Controvèrsies en el tractament de les comorbiditats de la DM2:

Quan cal començar el tractament i quin és el seu objectiu de la hipercolesterolèmia en la DM ?

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Conflictes d´interès: Cap

Outline

1. Background T2DM
2. Controversial topics:
    - Utility of risk functions in T2DM
    - When to start lipid-lowering agents (LLA)
    - What are the objectives of treatment
    - Which LLA are indicated
3. Conclusions

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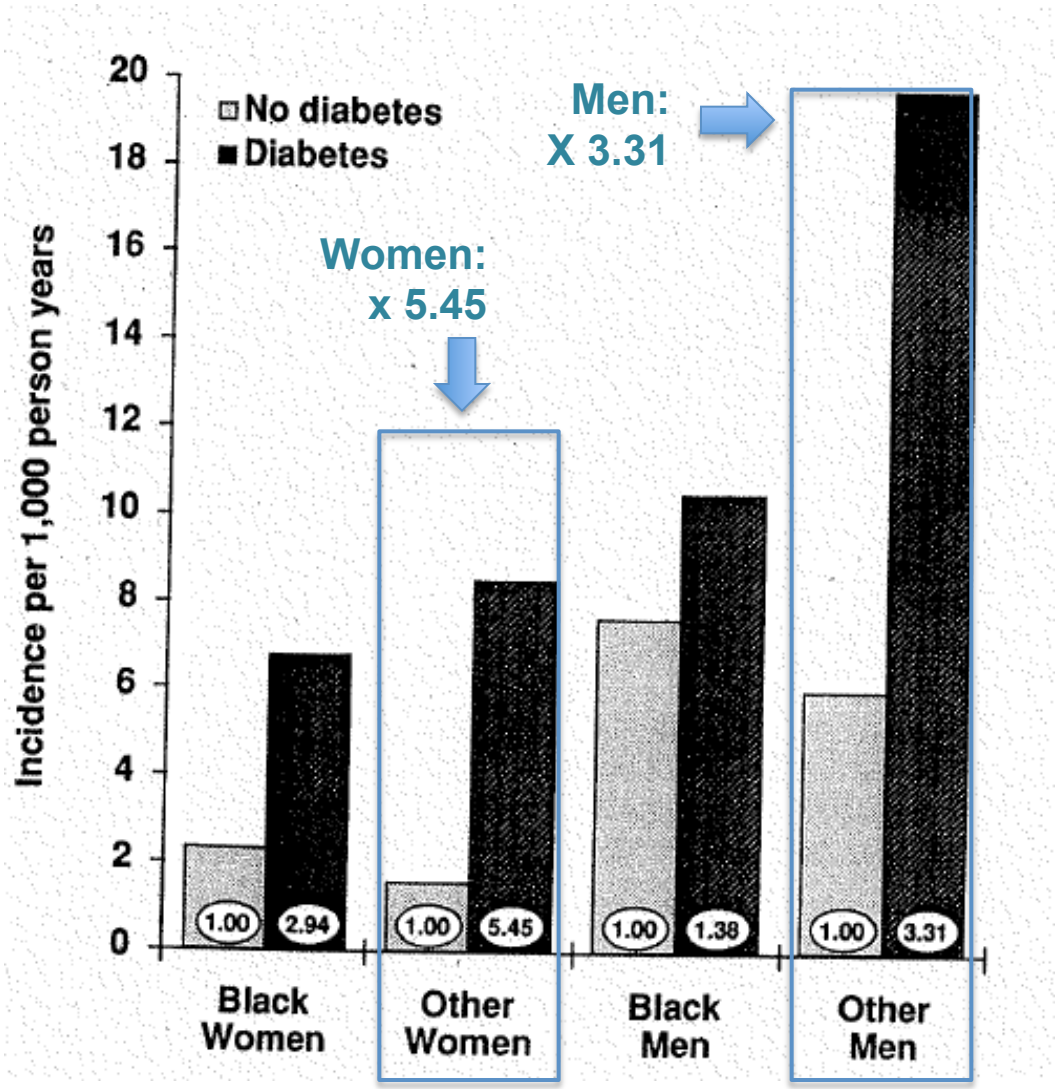
CHD in T2DM: The ARIC Study

Initiation: 1,987-89
Population-based cohort study (45-64 yrs, no previous CHD); Jackson (NC); n=13,446, black and non-black.
Follow-up: 4-7 yrs

CHD incidence adjusted for race, sex and age



Folsom AR. Diabetes Care 1997; 20:935-42.

Control of CV risk factors in T2DM at primary care in Catalonia (Spain)

Cross-sectional, retrospective, 2009, electronic clinical records, 286,791 T2DM subjects - 7.6% of a total population of 3,755,038 subjects aged 31-90 yrs). Only 63% T2DM subjects with all data available. No external quality control. Subjects with T1DM aged > 30 yrs are included. 78 % on drug therapy for DM. Diabetes duration was not accurate. A1c no standardized.

	Total	Men	Women
A1C ≤7% (n = 214,867; women = 102,063; ≥65 years = 139,161)	56.1	55.8	56.5
A1C ≤8%	79.6	79.1	80.1
A1C >10%	5	5.2	4.7
BP ≤130/80 mmHg (n = 242,842; women = 114,493; ≥65 years = 159,838)	31.7	32.0	31.4
BP ≤140/90 mmHg	63.5	63.5	63.1
TC <200 mg/dL (n = 221,623; women = 91,627; ≥65 years = 126,014)	61.3	67.3	54.6
LDL-C <100 mg/dL (n = 199,586; women = 95,426; ≥65 years = 130,529)	37.9	41.3	34.2
LDL-C <130 mg/dL	72.4	75.2	69.4
TGs <150 mg/dL (n = 195,285; women = 91,627; ≥65 years = 126,014)	39.6	38.8	40.4
BMI <30 kg/m^2 (n = 202,451; women = 94,777; ≥65 years = 130,851)	45.4	39.0	52.7
Nonsmoker (n = 195,632; women = 96,716; ≥65 years = 138,247)	65.9	45.1	88.8
Primary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <130 mg/dL (n = 145,605; women = 71,246; ≥65 years = 91,689)	12.9	13.3	12.7
Secondary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <100 mg/dL (n = 34,310; women = 12,200; ≥65 years = 27,386)	12.1	13.3	9.9

Vinagre I. Diabetes Care 2012; 35:4774-9..

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   - **Utility of risk functions in T2DM**
   - **When to start lipid-lowering agents (LLA)**
   - **What are the objectives of treatment**
   - **Which LLA are indicated**
3. **Conclusions**

Strategies to tackle with this issue

Epidemiological studies

Risk functions /categories of CV risk (calibrated)

Therapeutic guidelines ("EXPERT OPINIONS", Evidence-based ?, cost-effectiveness ?)

