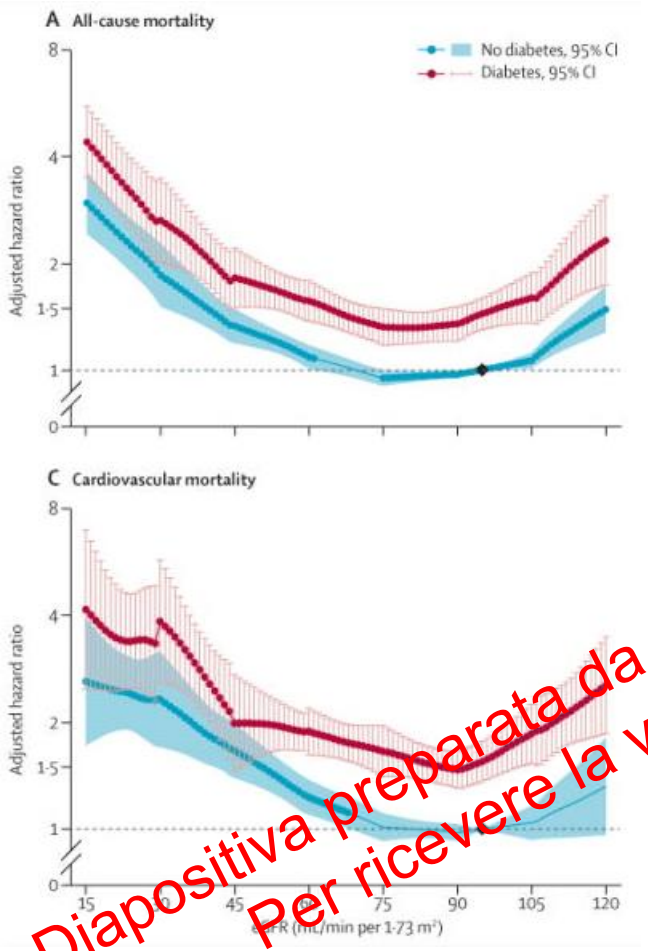
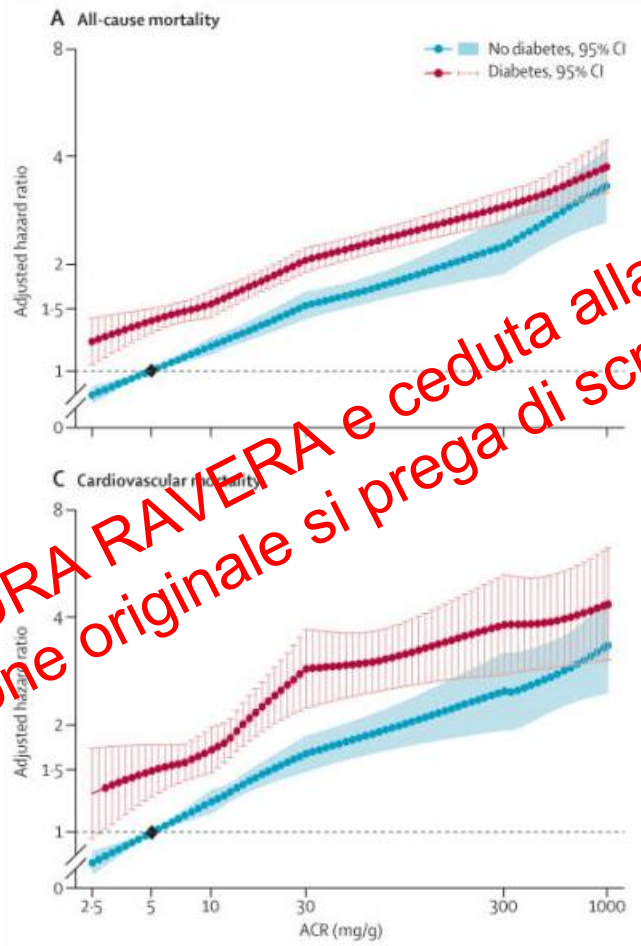
Ipertensione e ipercolesterolemia nella DKD: quali goals terapeutici?

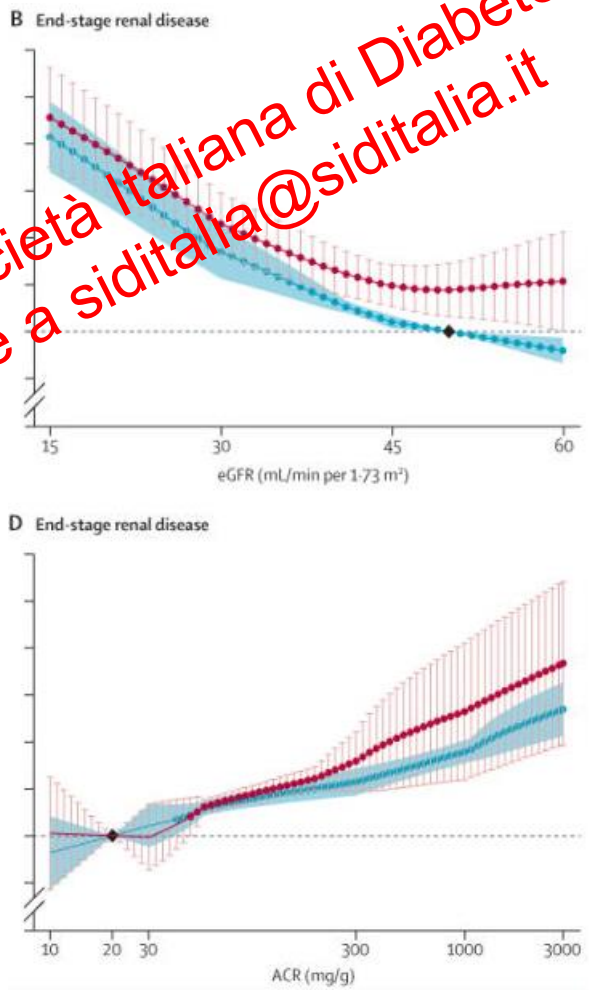
Maura Ravera

Clinica Nefrologica, Dialisi e Trapianto,
Ospedale Policlinico San Martino
Genova

HR for all-cause mortality, CV mortality, and ESRD in the combined general and high-risk populations according to GFR and ACR in participants with and without diabetes: 1 024 977 participants, of whom 128 505 (13%) had diabetes.







Fox CS et al, CKD Prognosis Consortium, Lancet 2012

Major risk factors and markers for development and progression of renal damage in diabetes

TRADITIONAL

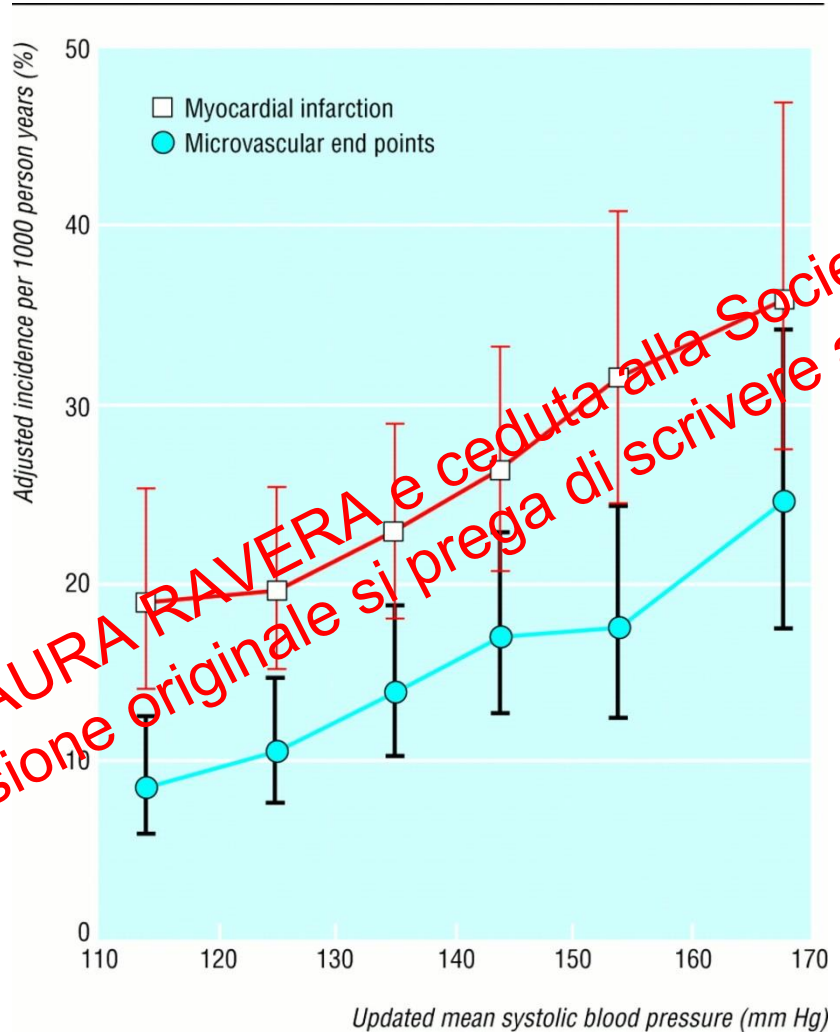
Older age
Male sex
Hypertension
Higher LDL cholesterol
Low HDL cholesterol
Diabetes
Smoking
Physical inactivity
Menopause
Family history of CVD
Left ventricular hypertrophy

NON-TRADITIONAL

Albuminuria/proteinuria
RAAS activity
Lipoprotein(a)
↑ Oxidized LDL
"Small dense" LDl-chol particles
Anemia
Abnormal calcium-phosphate metabolism
Extracellular fluid overload
↑Oxidative stress
Inflammation (C-reactive protein)
Malnutrition, Thrombogenic Factors
Altered nitric oxide/endothelin balance

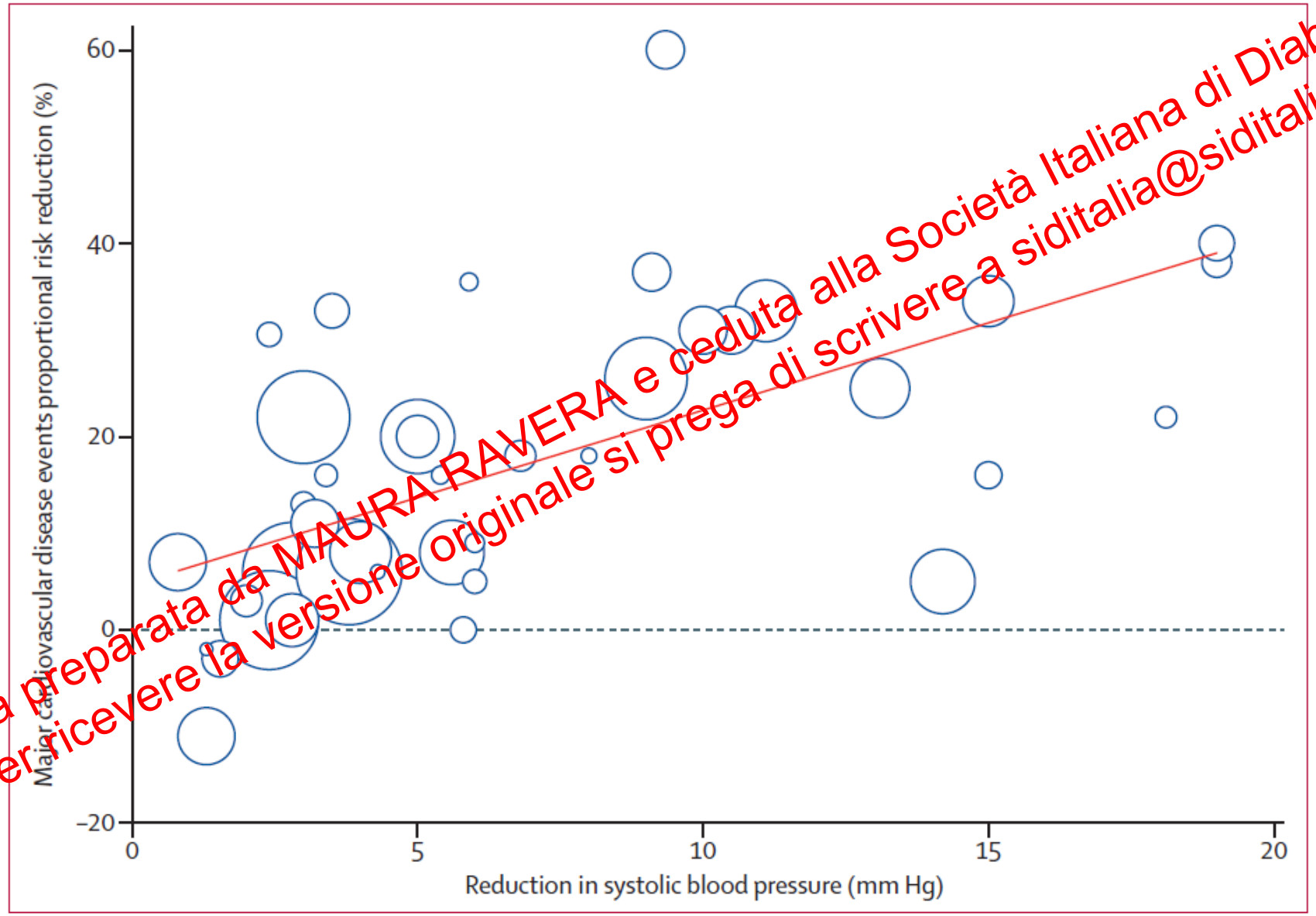
Menon V. et al, Am J Kidney Dis 2005

Incidence rates (95% confidence interval) of myocardial infarction and microvascular end points by category of updated mean systolic blood pressure, adjusted for age, sex, and ethnic group expressed for white men aged 50–54 years at diagnosis and mean duration of diabetes of 10 years: UKPDS 36



Amanda I Adler et al. BMJ 2000;321:412-419

Risk reduction in major CV events according to the difference in achieved SBP: a systematic review and meta-analysis of 123 studies with 613 815 pts



Ettehad, *Lancet* 2016; 387: 957–67

Threshold for treatment and Goal

- ✓ **When should antihypertensive drug treatment be initiated?**
- ✓ **What levels should SBP be lowered?**

Recent guidelines on BP goals

	ACC/AHA, 2017	ADA, 2019	ESC/ESH, 2018
	Threshold	Threshold	Threshold
DM	≥ 130/80	≥ 140/90	≥ 140/90
CKD	≥ 130/80	≥ 130/80	≥ 140/90

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Recommendations for Treatment of Hypertension in Patients With DM

References that support recommendations are summarized in Online Data Supplements 46 and 47 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR]	1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.[S9.6-1–S9.6-8]
	DBP: C-EO	
I	A[SR]	2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (ie, diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.[S9.6-1,S9.6-9,S9.6-10]
IIb	B-NR	3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.[S9.6-11,S9.6-12]

Recommendations for Treatment of Hypertension in Patients With CKD

References that support recommendations are summarized in Online Data Supplements 37 and 38 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR]	1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.[S9.3-1–S9.3-6]
	DBP: C-EO	
IIa	B-R	2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.[S9.3-3,S9.3-7–S9.3-12]
IIb	C-EO	3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (S9.3-7,S9.3-8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

Hypertension. 2018;71:e13-e115.

