

INQUADRAMENTO e strategie terapeutiche DELL'ANZIANO DIABETICO



Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.
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Terapia antiipertensiva nell'anziano con diabete

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24 ottobre 2017
Royal Hotel Continental



Il dr. ROBERTO TREVISAN dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche.

- **NOVO**
- **SANOFY**
- **LILLY**
- **NOVARTIS**
- **ASTRA ZENECA**
- **MEDTRONIC**
- **MERCK**
- **TAKEDA**
- **SERVIER**
- **JANSSEN**

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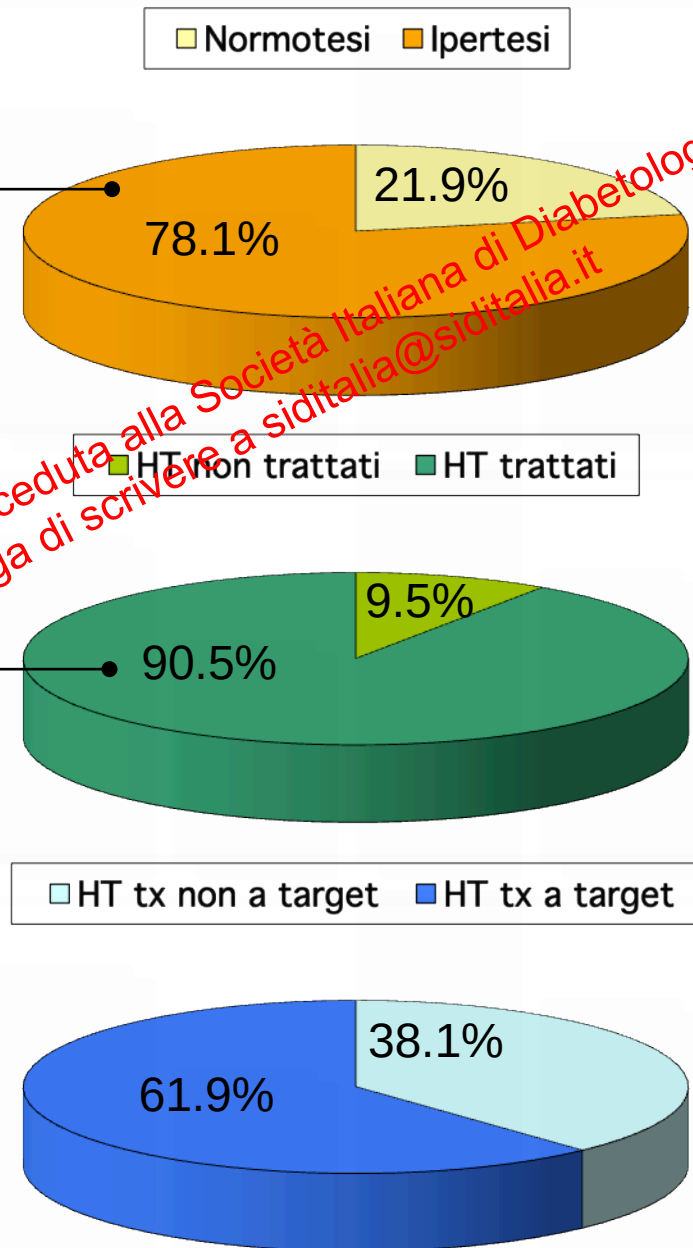


Prevalence and comorbidities

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The *Renal Insufficiency And Cardiovascular Events (RIACE)* Study

Prevalence of arterial hypertension, treated for hypertension and treated at target among 15,773 individuals with type 2 diabetes (JNC8 criteria)