Risk functions in Spain

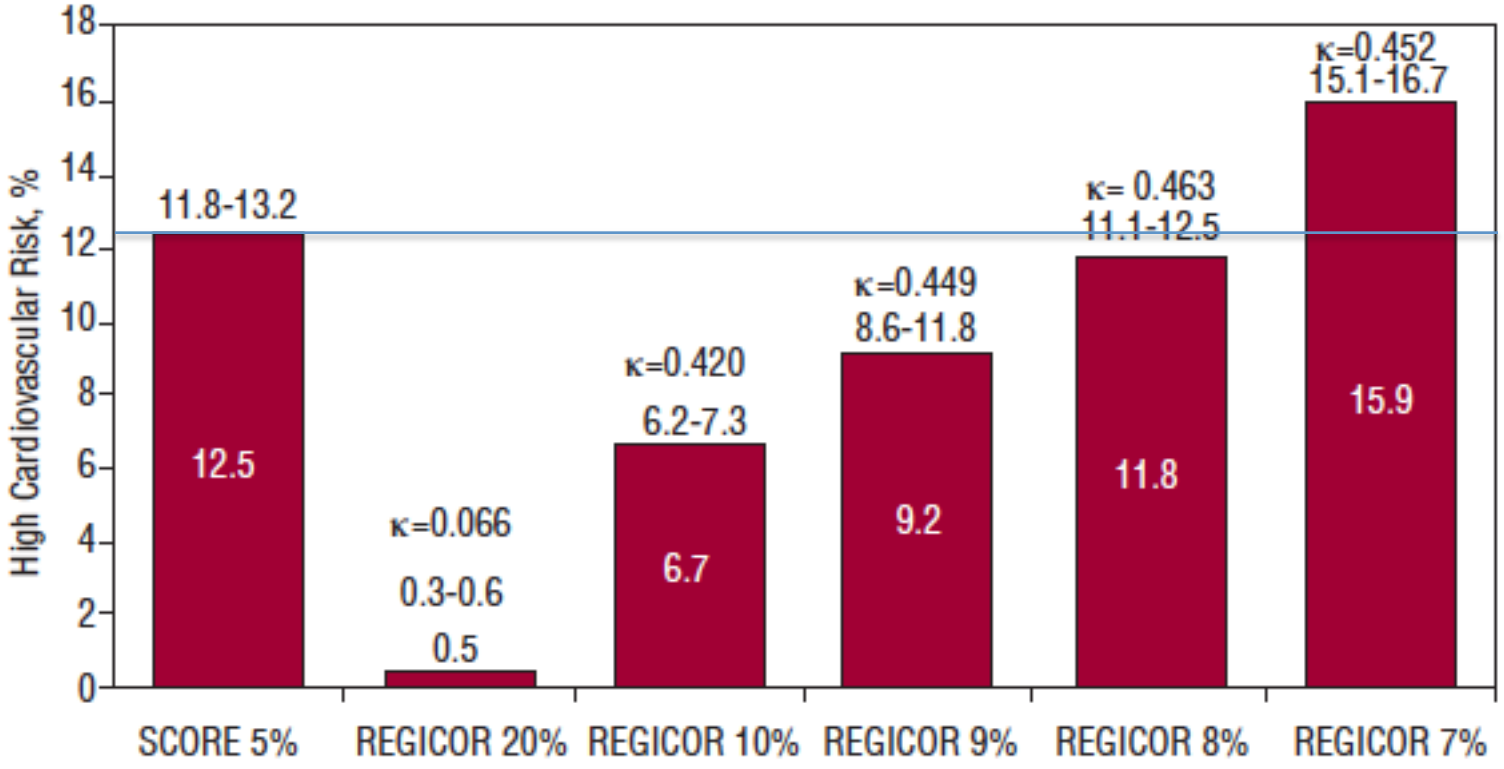
	Original Framingham	Calibrated REGICOR	SCORE
Age range to which it can be applied	35-74 years	35-74 years	40-65 years
Type of event considered	Morbidity and mortality	Morbidity and mortality	Mortality
Events considered	AMI, fatal or nonfatal; angina; silent AMI	AMI, fatal or nonfatal; angina; silent AMI	Death from coronary disease, stroke, peripheral vascular disease, heart failure, dissecting aortic aneurysm, and other
Data acquisition methodology	Cohort study	Calibration of a function based	Cohort study
Population from which relative risk was obtained	United States	United States	2.3%, Spain; 39.7%, s outhern and central Europe; 58%, northern Europe
Population from which baseline risk was obtained for the function for low-risk areas	–	Spain	6.1%, Spain; 93.9%, Italy, Belgium, and France (men only)
Assesses diabetic patients	Yes	Yes	No
Data on HDL-C used	Yes	Yes	No
Validated for Spain	Yes	Yes	No

AMI, acute myocardial infarction; HDL-C indicates high-density lipoprotein cholesterol.
Adapted from Ramos et al.[35]

ONLY applicable for PRIMARY PREVENTION !!!!!!!!

Agreement between REGICOR AND SCORE IN HIGH CV RISK (I)

Valencian primary care, 8,942 subjects (40-65 yrs) with a lipid profile and no CVD, 322 with diabetes



Gil-Guillén V. Rev Esp Cardiol 2007; 60:1042-1050.

Agreement between REGICOR AND SCORE IN HIGH CV RISK (II)

Valencian primary care, 8,942 subjects (40-65 yrs) with a lipid profile and no CVD, 322 with diabetes

Classification SCORE / REGICOR	High risk with SCORE but not with REGICOR	High risk with REGICOR but not with SCORE
N	711	198
Pts. with DM	191	0

191/322 = 59 % of subjects with DM not classified as having high CV risk with REGICOR

Gil-Guillén V. Rev Esp Cardiol 2007; 60:1042-1050.

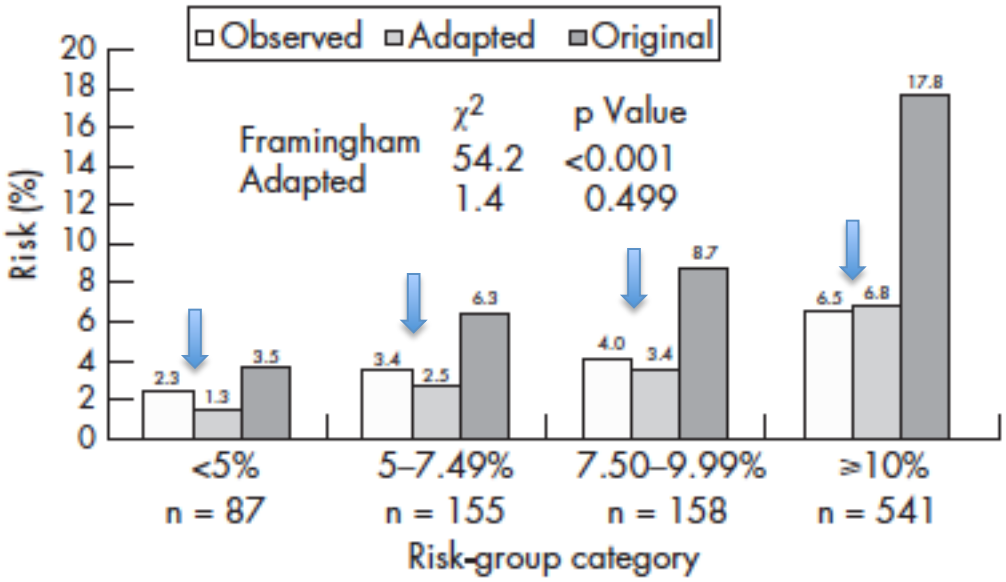
Validity of the Framingham–REGICOR function in DM: The VERIFICA study

N= 5,732 (4,933 from a retrospective sample from 67 Spanish primary care willing to participate; 1,480 from a population randomly selected prospective cohort - 1,995-98)
Follow-up 5 yrs
Sample size calculated for a likely observed CHD rate of 10 %.
Final observed CHD rates:

- **Men: 4.0 %**
- **Women: 1.7 %**
- **All non-diabetics: 2.5 %**
- **All diabetics: 5.3 %**

