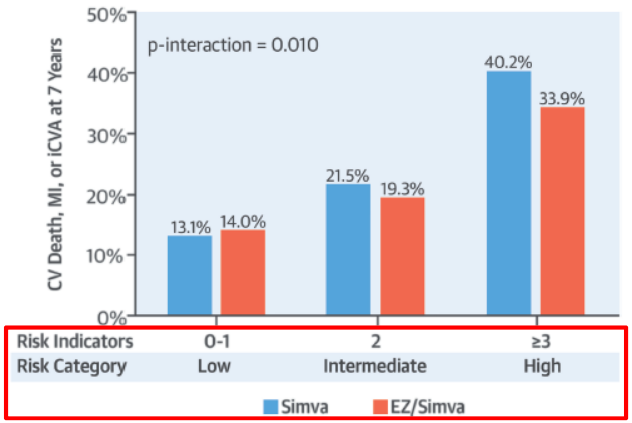
J Am Coll Cardiol 2016;67:353–61

Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention

Erin A. Bohula, MD, DPHIL,[a] David A. Morrow, MD, MPH,[a] Robert P. Giugliano, MD, SM,[a] Michael A. Blazing, MD,[b] Ping He, MS,[a] Jeong-Gun Park, PHD,[a] Sabina A. Murphy, MPH,[a] Jennifer A. White, MS,[b] Y. Antero Kesaniemi, MD, PHD,[c] Terje R. Pedersen, MD, PHD,[d] Adrian J. Brady, MD,[e] Yale Mitchel, MD,[f] Christopher P. Cannon, MD,[a] Eugene Braunwald, MD[a]