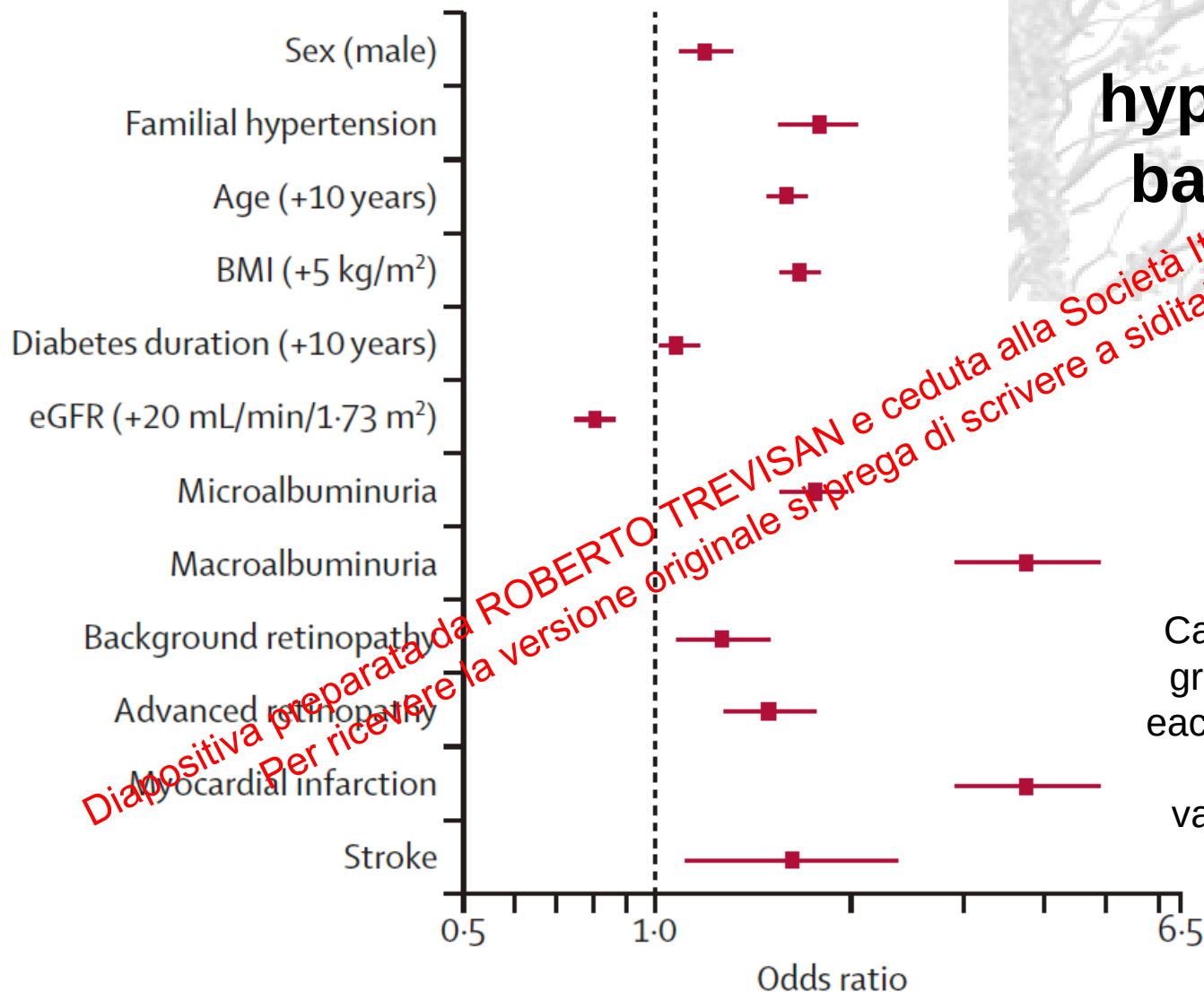


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The RIACE Study Group
(unpublished data)

The **R**enal **I**nsufficiency **A**nd **C**ardiovascular **E**vents (**RIACE**) Study

Diabetes and hypertension: the bad companions



Analysis of data from the 15,773 patients with T2DM assessed by the RIACE (Renal Insufficiency And Cardiovascular Events) study group. Plots are odds ratio of each characteristic (calculated for 1 SD of the continuous variable) in a multiple logistic model.