REGICOR is UNDERPOWERED

Data for all diabetics included

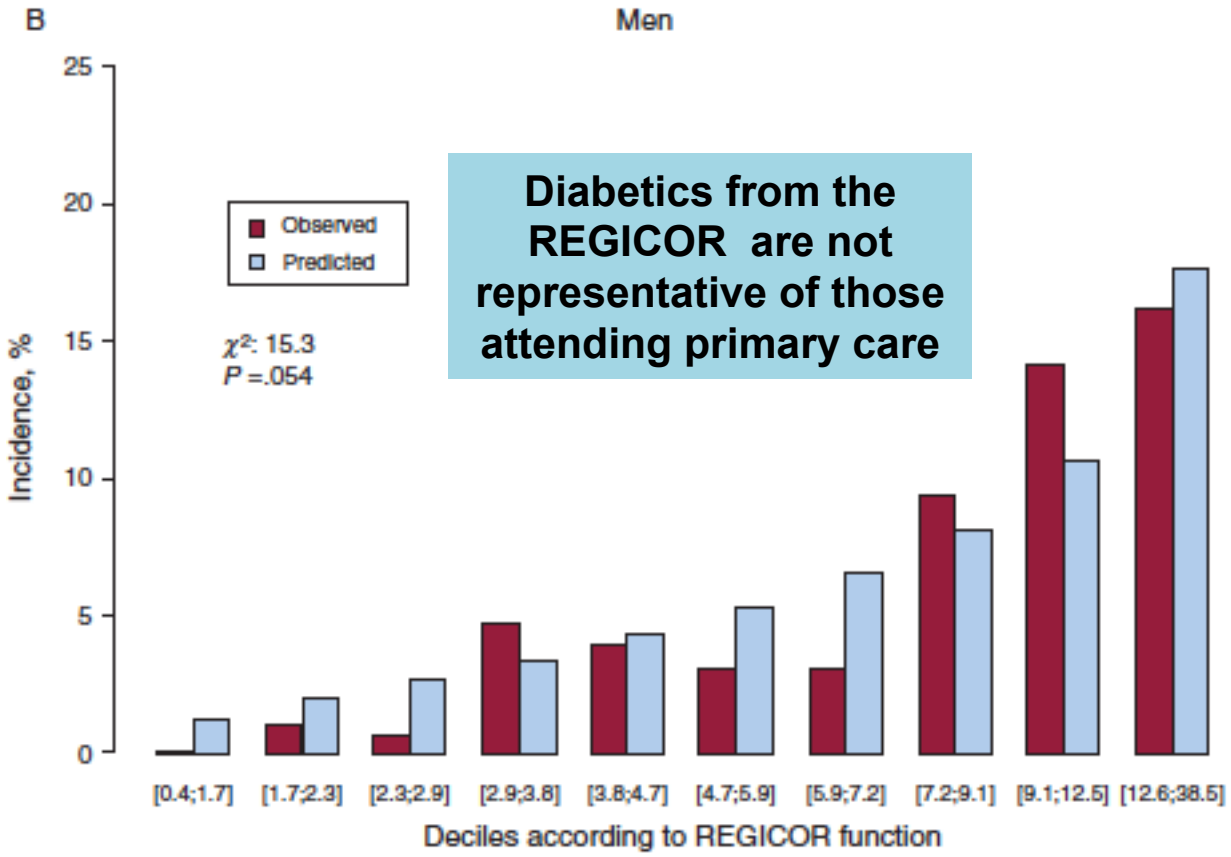


Framingham original function

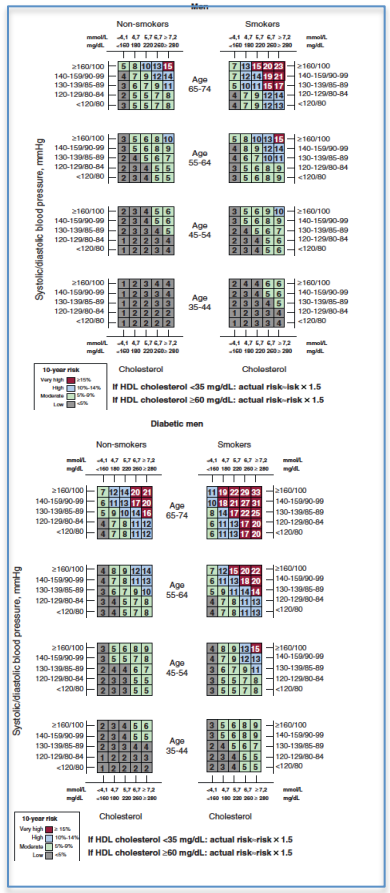
Marrugat J. J Epidemiol Community Health 2007; 61:40-47.

REGICOR: Validity for a 10-yr CVD risk calculation

N = 3,848 people from Girona (randomly selected from 1991 and 2001 census). Mean follow-up 7.1(2.8) yrs. No history of previous CVD. Diabetics: 537 (14 %); on drug treatment for DM: 158 (29 %)

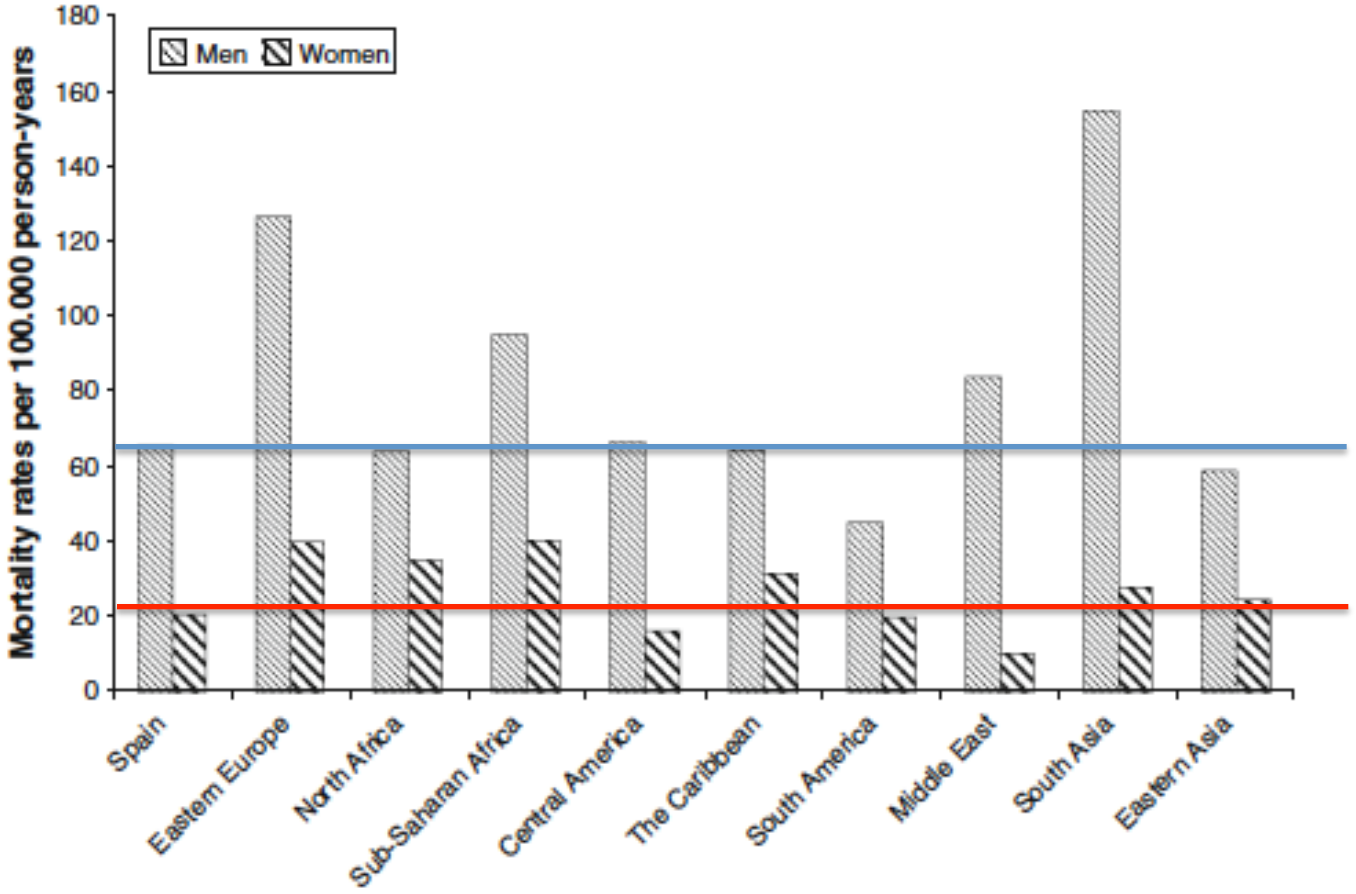


Diabetics from the REGICOR are not representative of those attending primary care



Marrugat J. Rev Esp Cardiol 2011; 64:385-394.