Diabetes and Hypertension: A Position Statement by the American Diabetes Association

CONFIRMED

American Diabetes Association. Diabetes Care

Position Statements

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2019*

American Diabetes Association

Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123.

https://doi.org/10.2337/dc19-S010

Table 23 Office blood pressure treatment target range

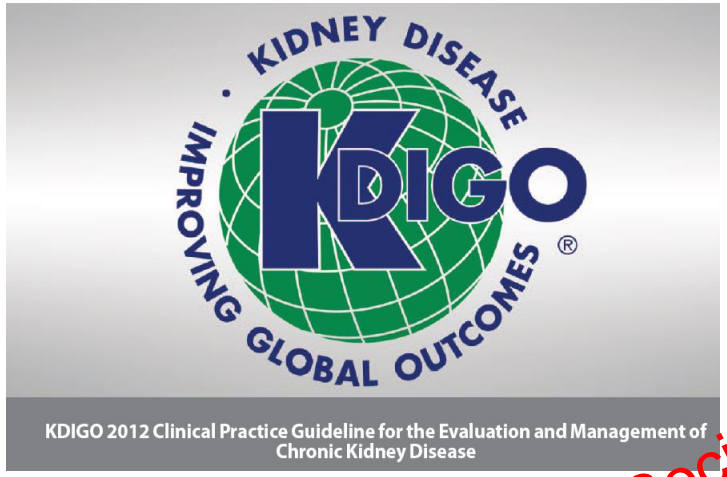
ESC-ESH 2018

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

[a]Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

[b]Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.



BP and RAAS interruption

3.1.1: Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment as described in the KDIGO 2012 Blood Pressure Guideline. (*Not Graded*)

3.1.4: We recommend that in both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (*1B*)

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of >30 mg/24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (*2D*)

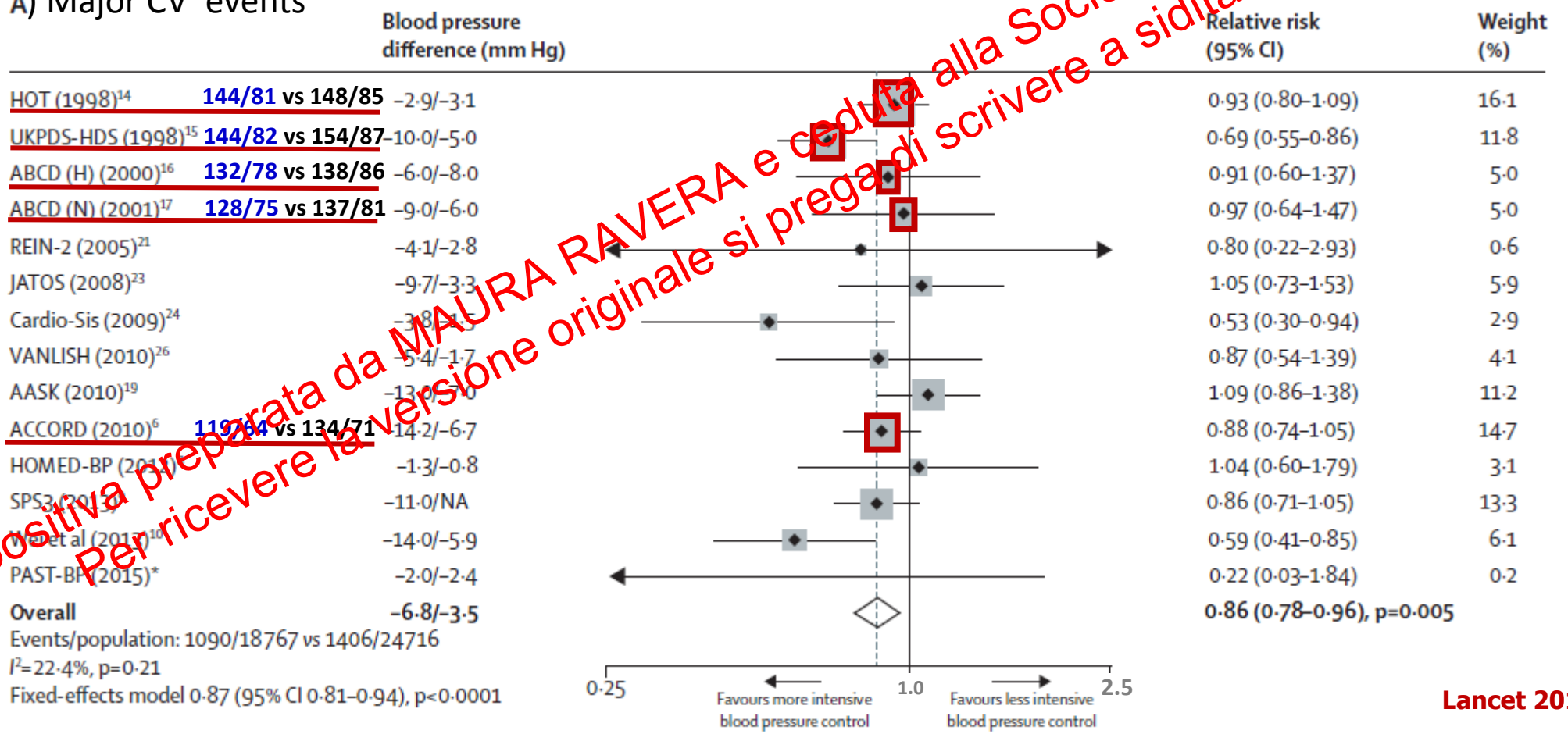
3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (or equivalent*). (*2D*)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent*). (*1B*)

Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis

Xinfang Xie, Emily Atkins, Jicheng Lv, Alexander Bennett, Bruce Neal, Toshiharu Ninomiya, Mark Woodward, Stephen MacMahon, Fiona Turnbull, Graham S Hillis, John Chalmers, Jonathan Mant, Abdul Salam, Kazem Rahimi, Vlado Perkovic, Anthony Rodgers

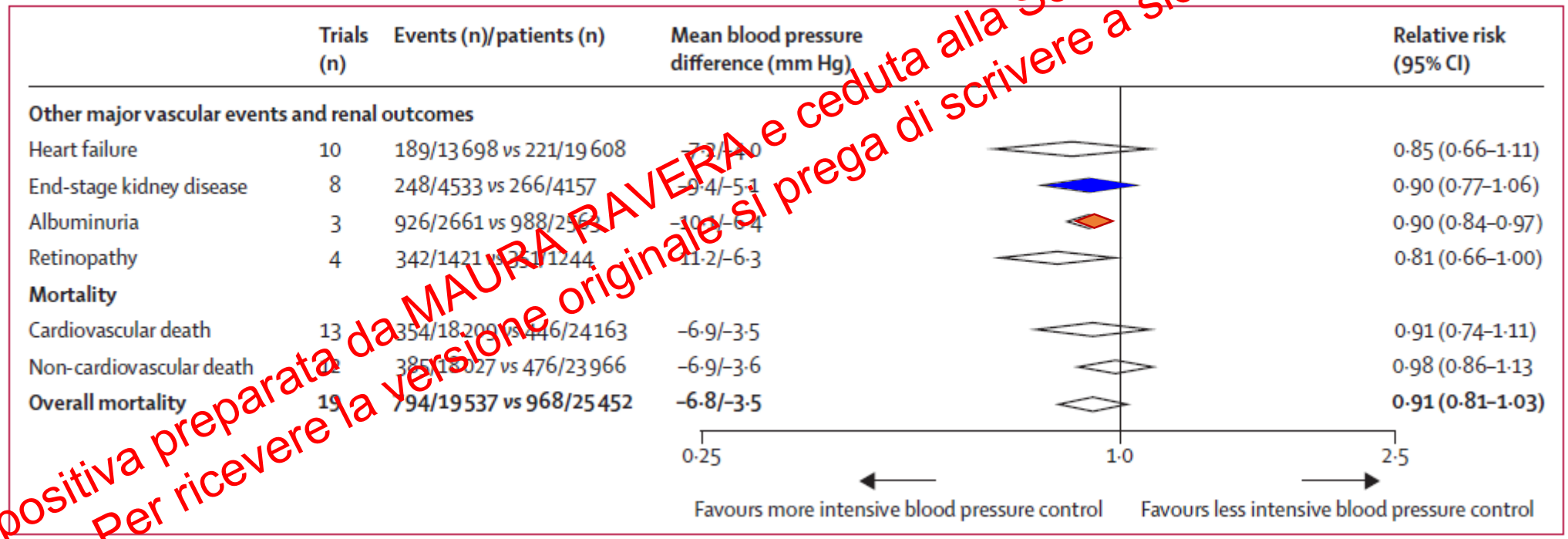
A) Major CV events



Lancet 2015

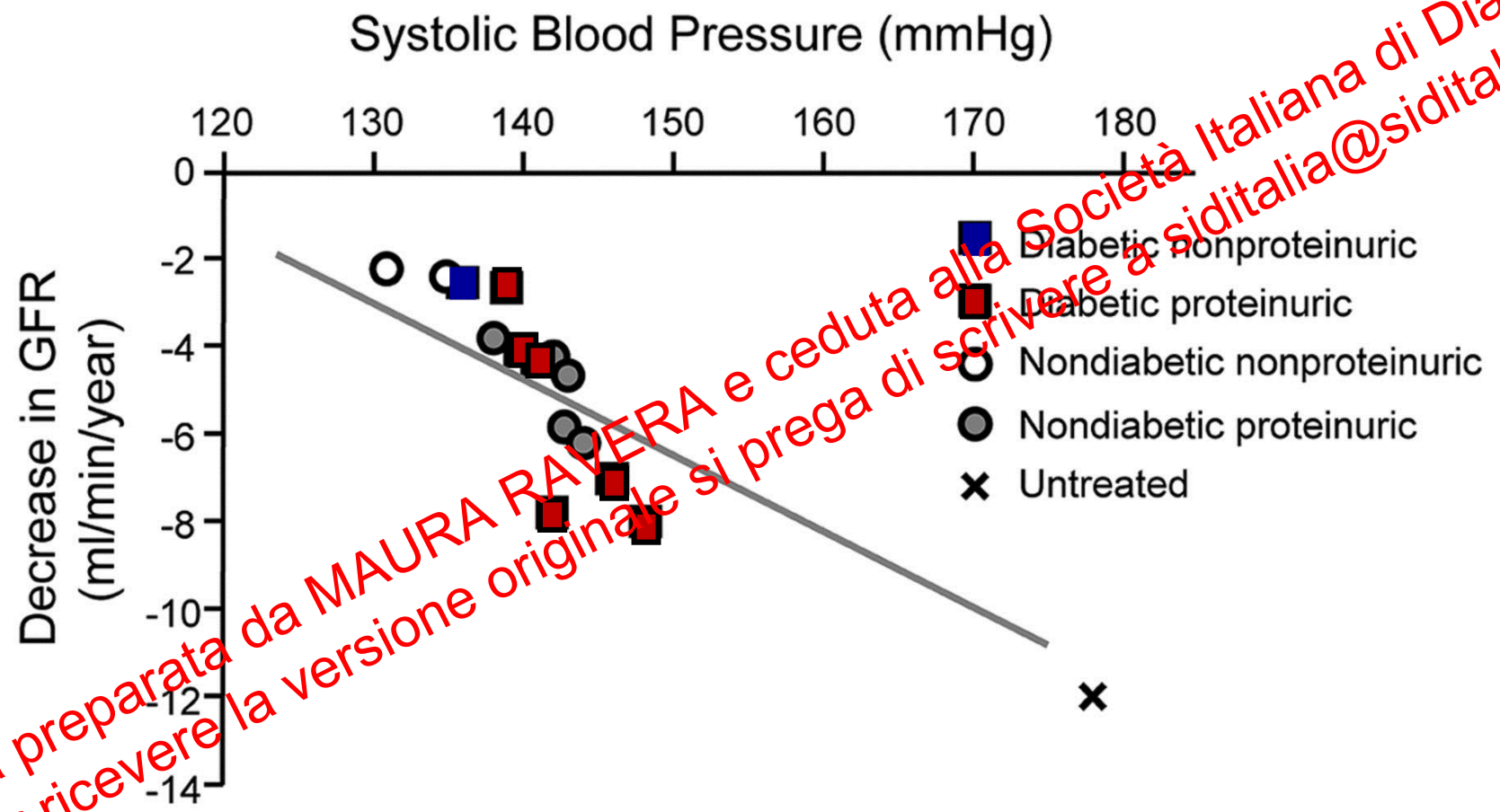
Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis

Xinfang Xie, Emily Atkins, Jicheng Lv, Alexander Bennett, Bruce Neal, Toshiharu Ninomiya, Mark Woodward, Stephen MacMahon, Fiona Turnbull, Graham S Hillis, John Chalmers, Jonathan Mant, Abdul Salam, Kazem Rahimi, Vlado Perkovic, Anthony Rodgers



Lancet 2015

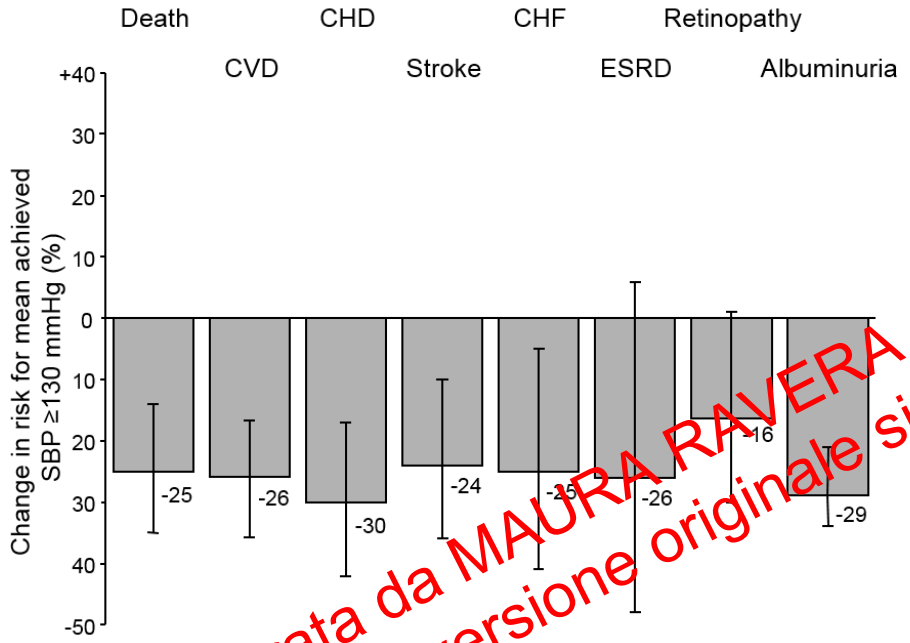
Data from prospective clinical trials on nephropathy progression with a follow-up duration ≥2 years showing the relationships between the systolic blood pressure values achieved during antihypertensive drug treatment and the decrease in glomerular filtration rate (GFR).