CENTRAL ILLUSTRATION TRS 2°P

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9

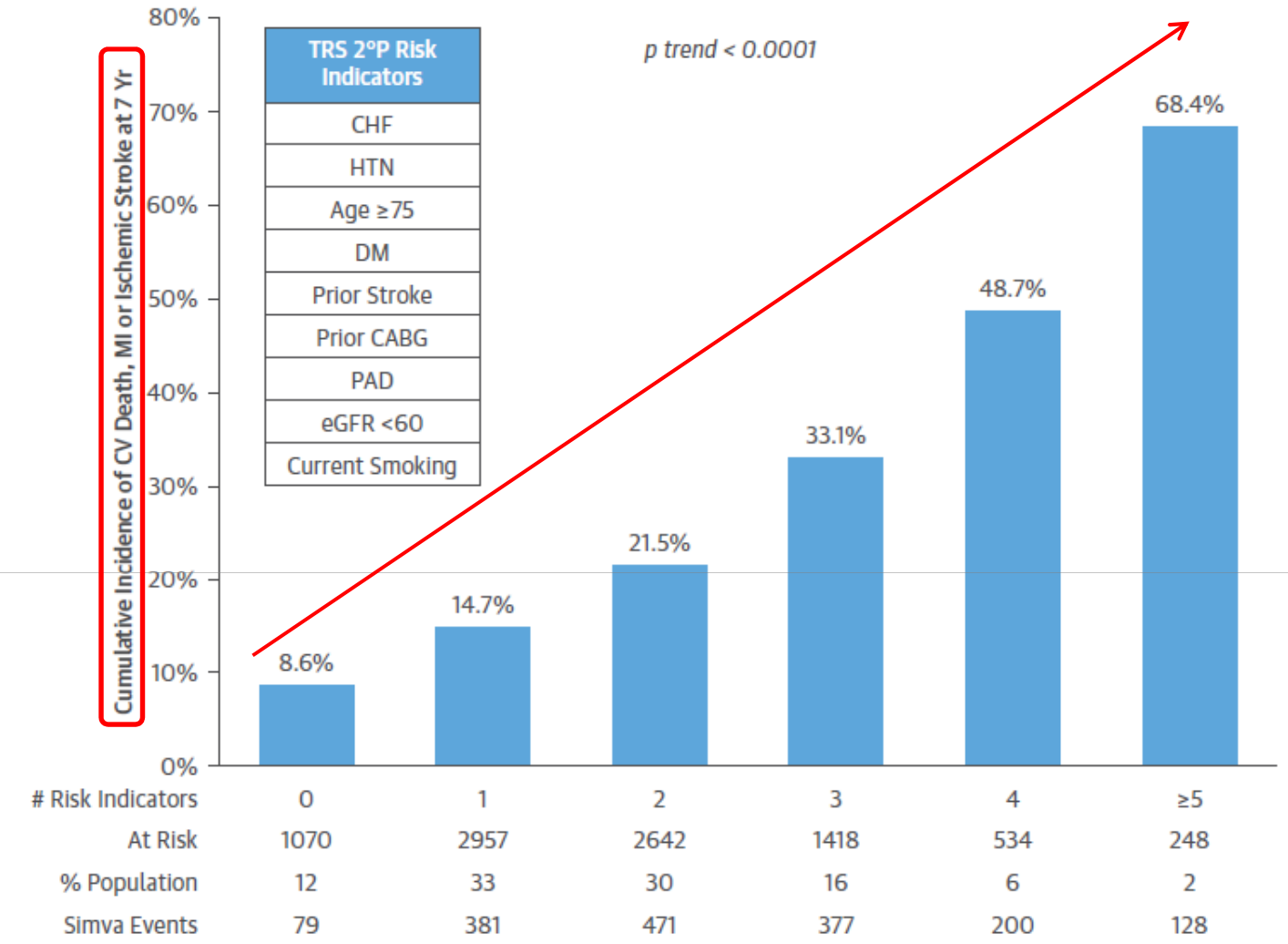


Bohula, E.A. et al. J Am Coll Cardiol. 2017;69(8):911-21.

In patients stabilized after acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the TRS 2°P, a simple risk stratification tool using 9 readily available clinical characteristics, identified a strong gradient of risk for cardiovascular death, MI, or ischemic stroke and an increasingly favorable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile. CABG = coronary artery bypass graft; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; EZ = ezetimibe; HTN = hypertension; iCVA = ischemic cerebrovascular accident; MI = myocardial infarction; PAD = peripheral artery disease; Simva = simvastatin; TRS 2°P = TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention.