Birthplace and CVD mortality in Spain



Age-adjusted CVD mortality (20-65 yrs, 2001-2005) in residents in Spain

Data from Spanish Death Register and Municipal population Register (2,001-5): NIE

Regidor E. Eur J Epidemiol 2009; 24:503-512

Specific CV risk factors in T2DM not considered in REGICOR

Retinopathy Predicts Cardiovascular Mortality in Type 2 Diabetic Men and Women

Juutilainen A. Diabetes Care 2007;30:292-299

Adjusted HR for CHD mortality and PDR: men: 2.5; women:5.0

Microalbuminuria and Cardiovascular Autonomic Dysfunction Are Independently Associated With Cardiovascular Mortality: Evidence for Distinct Pathways

The Hoorn Study

Beijers HJBH. Diabetes Care 2009;32:1698-1703

Adjusted HR for CVD mortality: Micro: 2.1; CAN 1.7

Statins: Primary prevention in T2DM: CARDS

DB-RCT (n=2,838) with T2DM (40-75 yrs.), no previous CVD, LDL-C < 160, TGs < 600 and at least one of these: DR, micro-albuminuria, current smoking or HT.
Primary end-point (PEP): CHD events, coronary revascularization or stroke
Placebo vs. 10 mg atorvastatin
Intended follow-up: 5 yrs., STOPPED 2 YEARS EARLIER (median follow-up: 3.9 yrs.)

2,838 (64.5 yrs., LDL-C 116, BMI 29, DR 30%, albuminuria 17%, smokers 22%, HT 84%, A1c 7.8, T2DM duration 8 yrs., only on diet 16%)

Placebo (1,410)

10 mg atorvastatin (1,428)

127 pts with ≥ 1 major CV event

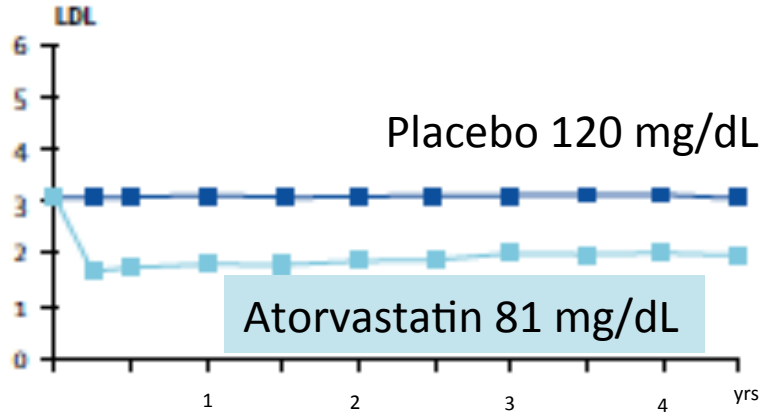
83 pts with ≥ 1 major CV event

37 % reduction in PEP
36 % reduction in acute CHD
48 % reduction in stroke

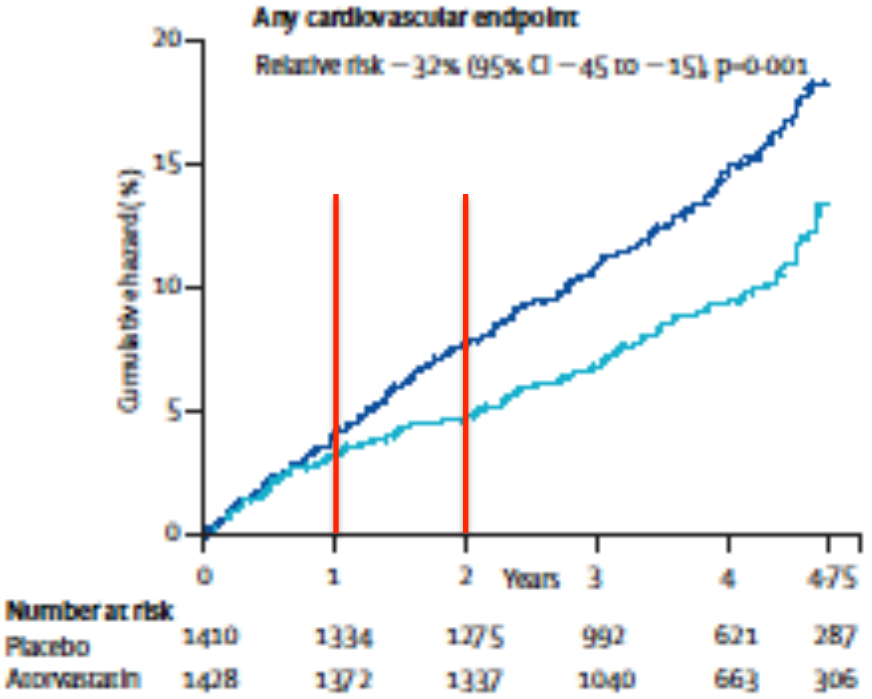
10 mg/d atorvastatin prevent at least 37 major CV events per 1000 pts with T2DM treated for 4 yrs.

Colhoun HM. Lancet 2004; 364:685—96.

Statins: Primary prevention in T2DM: CARDS



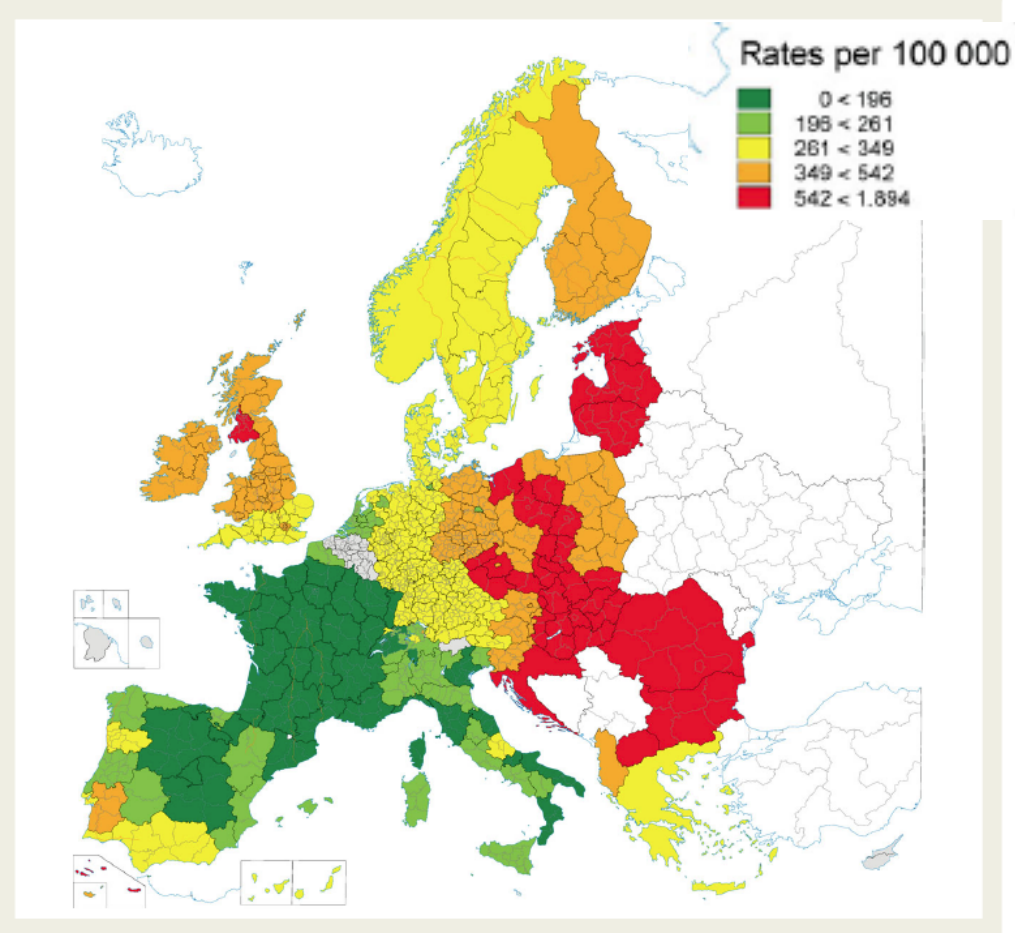
40 % reduction in LDL-C with atorvastatin



"The debate whether all people with this disorder warrant statin treatment should be now focus on whether any patients are at sufficiently low risk for this treatment to be withheld" (2,004)

Colhoun HM. Lancet 2004; 364:685—96.