Guido Grassi et al. Dia Care 2016;39:S228-S233

American Diabetes Association.

Effect of 10 mmHg reduction of SBP on outcomes in 40 trials on 100,354 diabetic individuals



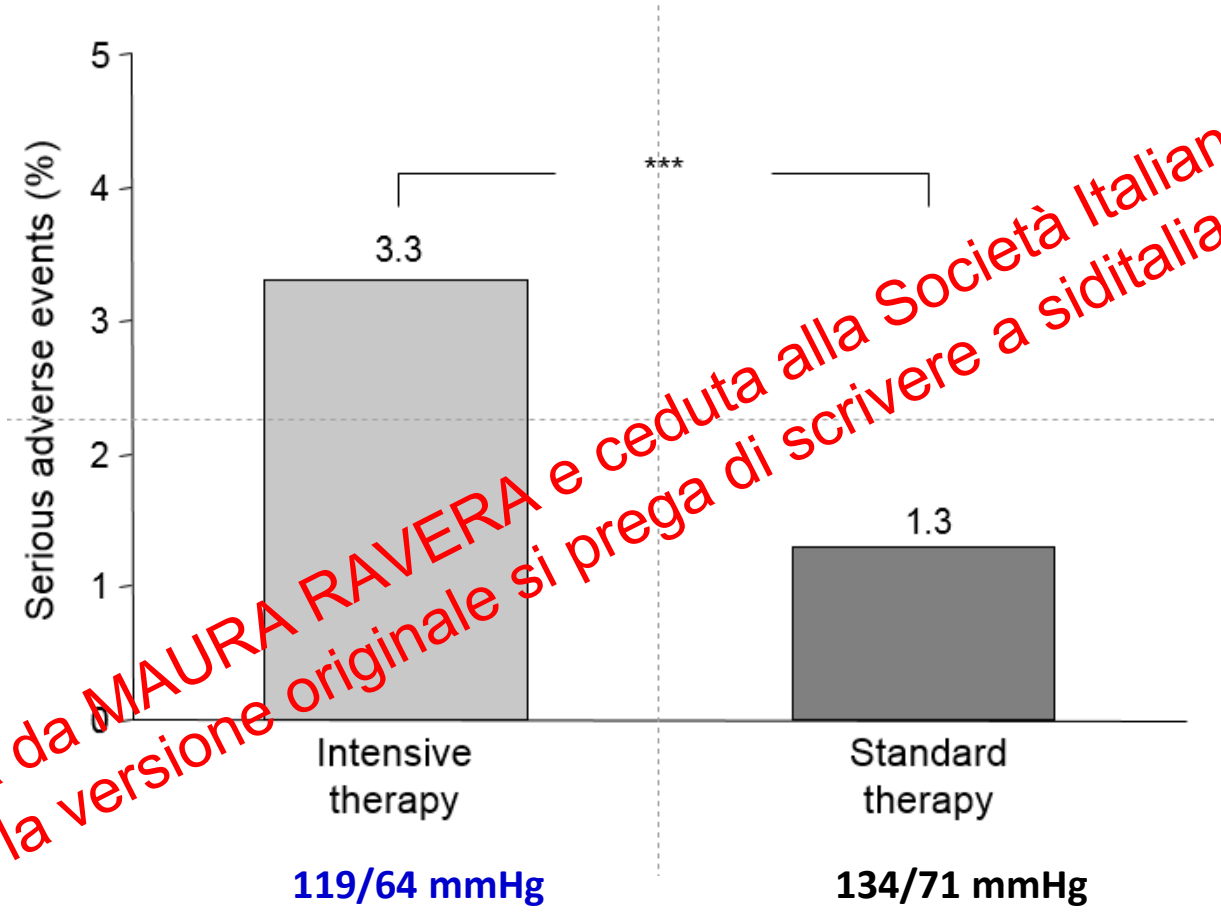
Mean SBP 138 mmHg

Mean SBP 122 mmHg

Mancia and Grassi (2018) Diabetologia DOI 10.1007/s00125-017-4537-3

Diabetologia

Serious adverse events attributed to antihypertensive treatment in the ACCORD study



Mancia and Grassi (2018) Diabetologia DOI 10.1007/s00125-017-4537-3

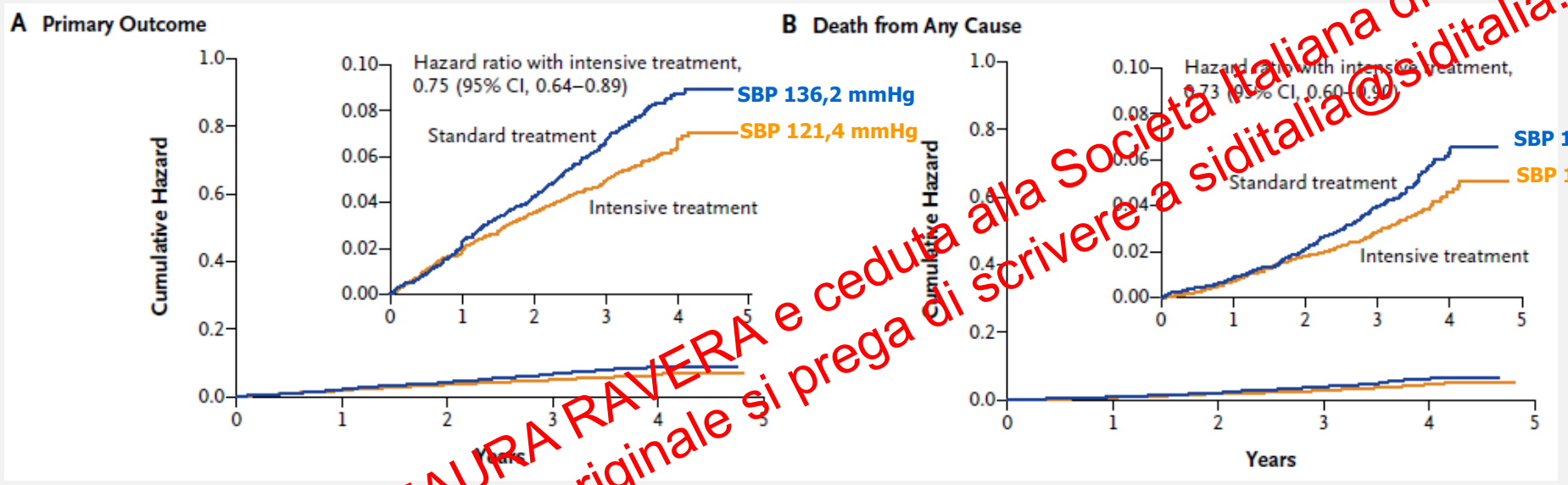
Diabetologia

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*



Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome†	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m²§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001

Wright JT jr, NEJM 2015: 373: 2103-16

Suggested drugs for BP therapy initiation

	ACC/AHA, 2017	ADA, 2019	ESC/ESH, 2018
DM	ACE-I/ ARB, CCB, Th like,	ACE-I/ ARB, Th like, CCB	ACE-I/ ARB, CCB, Th like
CKD	ACE-I/ ARB ± Th		ACE-I/ ARB, CCB, Th
Albuminuria	ACE-I/ ARB	ACE-I/ ARB	ACE-I/ ARB
	ACE-I + ARB not recommended	ACE-I + ARB not recommended	ACE-I + ARB not recommended

Th like = Thiazide like diuretics (indapamide, chlortalidone)
CCB = long acting dihydropyridine CCB

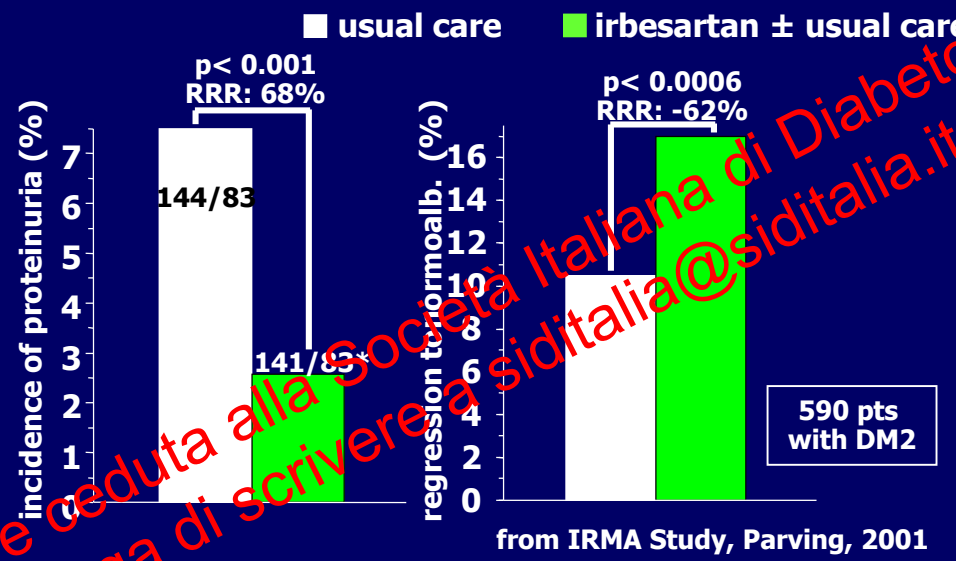
Optimal renoprotective effect in different stages of diabetic nephropathy

SECONDARY PREVENTION: ACE-I

	No. of events/patients Per-Ind	Placebo	Median blood pressure	Favors Per-Ind	Favors Placebo	Hazard ratio (95% CI)	P for trend
All renal events							
All participants	1243/ 5569	1500/ 5571				0.79 (0.73 to 0.85)	
Baseline systolic blood pressure (mmHg)							
<120	134/ 615	167/ 560	113 mmHg			0.70 (0.56 to 0.88)	0.75
120-139	367/ 1736	431/ 1793	131 mmHg			0.85 (0.74 to 0.97)	
140-159	439/ 1945	563/ 2003	149 mmHg			0.75 (0.66 to 0.85)	
≥160	303/ 1273	339/ 1215	172 mmHg			0.81 (0.70 to 0.95)	
Baseline diastolic blood pressure (mmHg)							
<70	208 / 846	240 / 881	66 mmHg			0.84 (0.70 to 1.02)	0.85
70-79	387/ 1748	481/ 1758	75 mmHg			0.77 (0.67 to 0.88)	
80-89	386/ 1862	479/ 1834	84 mmHg			0.76 (0.66 to 0.87)	
≥90	262/ 1113	300/ 1098	95 mmHg			0.81 (0.69 to 0.96)	