Prevalence and comorbidities



BP thresholds for intervention

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Blood Pressure Control in Patients with Diabetes

		ESC/ESH ESC/EASD 2013 ¹	KDIGO 2013 ²	JNC8 2014 ³	AACE/ACE 2016 ⁴	ADA 2017 ⁵ AMD-SID 2018
DM	SPB	<140	<140	<140	<130	<140
	DBP	<85	<90	<90	<80	<90
	RAS blockers	Suggested			Recommended	
	Double RAS blockade	Avoided				
DM & DKD	SPB	<130	<130	<140	<130	<130
	DBP	<85	<80	<90	<80	<80
	RAS blockers	Recommended	Suggested/ Recommended	Recommended	Recommended	Recommended
	Double RAS blockade		Insufficient evidence			

The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). **European Heart Journal** 34: 3035-3087, **2013**. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. **Kidney International** Vol 2, Issue 5, December **2013**. Eight Joint National Committee (JNC 8). **JAMA** 311: 507-520, **2014**. Garber AJ, et al, the AACE/ACE Task Force, **Endocrine Practice** 22: 84-113, **2016**. American Diabetes Association. Cardiovascular disease and risk management. Sec. 9. In Standards of Medical Care in Diabetes - 2016. **Diabetes Care** 40 (Suppl. 1): S75–S87, **2017**.



Prevalence and comorbidities



BP thresholds for intervention



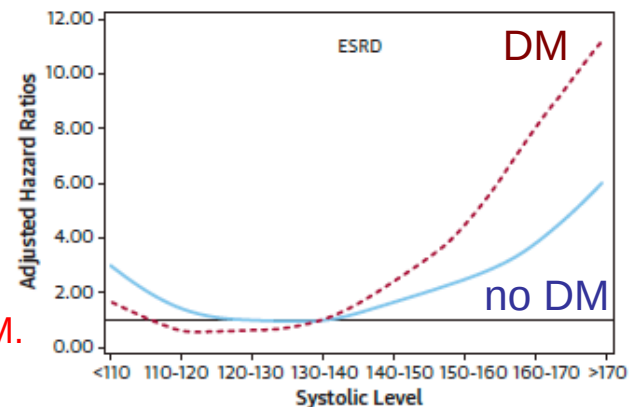
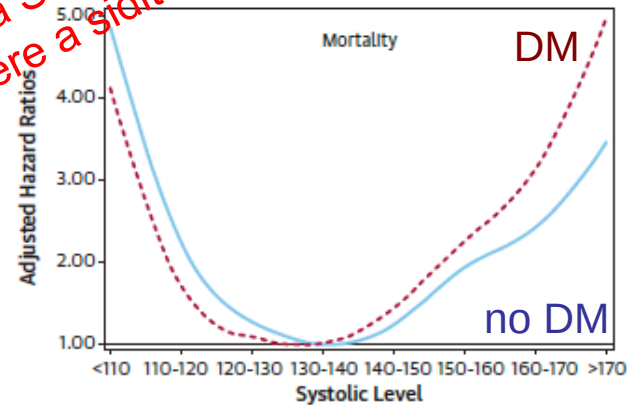
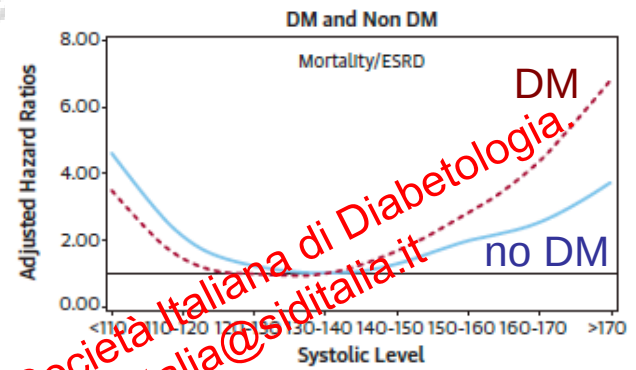
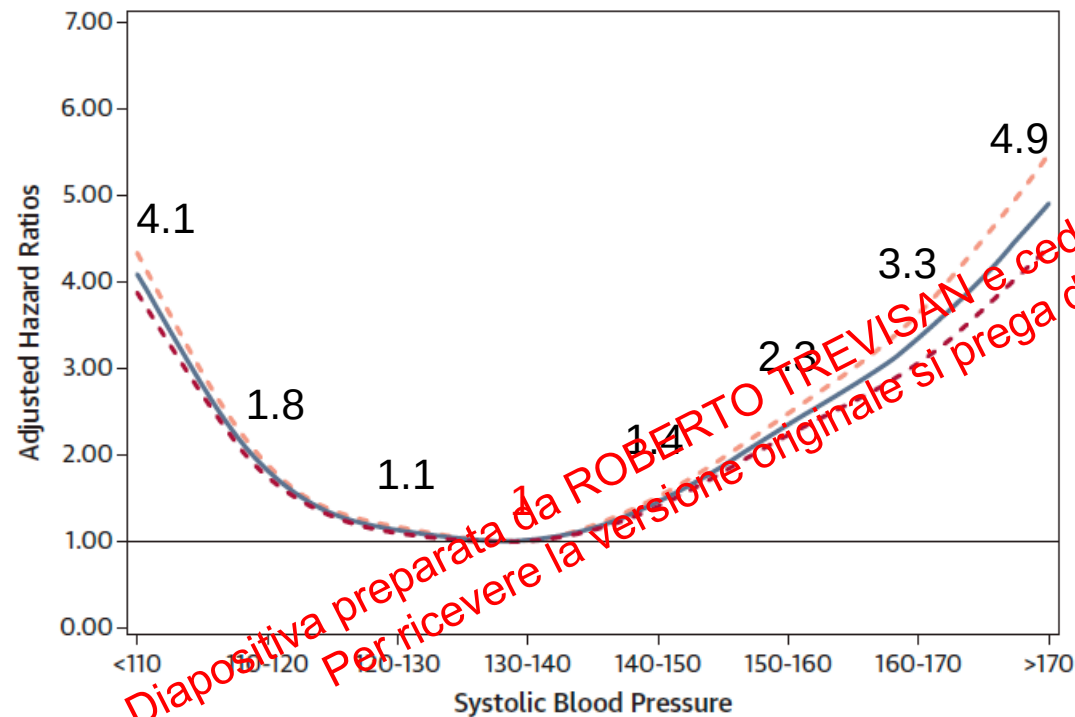
“J-curve hypothesis”, i.e. the marginal benefit of reducing BP to very low values and the target organ heterogeneity