CVD mortality gradient in Europe

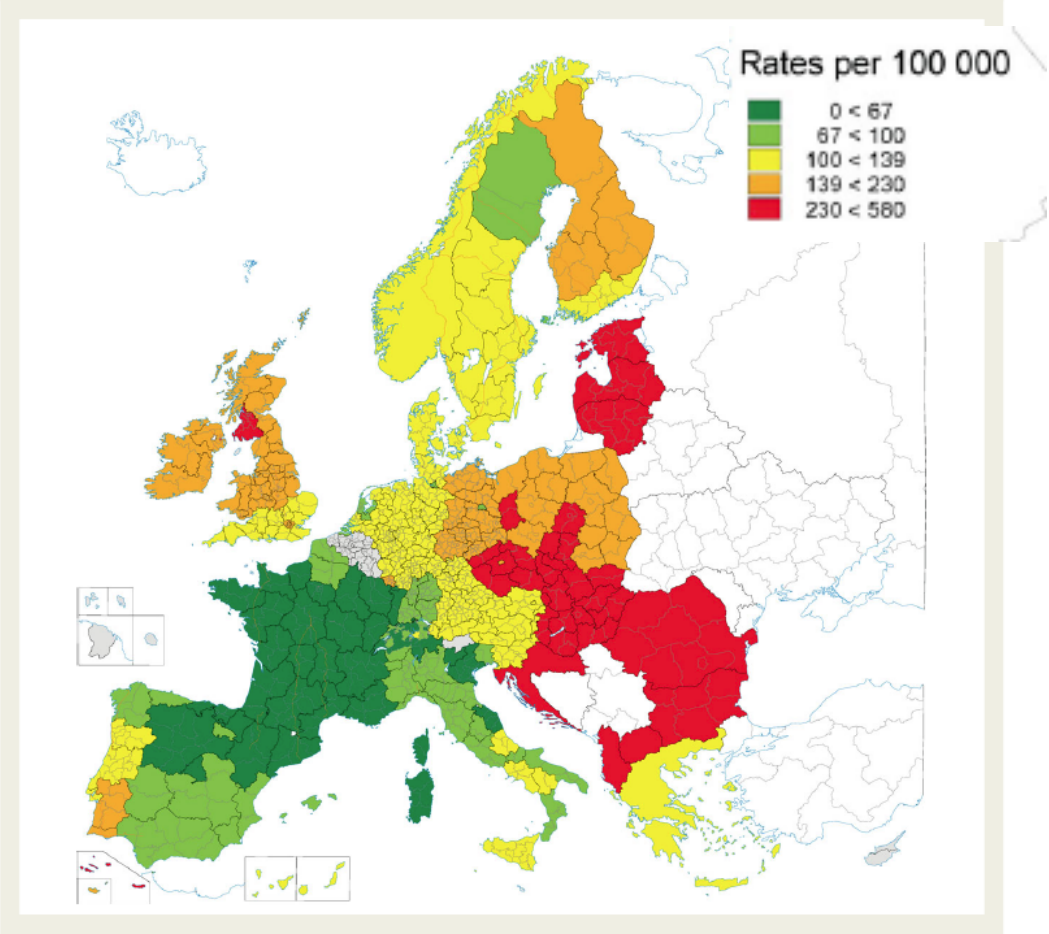


Age-standardized rates in MEN (45-74 yr)

Data from Eurostat and National Statistical Offices (2,000)

Müller-Nordhorn J. Eur Heart J 2008; 29:1316-1326

CVD mortality gradient in Europe



Age-standardized rates in WOMEN (45-74 yr)

Data from Eurostat and National Statistical Offices (2,000)

Müller-Nordhorn J. Eur Heart J 2008; 29:1316-1326

Statins: Primary prevention in Japan: MEGA

OL-RCT (n=7,832 Japanese) with TC 219-269, no previous CHD or stroke
Primary end-point (PEP): CHD events
Diet vs. diet + 10-20 mg pravastatin (20 if TC was not < 219 with 10 mg)
Mean follow-up: 5.3 yrs.

7,832 (58 yrs., CT 241, LDL-C 156, BMI 24, HT 42%
T2DM 21%,smokers 20%, about 20% with 20
pravastatin in the end of the study)

Diet (3,966)

3.2% reduction in LDL-C
LDL-C: 150 mg/dL
101 events

Diet + Pravastatin
(3,866)

18.0 % reduction in LDL-C
LDL-C: 127 mf/dL
66 events

33 % reduction in CHD events
No differences between patients
with and without T2DM

Nakamura H. Lancet 2006; 368:1155-63..

Statins: cost-effectiveness in primary prevention (general population)

Systematic review PubMed up to 1/2/2011; USA

Study, 1st Author	Year	Population	Drug Studied	Time Horizon	Outcome Measured
Prosser LA	2000	Age 35-84, LDL >159	Pravastatin	30 years	QALY
Caro JJ	2003	Age >45	Pravastatin	5 years	LYG
Pignone M	2006	45-year old men	Pravastatin	Lifetime	QALY
Pletcher MJ	2009	Age >35	All statins	30 years	QALY

Methodological differences among studies. QALY, quality adjusted life year; LYG, life year gained; LDL, low density lipoprotein cholesterol.

10-yr CHD risk
- 10 %
- 5 %

Cost-effectiveness threshold
- $70/month (€53)
- $50/month (€39)

Increase CE
- Lower price of generics
- Add indirect costs
- Lifetime calculations
- Higher cost to treat acute CV events

Decrease CE
- Adverse effects
- Non-adherence
- 10-yr calculation

Mitchell AP. BMC Research Notes 2012; 5:373

Lifetime cost-effectiveness of simvastatin (HPS, n=20.536)

HPS: Pts. with CVD or diabetes (40-80yrs old). UK. 40 mg simvastatin vs placebo for 5 yrs.

	Five year risk of major vascular event at start of treatment			
	5%	10%	20%	40%
Cost (£) per life year gained				
Age at start (years):				
35	450*	–360*	–1070*	–1610*
45	330*	–360	–940	–1240
55	400*	–210	–680	–830
65	660*	50	–380	–450
75	1180*	450	–40	–110
85	2460*	1280*	490*	310*
Cost (£) per quality adjusted† life year gained				
Age at start (years):				
35	580*	–460*	–1370*	–2060*
45	430*	–480	–1210	–1600
55	550*	–280	–900	–1070
65	930*	70	–510	–590
75	1740*	650	–50	–140
85	3740*	1870*	690*	420*

HPS collaborative group. BMJ 2006 doi:10.1136/bmj.38993.731725.BE

Cost ("PVP") of some statins in Spain

Simvastatin	EFG 40	28c	3.11-4.14 €
Atorvastatin	EFG 10	28c	4.61 €
Atorvastatin	EFG 20	28c	9.21 €
Atorvastatin	EFG 40	28c	18.42 €
Atorvastatin	EFG 80	28c	36.84 €
Metformin	EFG1000	50c	2.28 €

Data obtained on 7 Feb 2013 2012; 5:373

Reasons for not using REGICOR in clinical practice

1. It was obtained for diabetics of the general population not for those attending primary care.
2. It is underpowered and infraestimates CV risk in diabetics
3. Do not take into account new ethnics minorities
4. Do not take into account specific and non-specific CV risk factors for diabetics
5. At least in diabetics, it does not make any sense its use if results of RCTs and cost-effectiveness analyses are considered.

Strategies to tackle with this issue

Epidemiological studies

Risk functions /categories of CV risk (calibrated)

Therapeutic guidelines ("EXPERT OPINIONS", Evidence-based ?, cost-effectiveness ?)