From ADVANCE, 2009

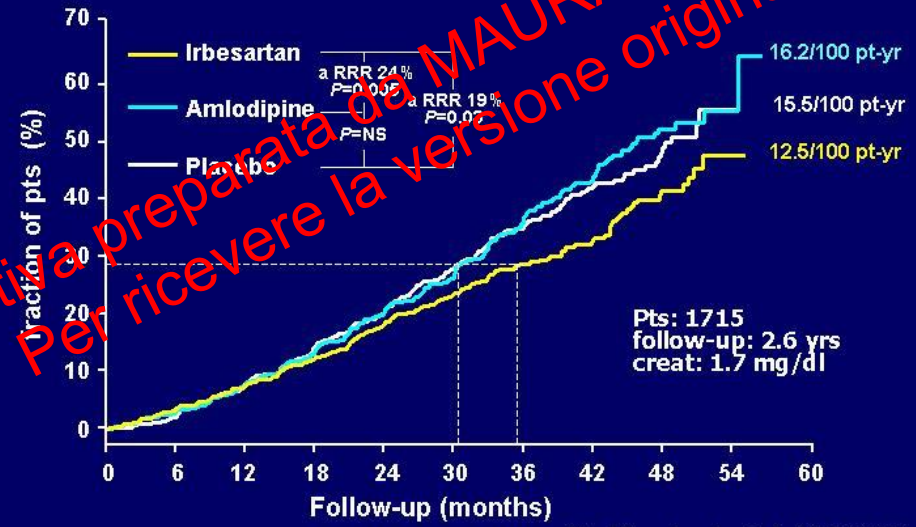
SECONDARY PREVENTION: ARB



from IRMA Study, Parving, 2001

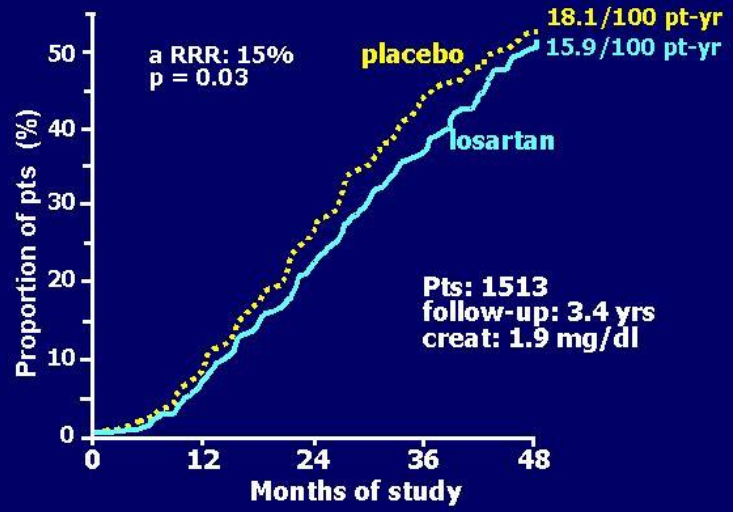
TERTIARY PREVENTION: ARB

IDNT: Primary Composite Endpoint (creat x 2, ESRD, or Death)



modified from Lewis et al., NEJM 2001

RENAAL: primary composite end point (creat x 2/ESRD/death)



from Brenner BM et al., NEJM 2001

Negative trials on dual RAS blockade

Study	ONTARGET	ALTITUDE	VA NEPHRON D
Study treatment			
Population	coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	UACR ≥200 mg/g, eGFR ≥30 mL/min or eGFR ≥30 and <60 mL/min, UACR ≥20 and <200 mg/g or Cardiovascular risk: eGFR ≥30 and <60 mL/min, UACR <20 mg/g, CVD history	mg/g, eGFR of 30-90 mL/min
N	25,620	8606	1448
Follow-up (y)	4.7	2.8	2.2
Primary endpoint	Composite outcome of CV death, MI, stroke, or hospitalization for CHF	Composite of CV death, resuscitated sudden death, MI, stroke, unplanned hospitalization for HF, ESRD, or kidney death or doubling of baseline serum creatinine concentration	Change in eGFR (a decline of ≥30 mL if the initial eGFR was ≥60 mL/min or a decline of ≥50% if the initial eGFR was <60 mL/min), ESRD, or death
Baseline blood pressure (mmHg)	134/77	135/74	137/73
Diabetes (%)	37	100	100
CVD history	49% MI 21% stroke/TIA	48%	23% CAD 16% CHF
Macroalbuminuria	N/A	58%	100%
Smoking (%)	13	13	N/A

Acute HD (*Hypotension*)

Hyperkalemia, Hypotension

AKI, Hyperkalemia

Mann Lancet 2008

Parving NEJM 2012

Fried NEJM 2013

Aldosterone Antagonists for Preventing the Progression of Chronic Kidney Disease: A Systematic Review and Meta-analysis

Sankar D. Navaneethan,*† Sagar U. Nigwekar,‡ Ashwini R. Sehgal,§ and Giovanni F.M. Strippoli†‖¶**

	Aldosterone antagonist			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bianchi 2006	0.89	0.54	83	2.11	0.72	82	27.8%	-1.22 [-1.41, -1.03]	
Chrysotomou 2006	2.04	1.9	11	2.97	3.7	10	3.1%	-0.93 [-3.48, 1.62]	
Furamatsu 2008	0.6	0.38	15	1.39	2.3	15	10.6%	-0.79 [-1.81, 0.39]	
Rossing 2005	1.06	0	20	1.56	0	20		Not estimable	
Schjoedt 2005	0.77	0.54	20	1.02	0.73	20	24.2%	-0.25 [-0.65, 0.15]	
Schjoedt 2006	3.06	1.74	20	4.2	1.82	20	10.6%	-1.14 [-2.24, -0.04]	
Tylicki 2008	0.51	0.42	18	1.21	0.84	18	2.4%	-0.70 [-1.13, -0.27]	
Total (95% CI)			187			185	**100.0**	**-0.80 [-1.27, -0.33]**	
Heterogeneity: Tau² = 0.20, Chi² = 20.56, df = (P=0.0010); I² = 71%									
Test for overall effect Z = 3.33 (P=0.0009)									

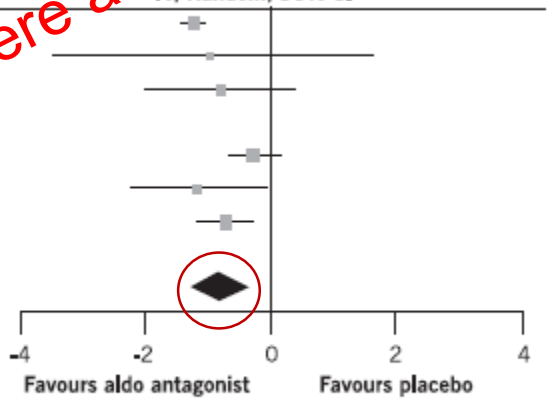


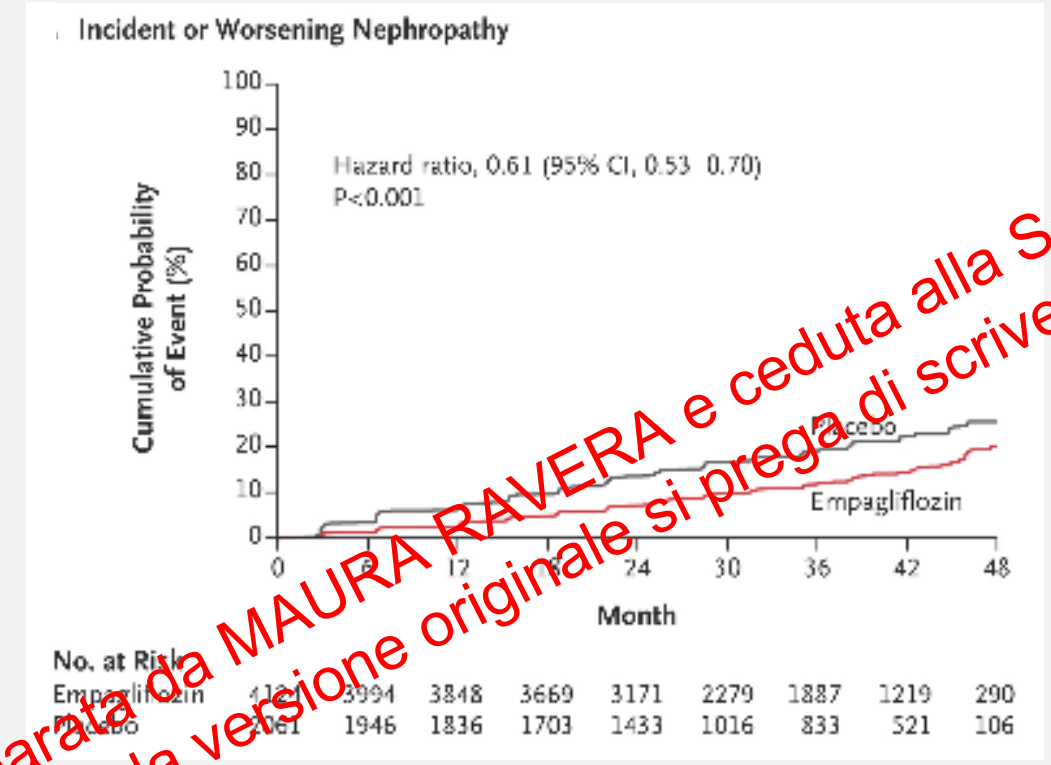
Figure 2. Effect of aldosterone antagonists plus ACEi and/or ARB compared with ACEI and/or ARB alone on the end of treatment proteinuria.

Clin J Am Soc Nephrol 4: 542–551, 2009

Ongoing Trials in type 2 DM

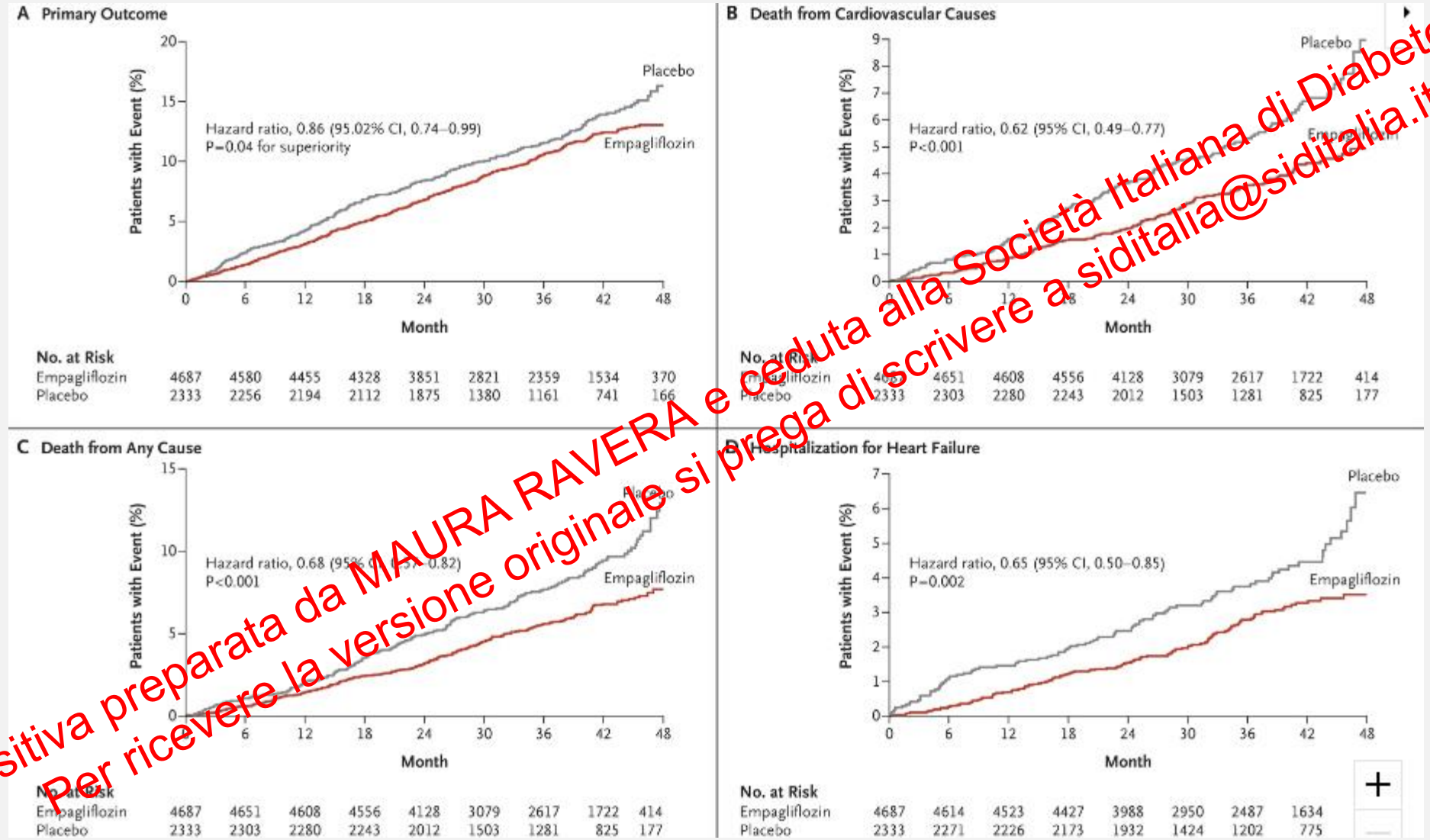
	ClinicalTrials.gov registration number	Drug (class)	n	Main inclusion criteria	Follow-up (years)	Mean age (years)	Mean type 2 diabetes duration (years)	Mean baseline HbA_{1c} (%)	Mean baseline eGFR (mL/min per 1·73 m²)	Baseline albuminuria status	Trial status (expected completion date)	Renal outcome
Renal Outcome												
FIDELIO-DKD	NCT02540993	Finerenone (MRA)	4800	Type 2 diabetes, macroalbuminuria, potassium ≤4·8 mmol/L	Up to 4	..	..	..	..	Macro 100%	Ongoing (April, 2020)	Primary: composite (ESKD, ≥40% reduction in eGFR, renal death)
DAPA-CKD	NCT03036150	Dapagliflozin (SGLT2 inhibitor)	4000	eGFR 25–75 mL/min per 1·73 m², increased albuminuria	Up to 4	..	..	..	..	..	Ongoing (November 2020)	Primary: composite (>50% reduction in eGFR, ESKD, cardiovascular death, renal death)
EMPA-KIDNEY	NCT03594110	Empagliflozin (SGLT2 inhibitor)	5000	eGFR 20-45 mL/min per 1·73 m² or 45-90 mL/min per 1·73 m² with albuminuria	~3·1						Ongoing (June, 2022)	Primary: composite of kidney disease progression (ESKD, eGFR <10 mL/min per 1·73 m², renal death, or ≥40% reduction in eGFR) or cardiovascular death
VERTIS-CV	NCT01986881	Ertugliflozin (SGLT2 inhibitor)	8000	Type 2 diabetes, CVD history	Up to 6·1	..	..	..	..	..	Ongoing (September, 2019)	Secondary: Composite (dSCr, ESKD, renal death)
FIGARO-DKD	NCT02545049	Finerenone (MRA)	6400	Type 2 diabetes, macroalbuminuria, potassium ≤4·8 mmol/L	Up to 4·4	..	..	..	..	Macro 100%	Ongoing (June, 2021)	Secondary: composite (ESKD, ≥40% reduction in eGFR, renal death), change in UACR
CV Outcome												
DAPA-HF	NCT03036224	Dapagliflozin (SGLT2 inhibitor)	4744	Type 2 diabetes, HFrEF (NYHA II–IV), LVEF ≤40%, high NT-proBNP	Up to 3	..	..	..	..	..	Ongoing (December, 2019)	Secondary: composite (>50% reduction in eGFR, ESKD, renal death)
EMPEROR-preserved	NCT03057951	Empagliflozin (SGLT2 inhibitor)	4126	HFpEF (NYHA II–VI), LVEF >40%, high NT-proBNP	Up to 3·2	..	..	..	..	..	Ongoing (June, 2020)	Secondary: eGFR slope, ESKD, or ≥40% reduction in eGFR
EMPEROR-reduced	NCT03057977	Empagliflozin (SGLT2 inhibitor)	2850	HFrEF (NYHA II–VI), LVEF ≤40%, high NT-proBNP	Up to 3·2	..	..	..	..	..	Ongoing (June, 2020)	Secondary: eGFR slope, ESKD, or ≥40% reduction in eGFR