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Impact of Achieved Blood Pressures on Mortality and End-Stage Renal Disease Among a Large, Diverse Hypertension Population

398,419 treated hypertensive subjects (30% with DM)

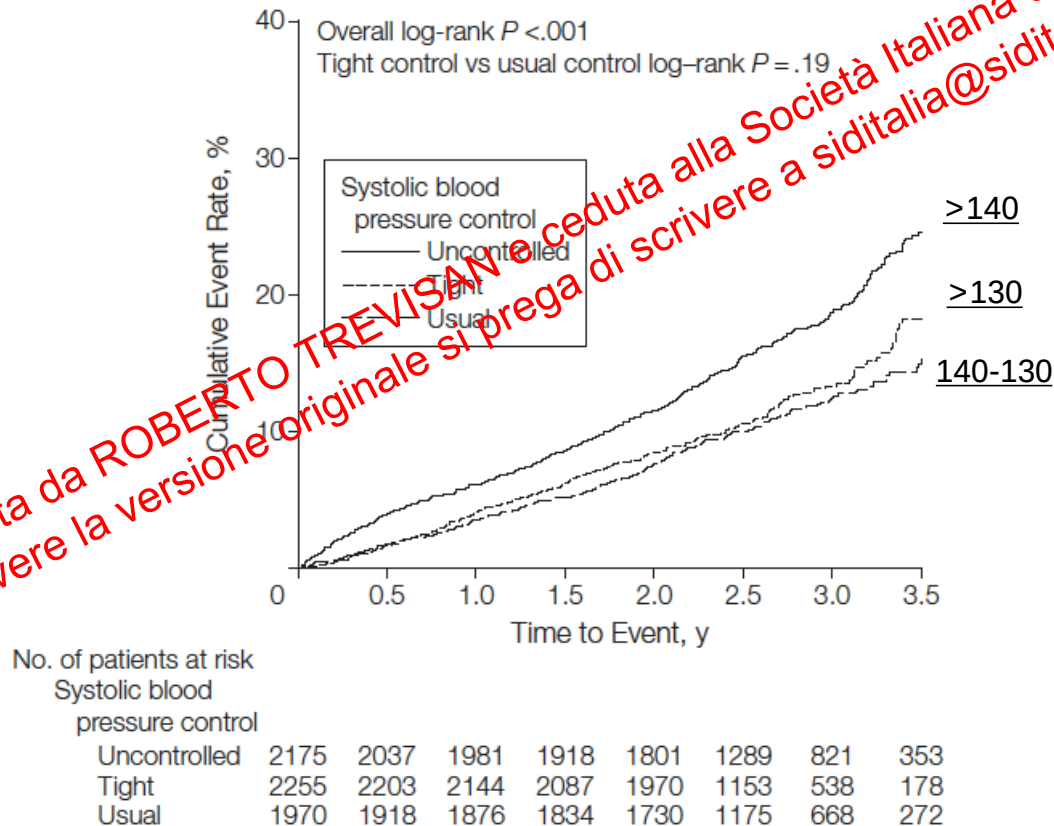
Continuous Adjusted HR for Mortality/ESRD