Review of evidence (RCTs, meta-analyses)

Evidence-based Guidelines for T2DM

Cost-effectiveness analyses

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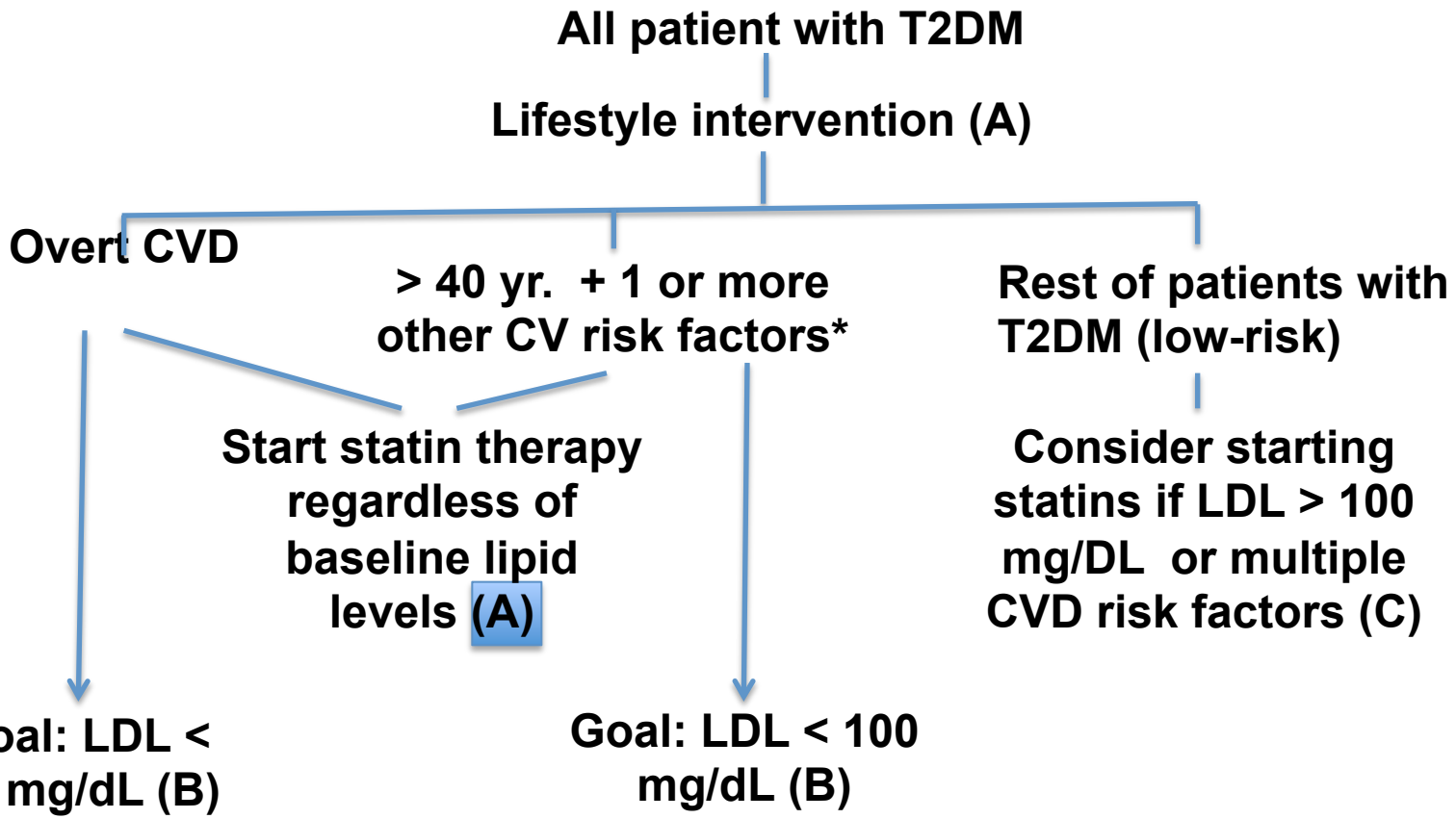
ADA: Dyslipidemia treatment

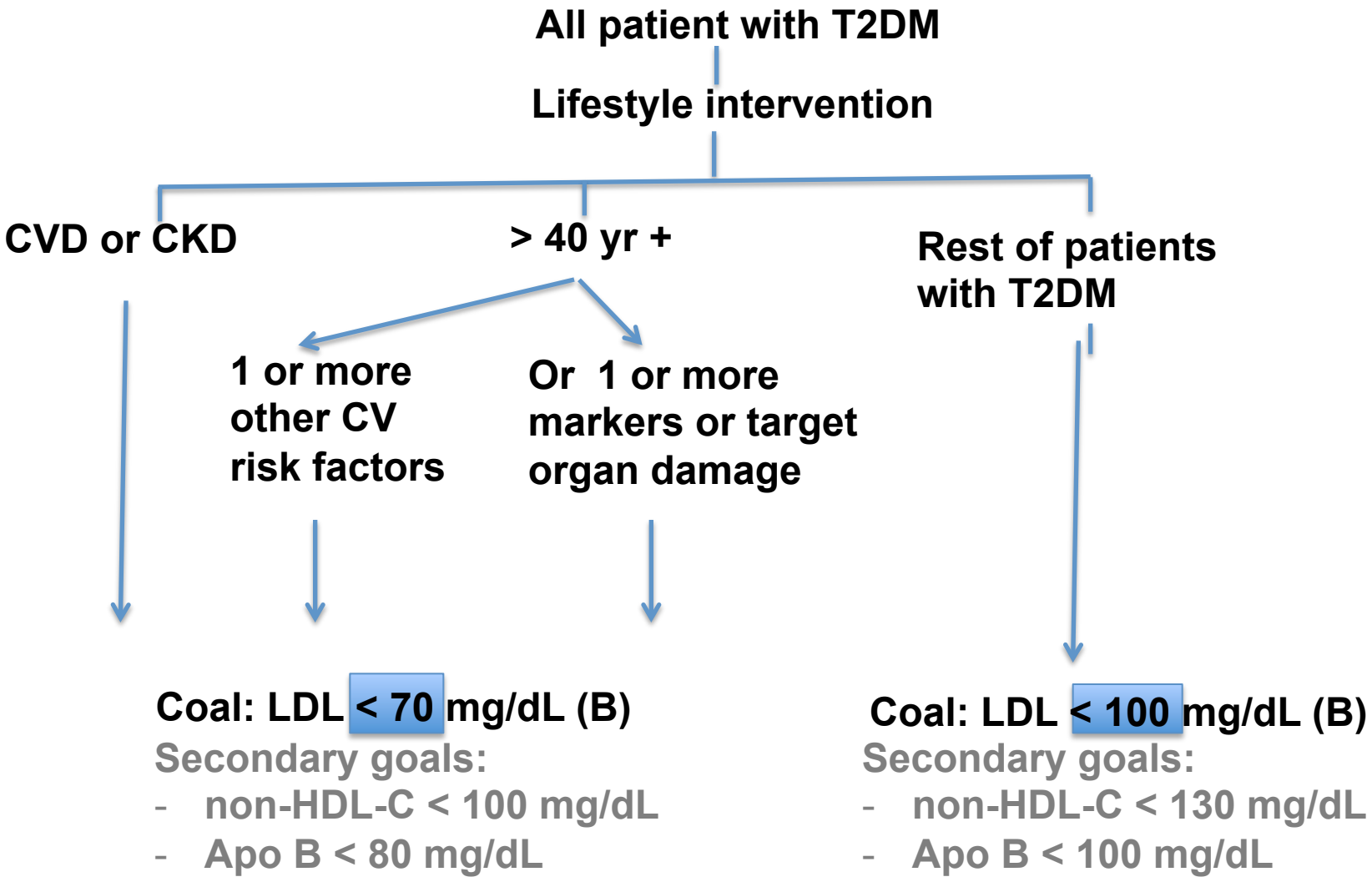


Alternative goal for statin-treated patients: ONLY reduction of 30-40% (B)

ADA. Diabetes Care 2013; 36:S11-S65

*Family history of CVD, hypertension, smoking, dyslipidemia or albuminuria

ESC/EAS: Dyslipidemia treatment



ESC/EAS guidelinesj. Eur Heart J 2011; 32:1769-1818

ADA: Dyslipidemia treatment

1.- Desirable goals (C)

- TG < 150 mg/dL
- HDL-C: men > 40; women > 50 mg/dL

BUT LDL-C goals targeted with STATINS remain the preferred strategy (A)

2.- COMBINATION THERAPY do not provide additional CV benefits above STATIN THERAPY ALONE and is not generally recommended (A)