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes: EMPA-REG OUTCOME



Wanner, N Engl J Med 2016

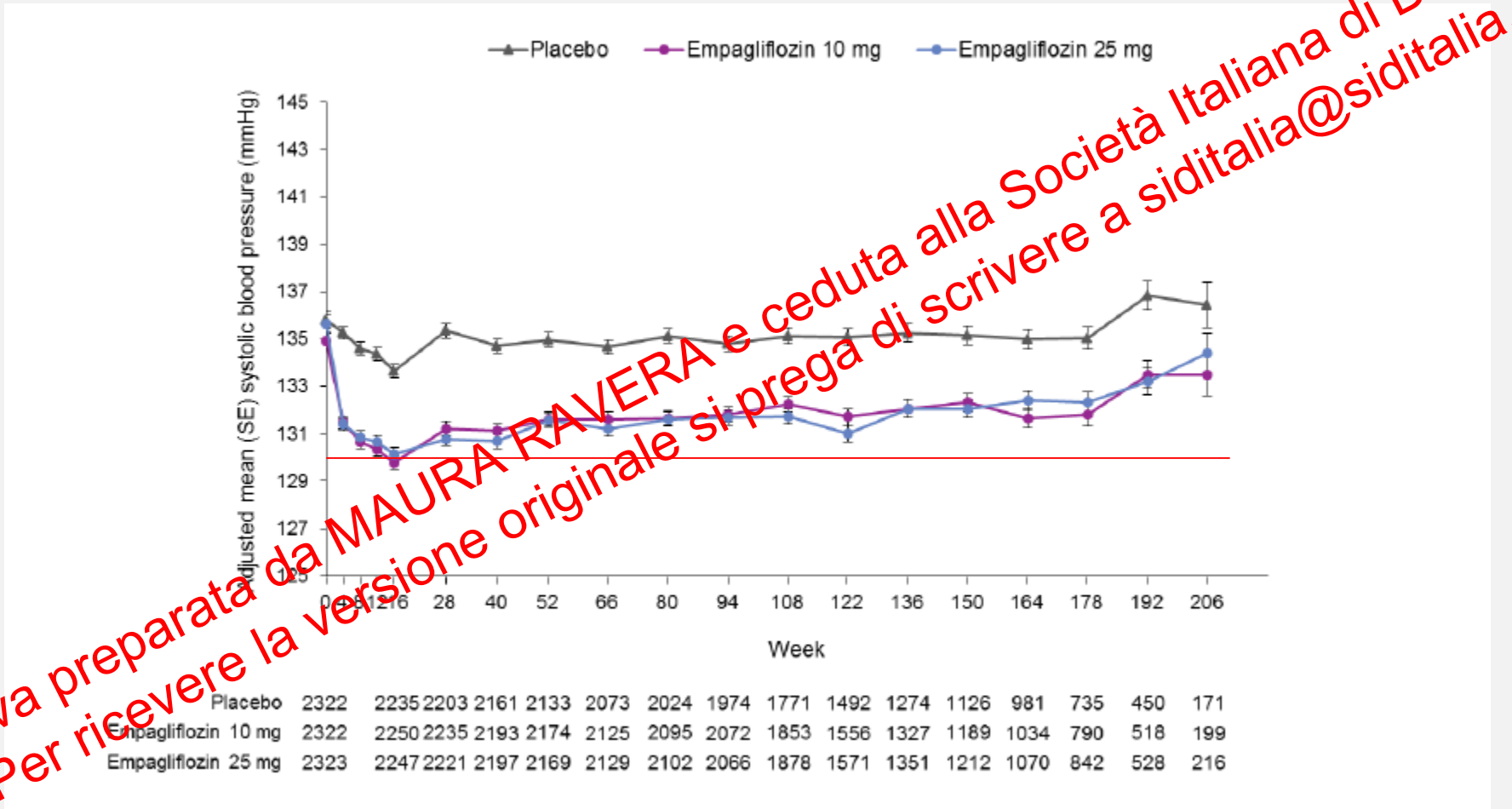
Cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in the pooled empagliflozin group and the placebo group: the EMPA-REG OUTCOME



Zinman, EMPA-REG Outcome, NEJM 2015

SBP changes in EMPA-REG OUTCOME

7020 pts, 26% <60 ml/min; 28% microalbuminuria; 11 % macroalbuminuria; f-up 2.6 yr



Zinman, EMPA-REG Outcome, NEJM 2015

Major risk factors and markers for development and progression of renal damage in diabetes

TRADITIONAL

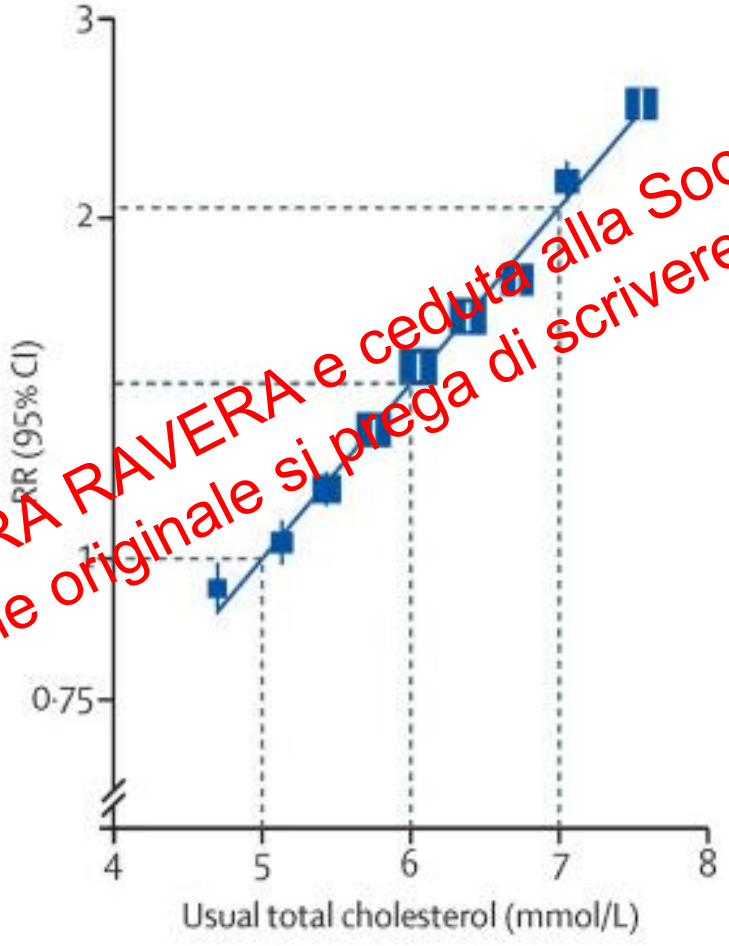
Older age
Male sex
Hypertension
Higher LDL cholesterol
Low HDL cholesterol
Diabetes
Smoking
Physical inactivity
Menopause
Family history of CVD
Left ventricular hypertrophy

NON-TRADITIONAL

Albuminuria/proteinuria
RAAS activity
Lipoprotein(a)
↑ Oxidized LDL
"Small dense" LDl-chol particles
Anemia
Abnormal calcium-phosphate metabolism
Extracellular fluid overload
↑Oxidative stress
Inflammation (C-reactive protein)
Malnutrition, Thrombogenic Factors
Altered nitric oxide/endothelin balance

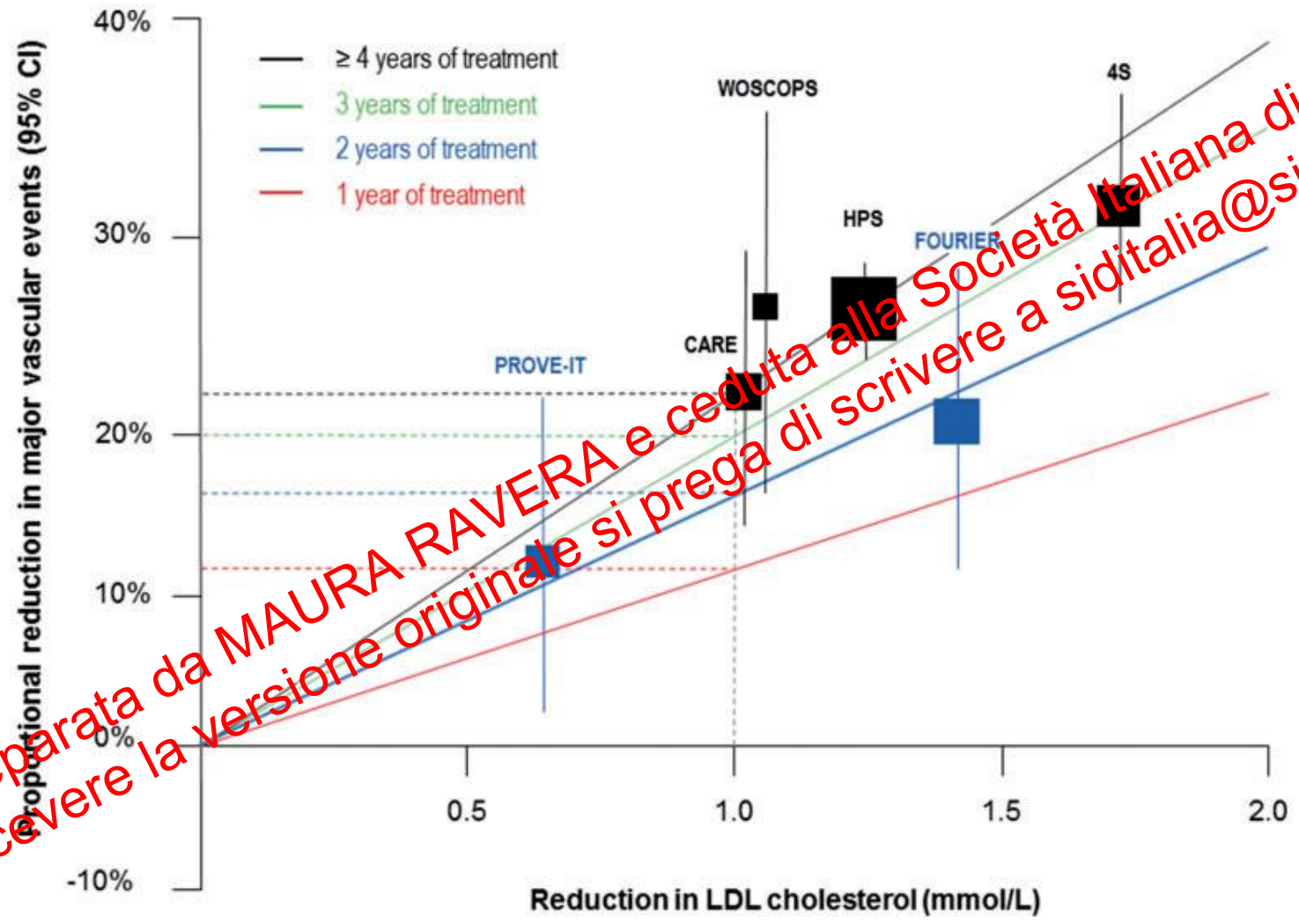
Menon V. et al, Am J Kidney Dis 2005

Association of total cholesterol with rates of coronary heart disease mortality



Collins, Lancet 2016, 388:2532-61

Proportional risk reduction for any given absolute LDL-C reduction by duration of statin therapy calculated using data from the Cholesterol Treatment Trialists' Collaboration



2017 Update of ESC/EAS Task Force; European Heart Journal

American Diabetes Association

Standards of Medical Care in Diabetes—2017

Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy. **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.

American Diabetes Association. Diabetes Care

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2019*

American Diabetes Association
Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123.
https://doi.org/10.2337/dc19-S010

Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, 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 • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9. *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.