J Am Coll Cardiol 2017;69:911–21

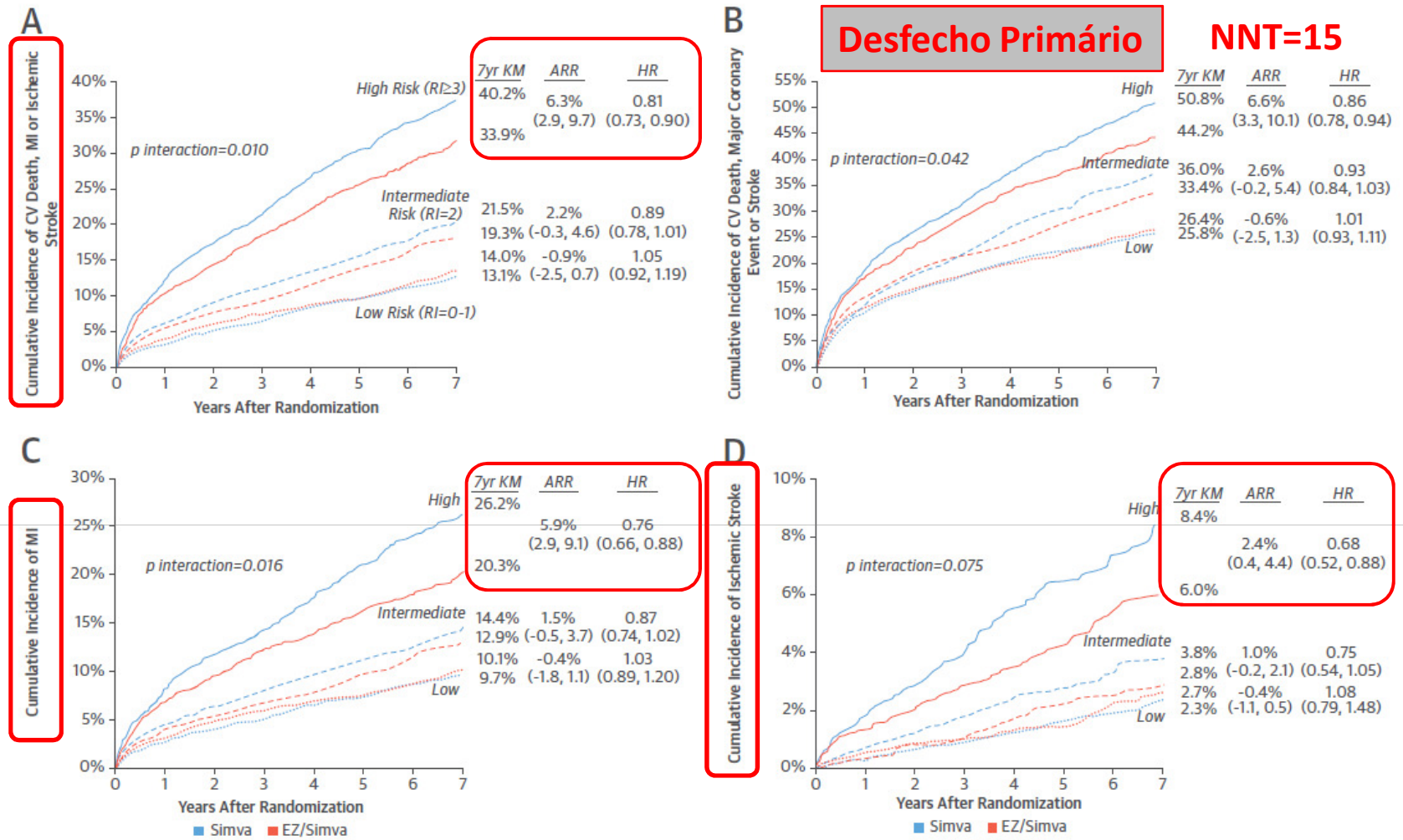
FIGURE 1 Risk Stratification of CV Death, MI, or Ischemic Stroke in the Control Arm (Placebo/Simvastatin)



The 7-year Kaplan-Meier estimates are shown. The basis of the p value is the chi-square test for trend. CABG = coronary artery bypass graft; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; MI = myocardial infarction; PAD = peripheral artery disease; Simva = simvastatin; TRS 2°P = TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention.

J Am Coll Cardiol 2017;69:911–21

FIGURE 3 Outcomes by Risk Category and Randomized Treatment



Kaplan-Meier (KM) curves stratified by low-, intermediate-, and high-risk category and randomized treatment (placebo/simvastatin [Simva] vs. ezetimibe [EZ]/simvastatin) for the first event of the following: **(A)** cardiovascular (CV) death, myocardial infarction (MI), or ischemic stroke; **(B)** CV death, MI, unstable angina, or coronary revascularization >30 days from randomization or stroke; **(C)** MI; and **(D)** ischemic stroke. The p interaction for treatment by risk category is shown. The basis of the p value is the chi-square test for trend < 0.0001 across risk groups within treatment arms for each endpoint. Hazard ratios (HR) and absolute risk reductions (ARR) with corresponding 95% confidence intervals for ezetimibe/simvastatin versus placebo/simvastatin within risk groups are shown. RI = risk indicators.

J Am Coll Cardiol 2017;69:911–21

Qual o real papel do ezetimibe? Conclusão

1. **Redução do LDL-C com ezetimibe diminui eventos cardiovasculares.**

2. **Há redução incremental de risco quando adicionado à terapia com Estatinas.**

3. **A droga é segura.**

4. **Benefício modesto, mas proporcional à redução do colesterol. Pacientes com LDL-c basal mais elevado, intolerantes às Estatinas e/ou mais graves parecem ter maior benefício clínico.**