3.- Statins are contraindicated in pregnancy

ADA. Diabetes Care 2013; 36:S11-S65

ESC/EAS: Dyslipidemia treatment

1.- “If targets are not achieved on maximally tolerated doses of STATINS, DRUGS COMBINATIONS may offer additional lowering of LDL-C but the evidence from OUTCOME studies is limited”

ESC/EAS guidelines. Eur Heart J 2011; 32:1769-1818

ESC/EAS: Dyslipidemia treatment

1.- STATIN RCTs in T2DM:
5-yr incidence of major CVD events is reduced a 20% per 38.5 mg/dL reduction in LDL-C

2.- Meta-analysis: This effect is INDEPENDENT of the initial LDL-C or other characteristics

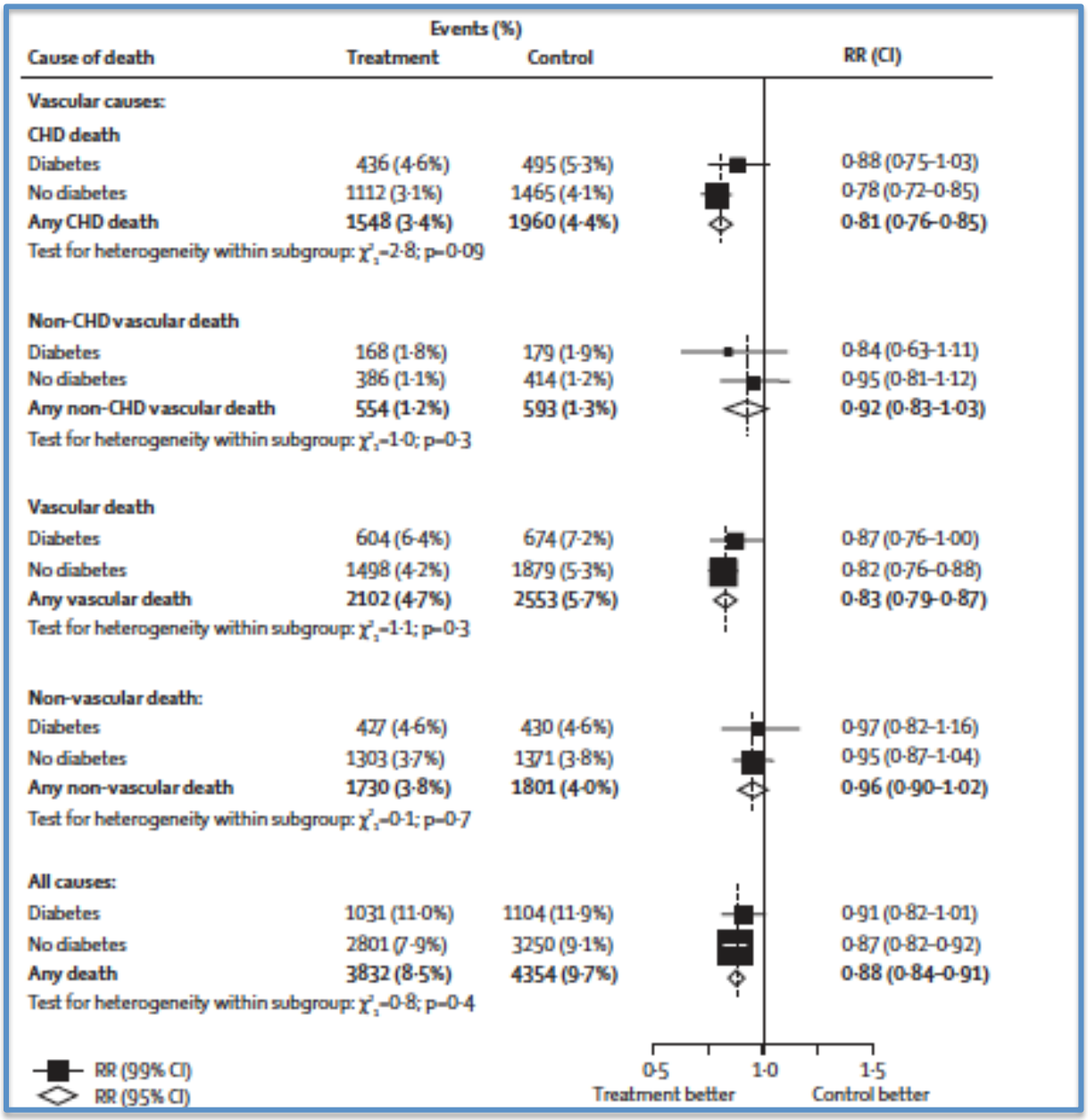
3.- Meta-analysis: Lower NNT in T2DM because the RRR is similar in subjects with and without T2DM, but the ABSOLUTE RISK is higher in T2DM.

ESC/EAS guidelines. Eur Heart J 2011; 32:1769-1818

Meta-analysis of STATINS RCTs in T2DM

1.-14 RCTs:
4S.
WOSCOPS
CARE
Post-CABG
AFCAPS/TexCAPS
LIPID
GISSI-P
LIPS
HPS
PROSPER
ALLHAT-LLT
ASCOT-LLA
ALERT
CARDS

2.- 18.686 DM subjects (1.466 T1DM) vs. 71.380 non-diabetics



CTT collaborators. Lancet 2008; 371:117-125

ESC/EAS: Dyslipidemia treatment

1.- Targeting TG and HDL-C in T2DM: FIELD study: Apo B/apoA1 ratio is as predictive of CVD events than non-HDL-C/HDL-C or TC/HDL-C ratios

2.- FIELD study

No significant 11 % reduction with FENOFIBRATE in CHD events (CHD death or non-fatal MI = primary end-point)

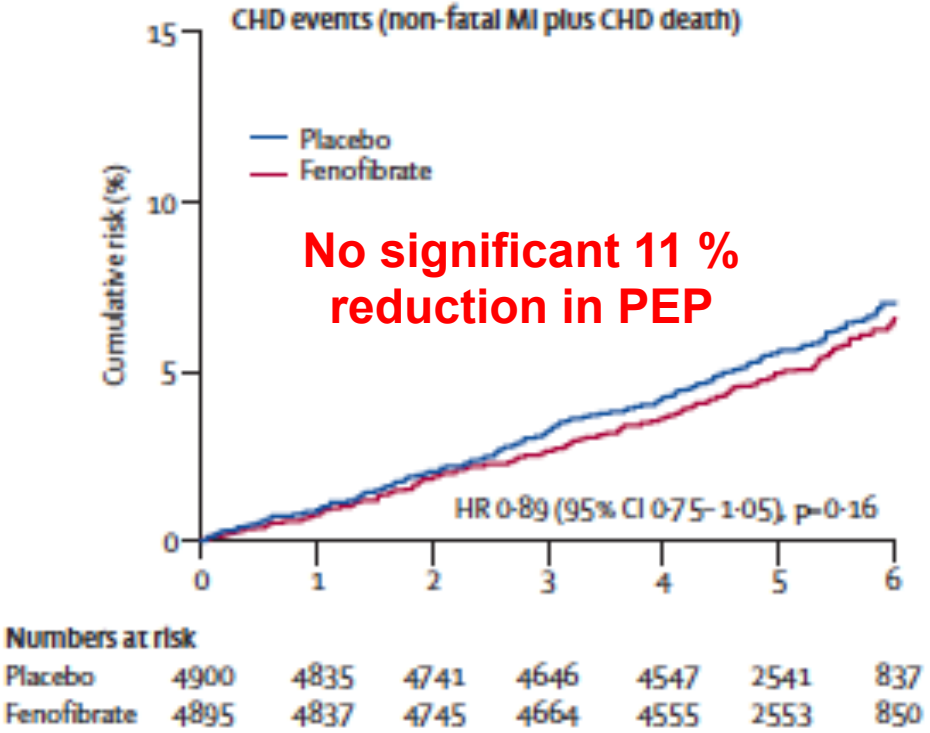
3.- FIELD study: *post-hoc analysis*

Fenofibrate reduces CVD events by 27 % if TGs > 200 mg/dL + reduced HDL-C (NNT=23)