AMERICAN COLLEGE of CARDIOLOGY

2018 Guideline on the Management of Blood Cholesterol

5 *In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.*

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Diabetes-specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

Table 5

- Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

AMERICAN COLLEGE of CARDIOLOGY

2018 Guideline on the Management of Blood Cholesterol

High-, Moderate-, and Low-Intensity Statin Therapy*

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§	Simvastatin 10 mg
	–	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

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*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Table 4 Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

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Treatment goal for LDL Cholesterol

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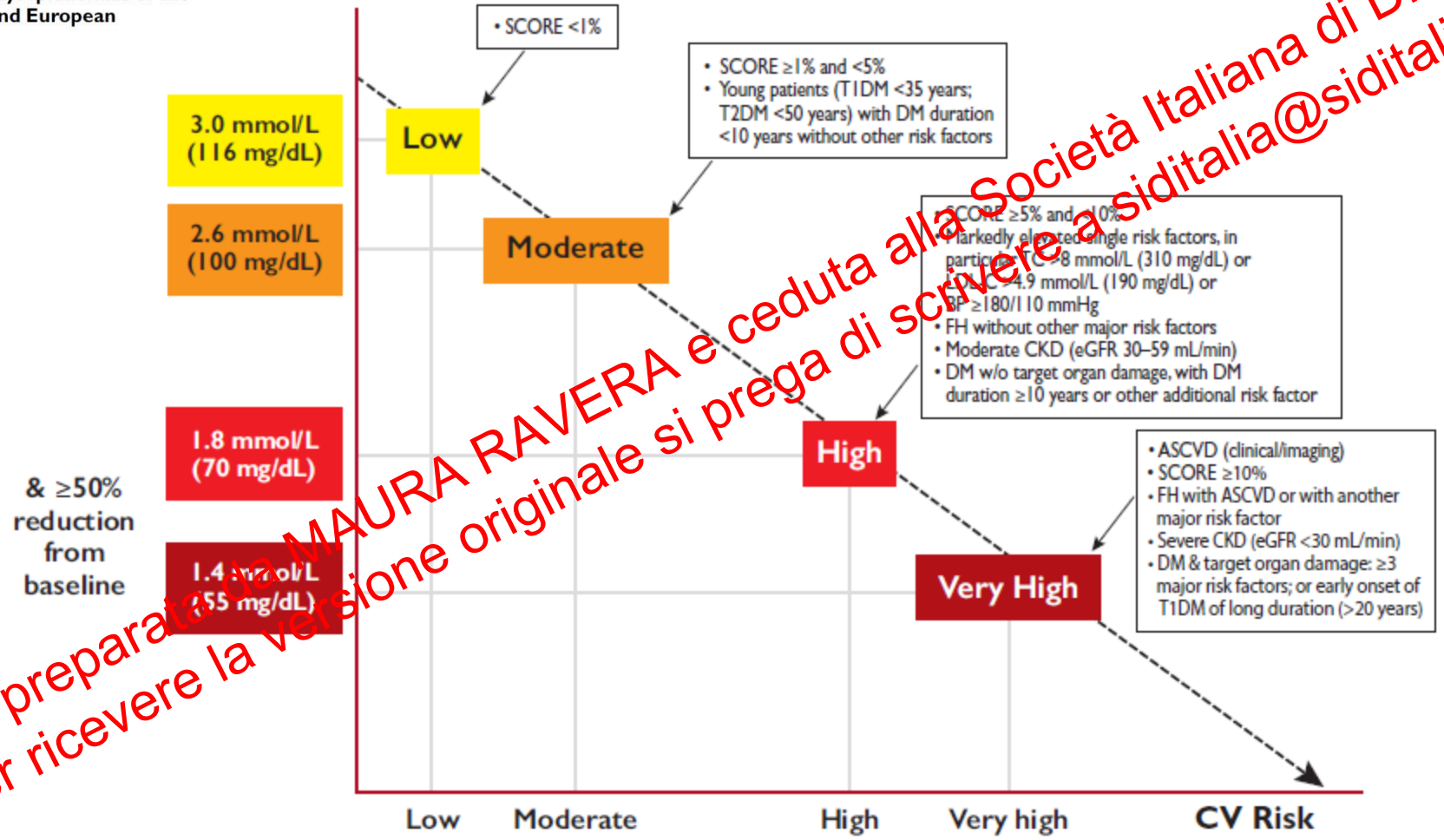

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The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Recommendations for lipid management in patients with moderate-to-severe (Kidney Disease Outcomes Quality Initiative stages 3–5) chronic kidney disease

Recommendations	Class[a]	Level[b]
It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3–5[c] CKD are considered to be at high or very-high risk of ASCVD.[489–493]	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.[214,222,495,496]	I	A
In patients already on statins, ezetimibe, or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.[220,221]	III	A

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a]Class of recommendation.
[b]Level of evidence.
[c]Defined as eGFR < 60ml/min/1.73m^2 on two measurements more than 3 months apart.

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Recommendations for pharmacological low-density lipoprotein cholesterol lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

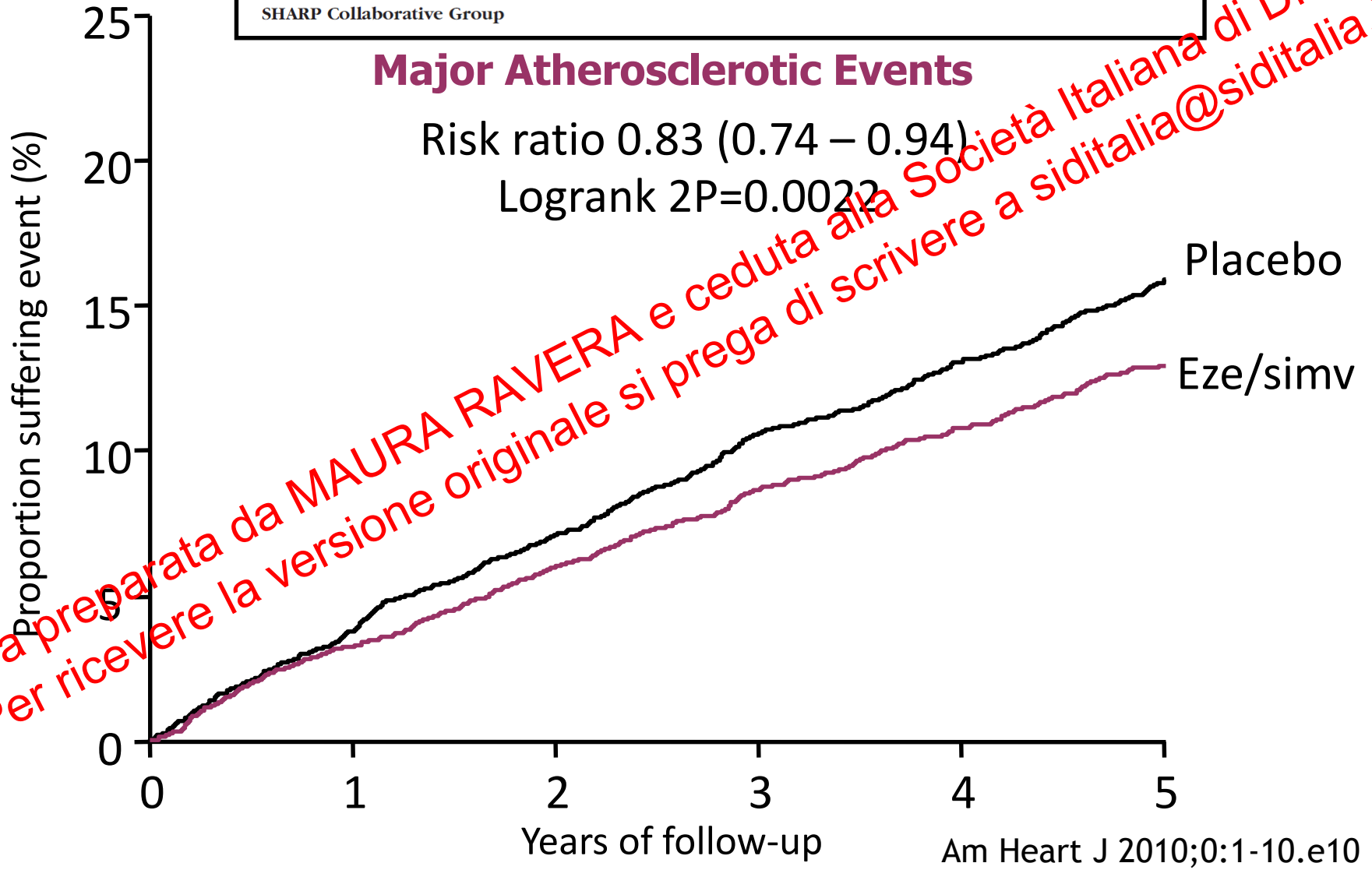
Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease

SHARP Collaborative Group

Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)

Logrank 2P=0.0022



Am Heart J 2010;0:1-10.e10

Statin versus placebo or no treatment for adults with chronic kidney disease not on dialysis: 50 studies including 45,285 pts

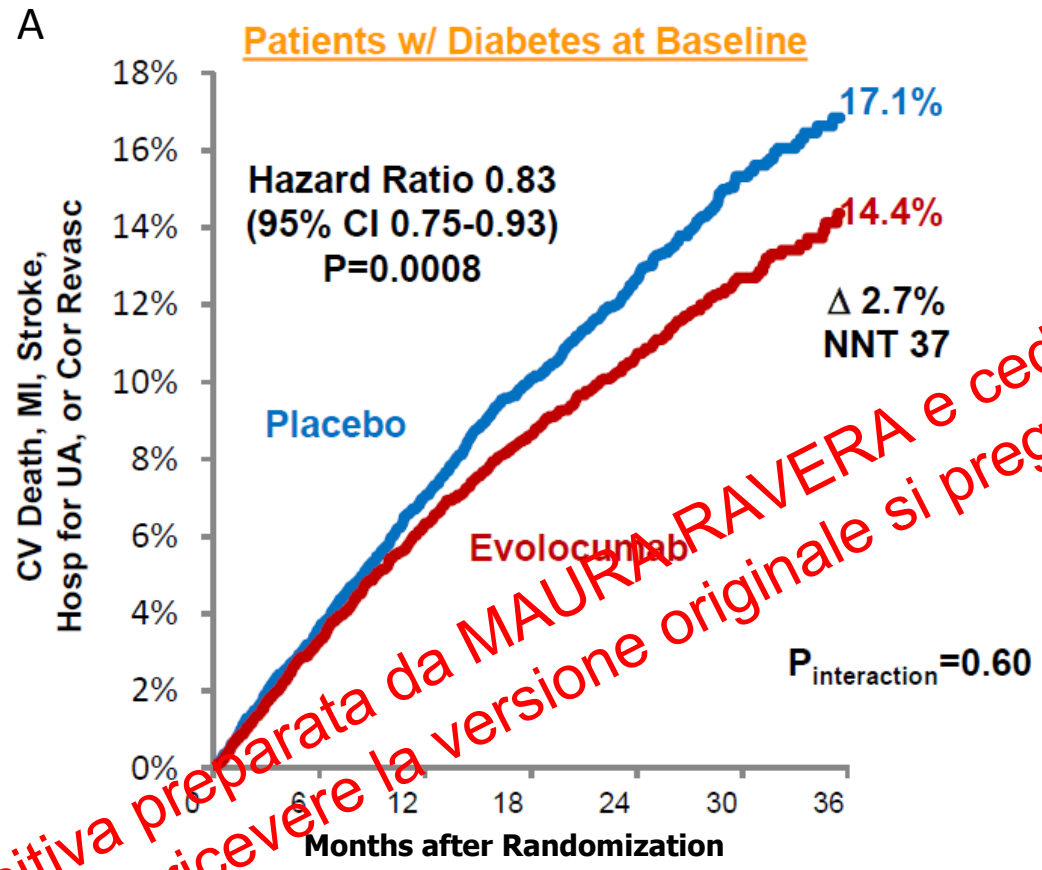
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk per year treated			
	Placebo or no treatment	Statins			
Major cardiovascular events	20 per 1000	14 per 1000 (13 to 16 per 1000) 6 fewer (4 to 7 fewer)	RR 0.72 (0.66 to 0.81)	36,033 (13)	⊕⊕⊕⊕ high
All-cause mortality	25 per 1000	20 per 1000 (17 to 23 per 1000) 5 fewer (2 to 8 fewer)	RR 0.79 (0.69 to 0.91)	28,276 (10)	⊕⊕⊕⊕ high
Cardiovascular mortality	15 per 1000	12 per 1000 (10 to 13 per 1000) 3 fewer (2 to 5 fewer)	RR 0.77 (0.69 to 0.87)	19,059 (7)	⊕⊕⊕⊖ moderate

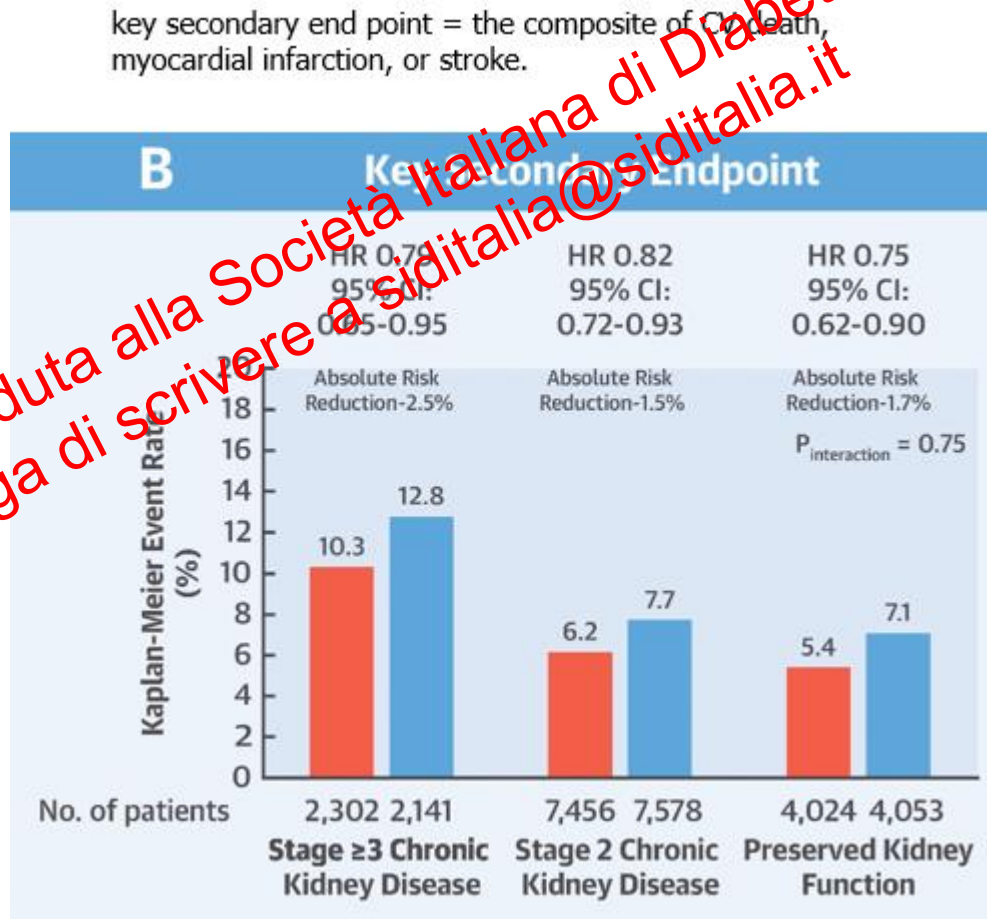
Palmer, Cochrane Database of Systematic Reviews 2014

Main outcome studies with anti-PCSK9 monoclonal antibodies

Study	Molecule	Dose	N	Diabetes %	Inclusion criteria	LDL-C at 12 mo, mg/dL	Primary composite CV endpoint	HR (95% CI)	Median f-up, yrs	CKD patients
Fourier, 2017	**Evolocumab**	140 mg every 2 weeks sc or 420 mg/4 weeks or placebo	**27,564**	**37**	CVD, LDL ≥70 mg/dl, statin therapy	**30**	1344 (9.8%) in evolocumab vs 1563 (11.3%) in placebo	**0,85** (0.79 -0.92) P< 0.001	2.2	Excluded if eGFR < 20 ml/min/1.73 m^2
Odissey Outcome, 2018	**Alirocumab**	75 mg every 2 weeks sc or placebo	**18,924**	**29**	Acute coronary syndrome 1 to 12 months earlier, LDL ≥ 70 mg/dl, non-HDL ≥100 mg/dl or apolipoprotein B ≥ 80 mg/dl, maximized statin therapy	**48**	903 (9.5%) in alirocumab group vs 1052 (11.1%) in placebo	**0.85** (0.78 - 0.93) P<0.001	2.8	Excluded if eGFR < 30 ml/min/1.73 m^2

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with diabetes and CKD



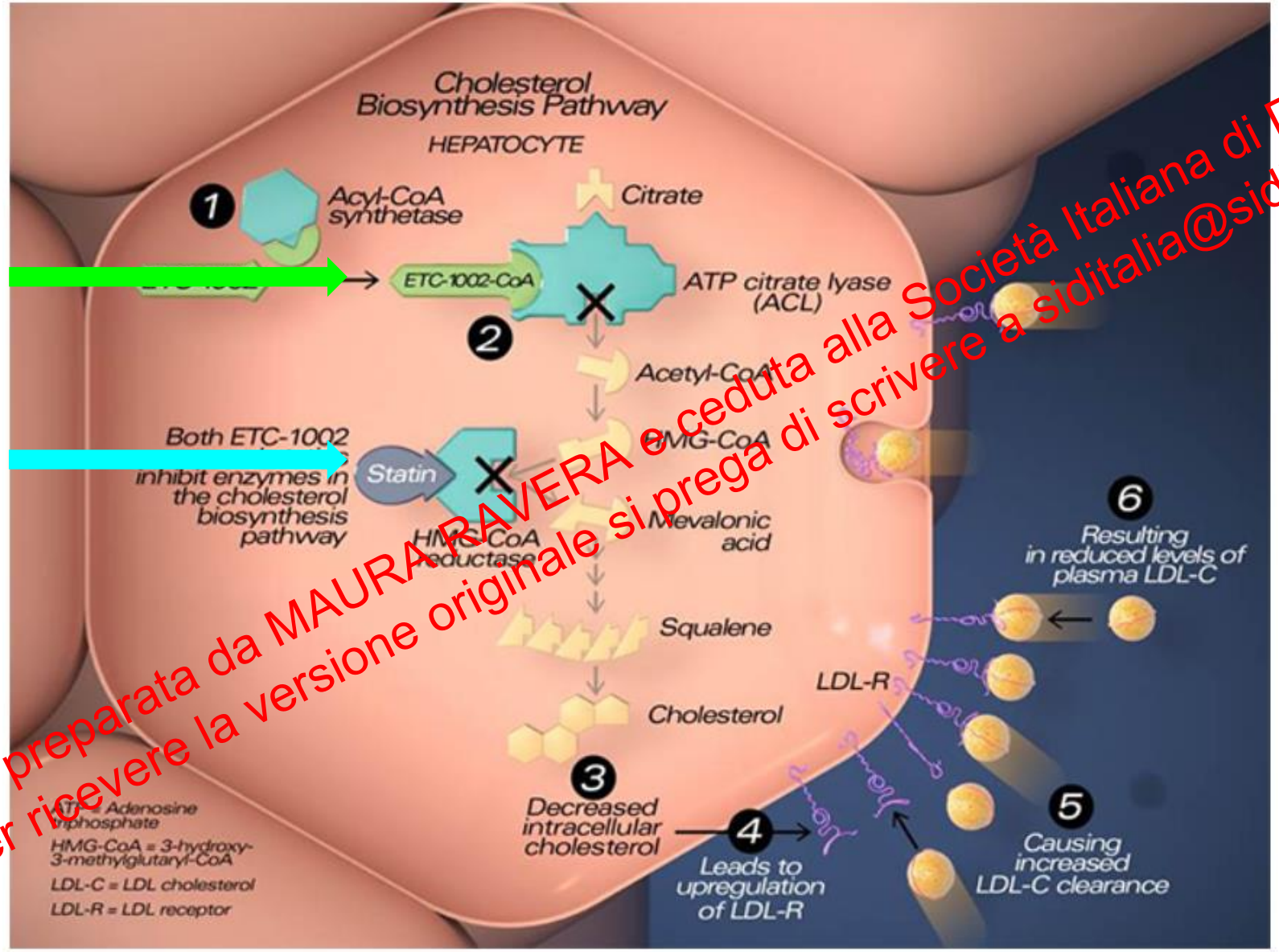


Diabetes n= 11,031

Sabatine et al, Lancet Diabetes Endocrinol. 2017

Charytan, JACC 2019

Bempedoic Acid



NIH U.S. National Library of Medicine

ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With **Bempedoic Acid** (ETC-1002) or Placebo	• Cardiovascular Diseases • Statin Adverse Reaction	• Drug: **Bempedoic acid** 180 mg tablet • Drug: Matching placebo tablet	• Birmingham, Alabama, United States • Birmingham, Alabama, United States • Huntsville, Alabama, United States • (and 1357 more...)
2	☐	Recruiting	**Bempedoic Acid** + Ezetimibe Fixed-Dose Combination (FDC) Study in Patients With Type 2 Diabetes and Elevated LDL-C	• Diabetes • Diabetes Mellitus, Type 2 • Cholesterolemia	• Drug: **Bempedoic acid** + Ezetimibe FDC Oral Tablet • Drug: Ezetimibe 10Mg Oral Tablet • Drug: Placebo Oral Tablet • Drug: Placebo oral capsule	• Clinical Trials Research Lincoln, California, United States • FInlay Medical Research Miami, Florida, United States • L-MARC Research Center Louisville, Kentucky, United States • Hampton Roads Center for Clinical Research Suffolk, Virginia, United States

DKD and BP
[summary]

- ✓ **BP target 130-140/70-80 mmHg**
- ✓ **In albuminuric patients SBP target < 130 but ≥ 120 mmHg**
- ✓ **In albuminuric patients ACE-i or ARB**
- ✓ **Potential for SGLT2 effects to be taken into account**
- ✓ **Results from ongoing RCTs with Finerenone awaited**

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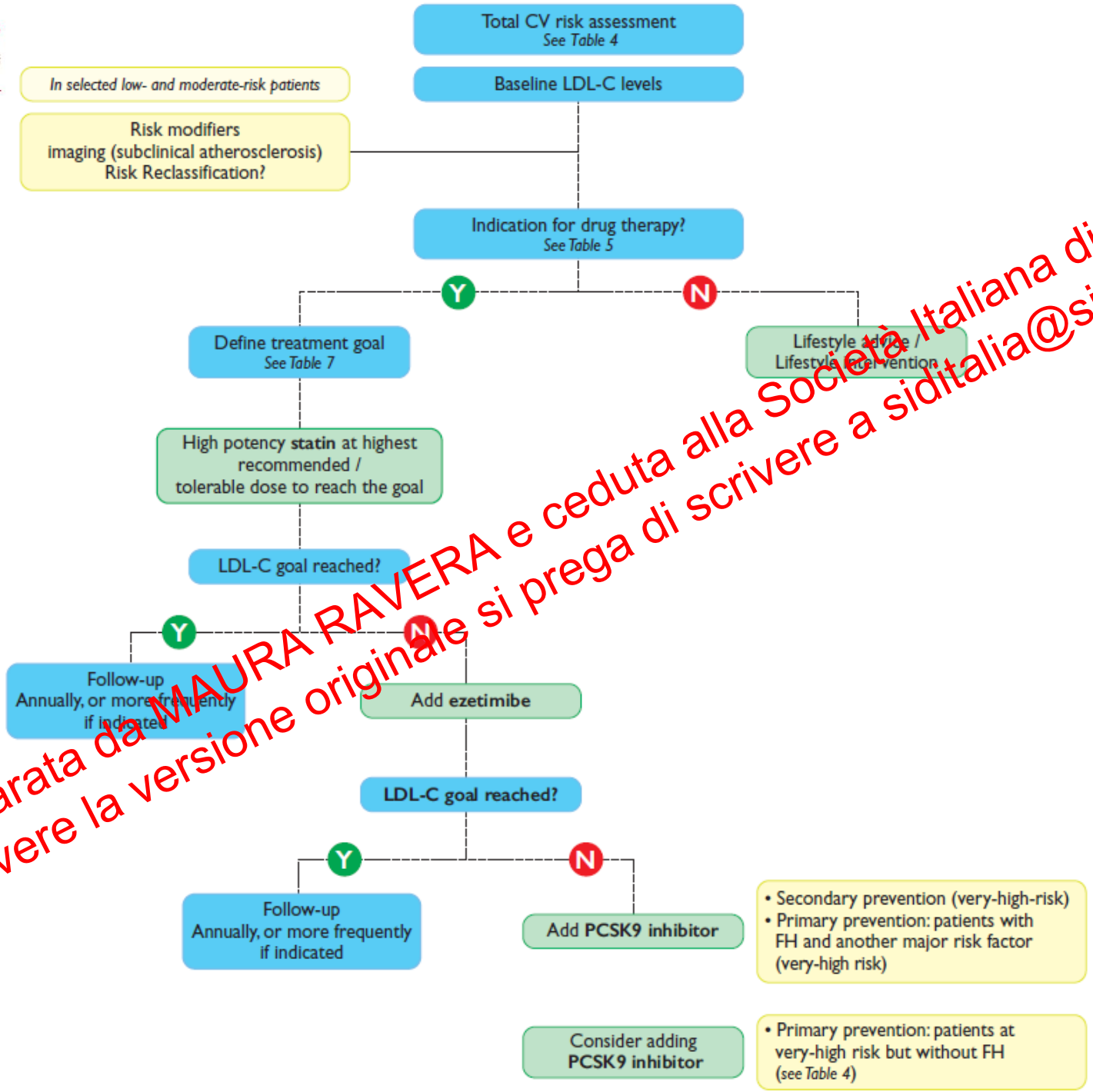
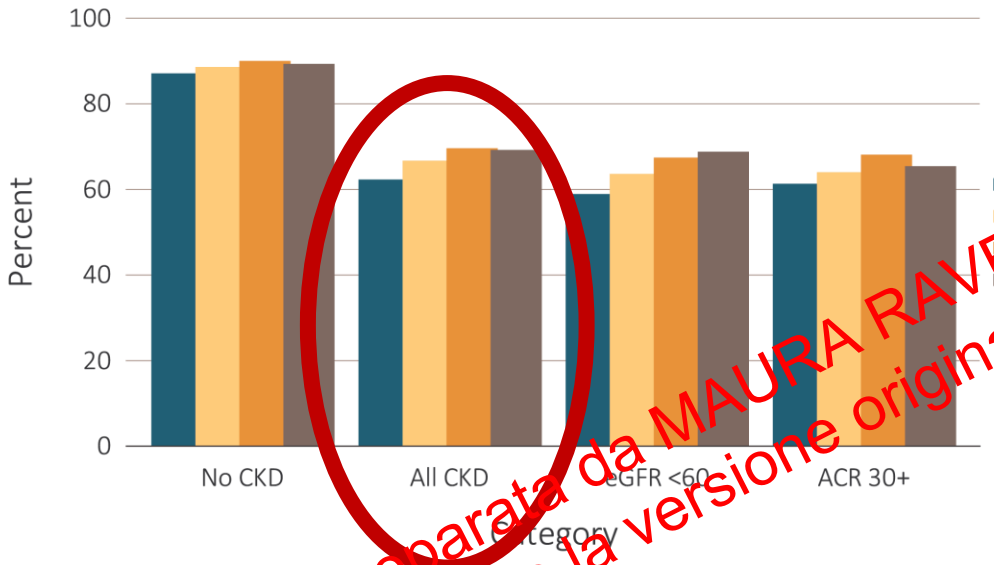
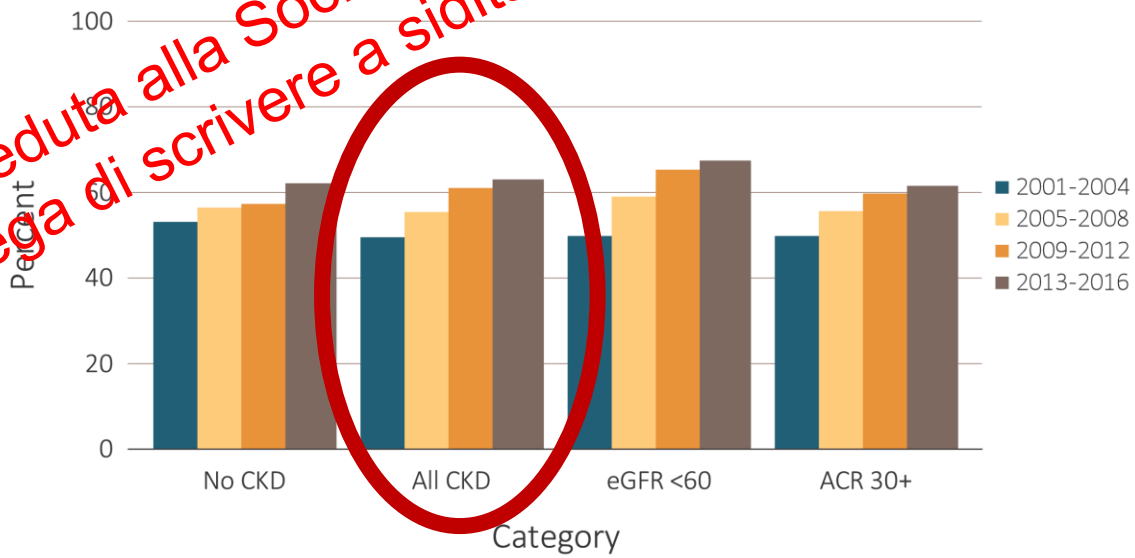