ESC/EAS guidelines. Eur Heart J 2011; 32:1769-1818

FIELD Study

AUS, NZ, FIN. Subjects with T2DM, 50-75 yrs
Starting date: 1.998-2.000. Duration: 5 hrs.
Fenofibrate (200 mg/d, n=4.895) vs. placebo (n=4.900)
Inclusion criteria: TC 116-251 mg/dL + TC/HDL-C > 4.0 or TGs 88.5-442.5.
Exclusion. Cr > 1.47
Pts: T2DM duration: 5 yrs., BMI 29.8, BP 140/82, current smokers: 9 %, previous CVD 22 %, microvascular disease 20%, LDL-C 118 mg/dL, HDL-C 42.5 mg/d, TG 154 mg/dL, A1c: 6.9 %, diet alone: 26 %, insulin alone 6 %,
Primary end-point: CHD events (non-fatal MI+CHD death)



The FIELD study investigators. Lancet 2005; 366:1849-1861

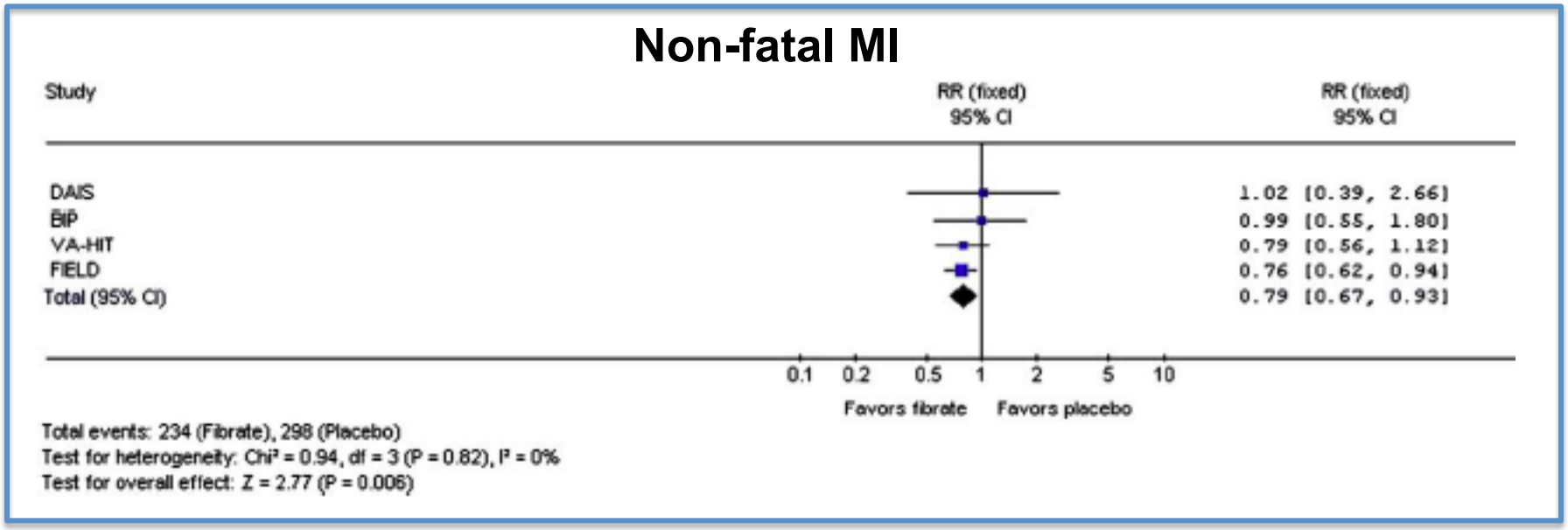
Fibrates in T2DM: Meta-analysis of6 RCTs

Meta-analysis of all long-term (> 1 yr) RCTs (fibrates vs. placebo) indexed in MEDLINE and Cochrane databases up to Dec-2007, which reported data on CVD events in subjects with DM. It also includes unpublished data.
Studies included: HHS, VA-HIT, BIP, SENDCAP, DAIS, FIELD
Statistical analysis: fixed or random effects model as appropriate

Main results:

-DO NOT IMPROVE all-cause mortality, CHD mortality, stroke or unstable angina.

- REDUCE non-fatal MI by 21 %



Sandeep A. Int J Cardiol 2010; 141:157-166

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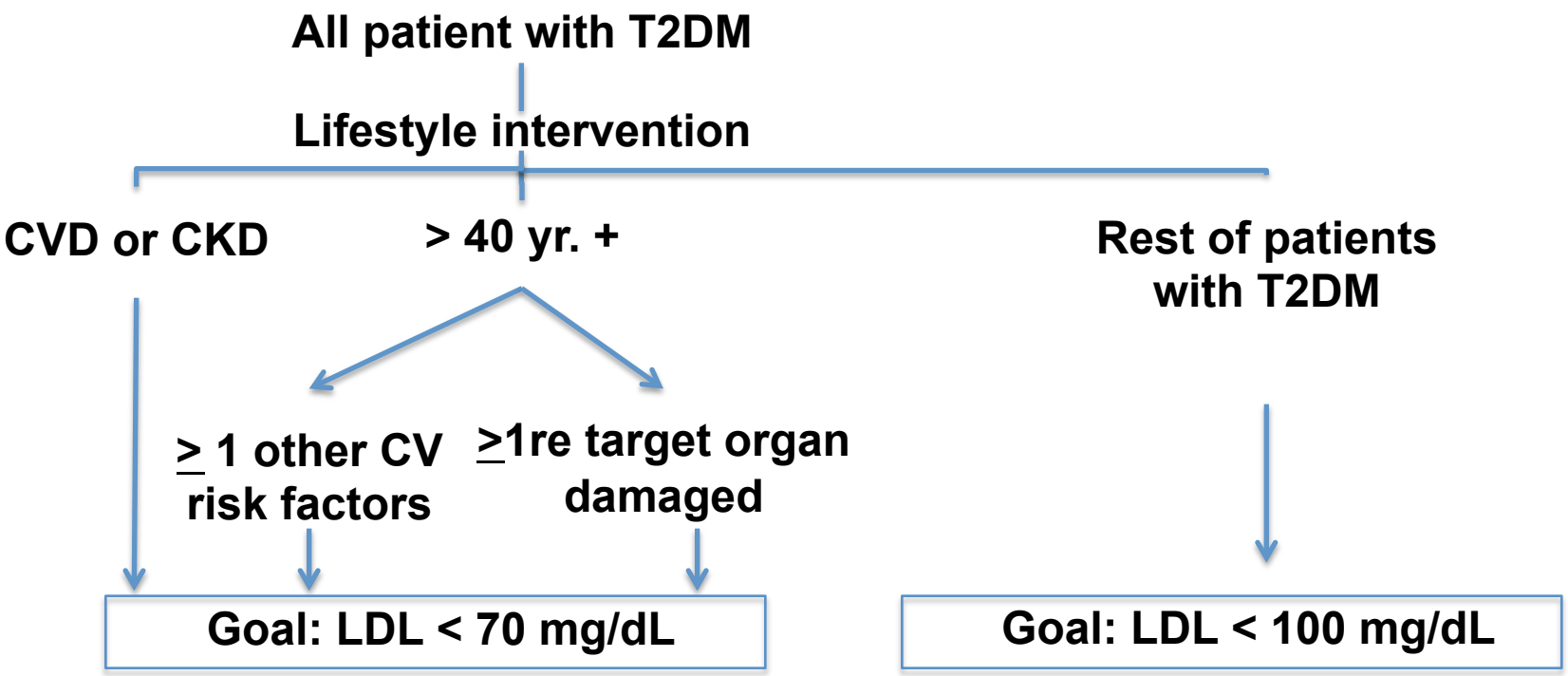
Conclusions

1.- Please, do not use REGICOR in T2DM; use MBE

2.- When to start and objectives :



Alternative goal: A reduction of 30-40% in LDL-C

3.- STATINS, STATINS, STATINS !!!: Why this diabetic is not on statin therapy ?