Time Trends of NHANES participants with and without CKD at target blood pressure, and with respect to cholesterol in the normal range, 2001-2016

Blood pressure target <140/90 mm Hg



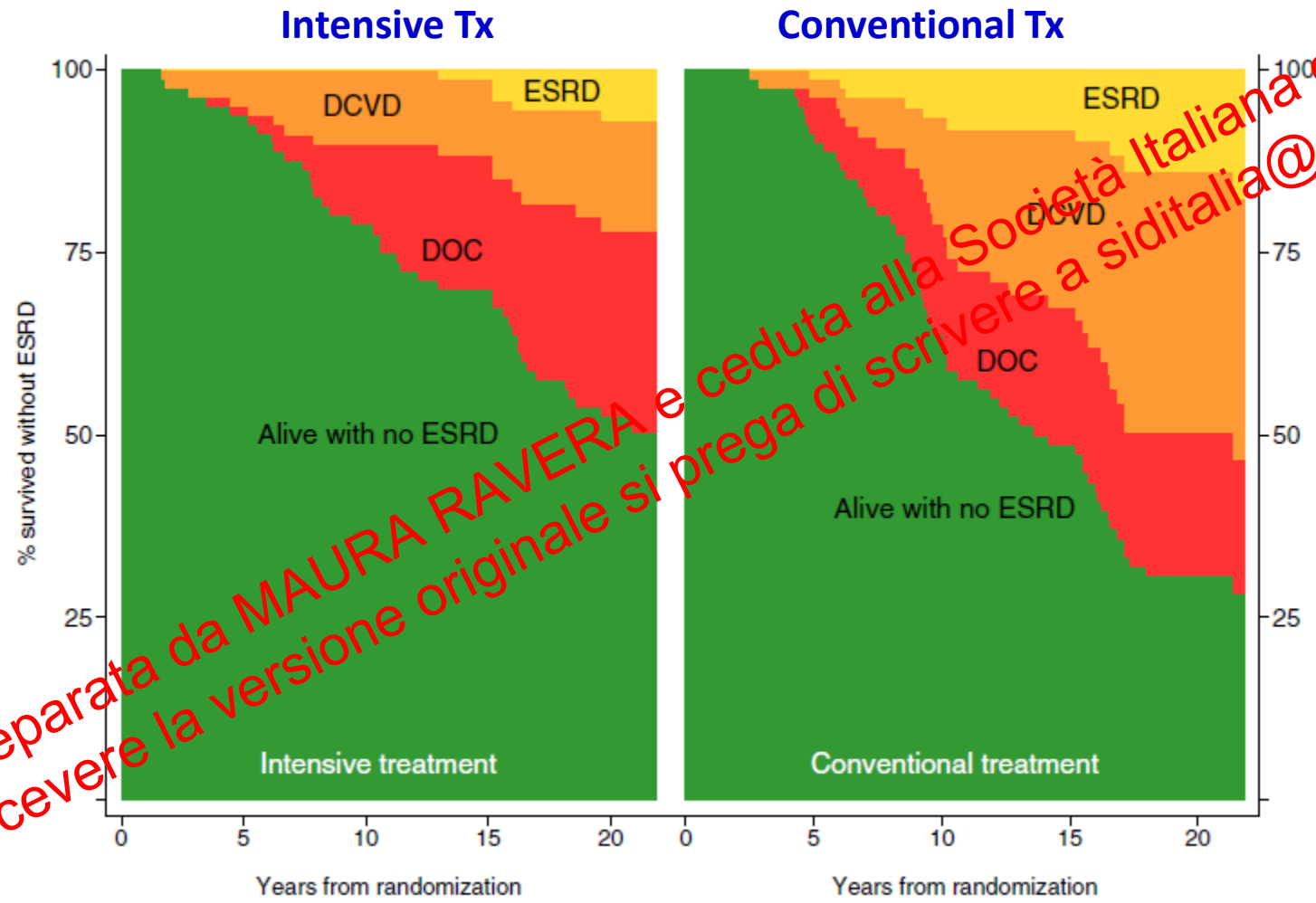
Total Cholesterol < 200 mg/dL



2018 Annual Data Report
Volume 1 CKD, Chapter 1

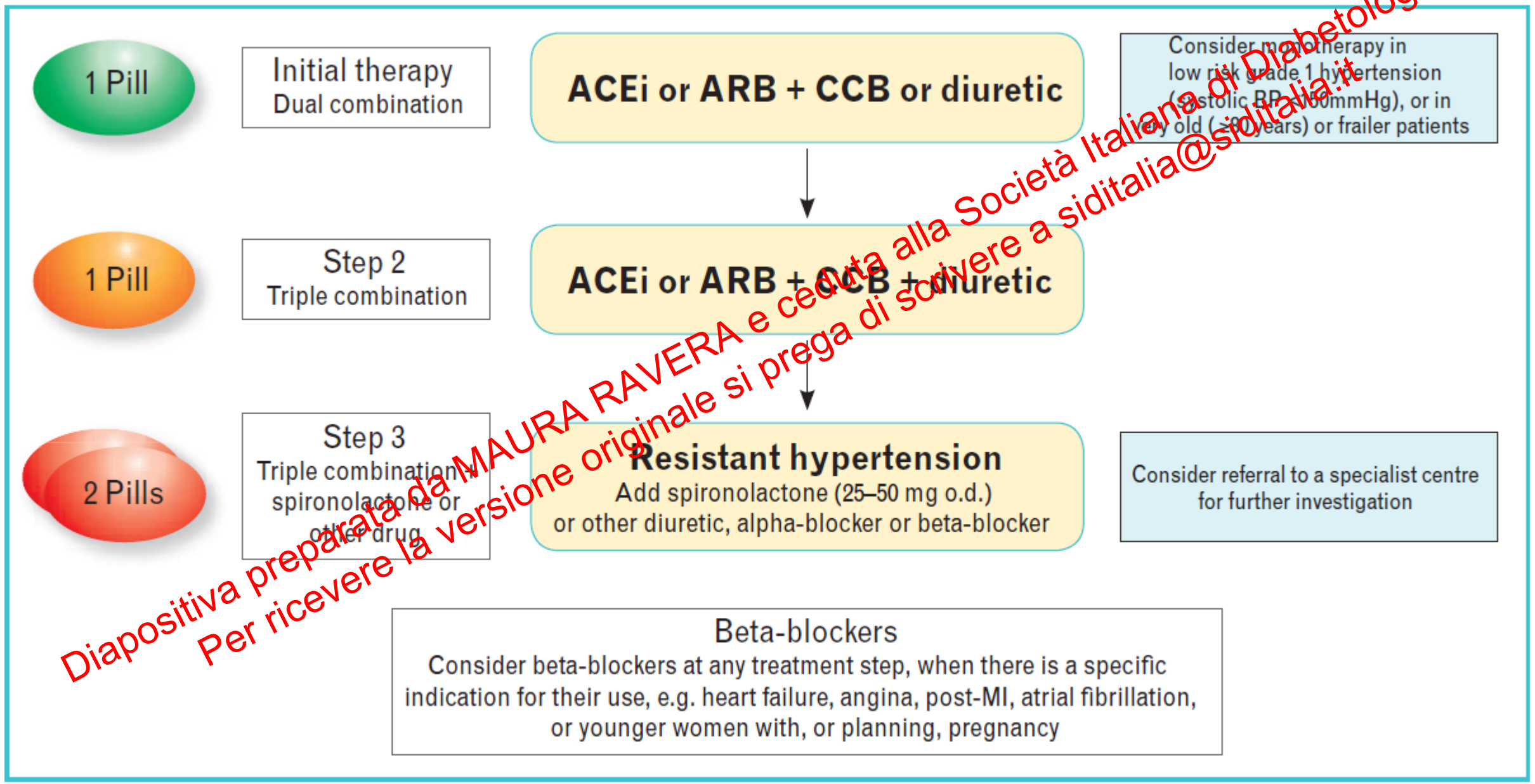
Progression to ESRD and mortality by treatment allocation: The Steno 2 Study

160 DM2 microalbuminurics assigned to conventional or intensified therapy for 7,8 yrs
Follow-up 21 years



Oellgaard J et al KI 2017

Core drug treatment strategy for Hypertension: 2018 ESC/ESH



Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

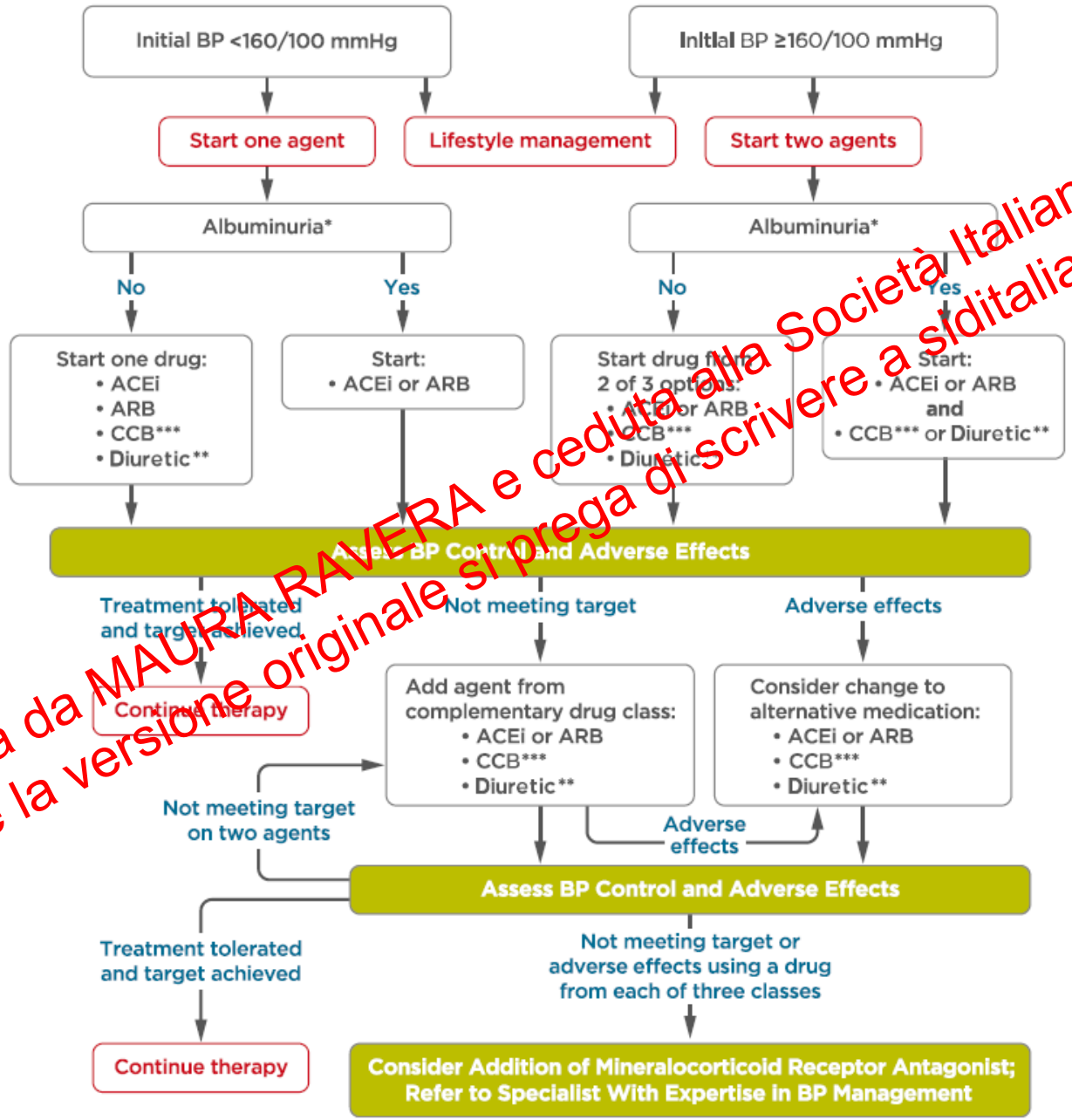


Table 6. Categories of BP in Adults* **ACC/AHA 2017**

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4); DBP, diastolic blood pressure; and SBP, systolic blood pressure.

ESC/ESH 2018

TABLE 3. Classification of office blood pressure[a] and definitions of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP, blood pressure.
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to systolic BP values in the ranges indicated. The same classification is used for all ages from 16 years.

ESC/ESH 2018

TABLE 9. Definitions of hypertension according to office, ambulatory, and home blood pressure levels

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Refers to conventional office BP rather than unattended office BP.

ESC/ESH Guidelines 2016

The following scheme may be proposed:

- **Evaluate the total CV risk of the subject.**
- **Involve the patient with decisions on CV risk management.**
- **Identify the LDL-C goal for that risk level.**
- **Calculate the percentage reduction of LDL-C required to achieve that goal.**
- **Choose a statin and a dose that, on average, can provide this reduction.**
- **Response to statin treatment is variable, therefore up-titration of the dose may be required.**
- **If the highest tolerated statin dose does not reach the goal, consider drug combinations.**
- **In addition, for subjects at very high and high risk, a ≥50% reduction in LDL-C should be achieved.**

The recommended therapeutic target for the level of cardiovascular risk, can be achieved through the progressive up-titration of the drug (“treat to target”) or using from the beginning the kind and the dose of drug appropriate to the patient's risk category, without further subsequent titration (“fire and forget”)

Acido bempedoico e trial CLEAR Harmony, Winsdom, etc
Farmco che riduce i livelli di clesterolo aumentando l'espressione per i recettori LDL
Effetto avverso principale: comparsa o peggioramento del diabete