Systolic BP 130 to 139 mmHg was associated with the lower risk.
Diastolic BP 60 to 79 mmHg was associated with the lowest risk.
The nadir SBP and DBP for the lowest risk were 137 and 71 mmHg.
The nadir SBP and DBP for the lowest risk was 131 and 69 mmHg, in DM.

Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

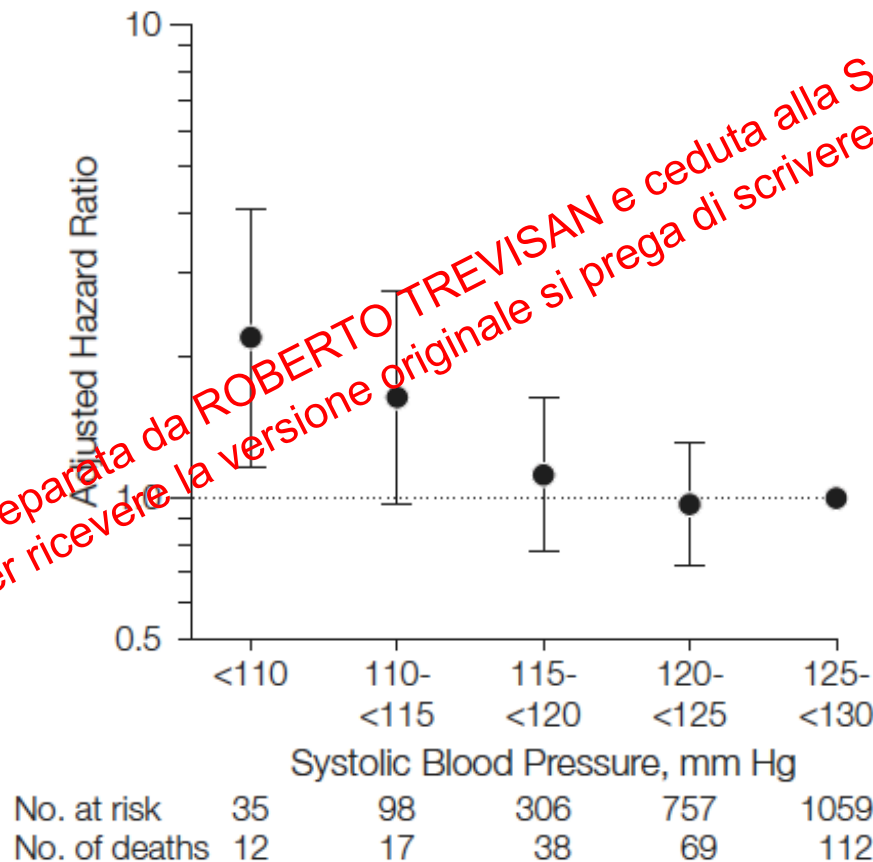
Figure 1. Cumulative Event Rate for Primary Outcome



Primary outcomes are a composite of the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.

Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

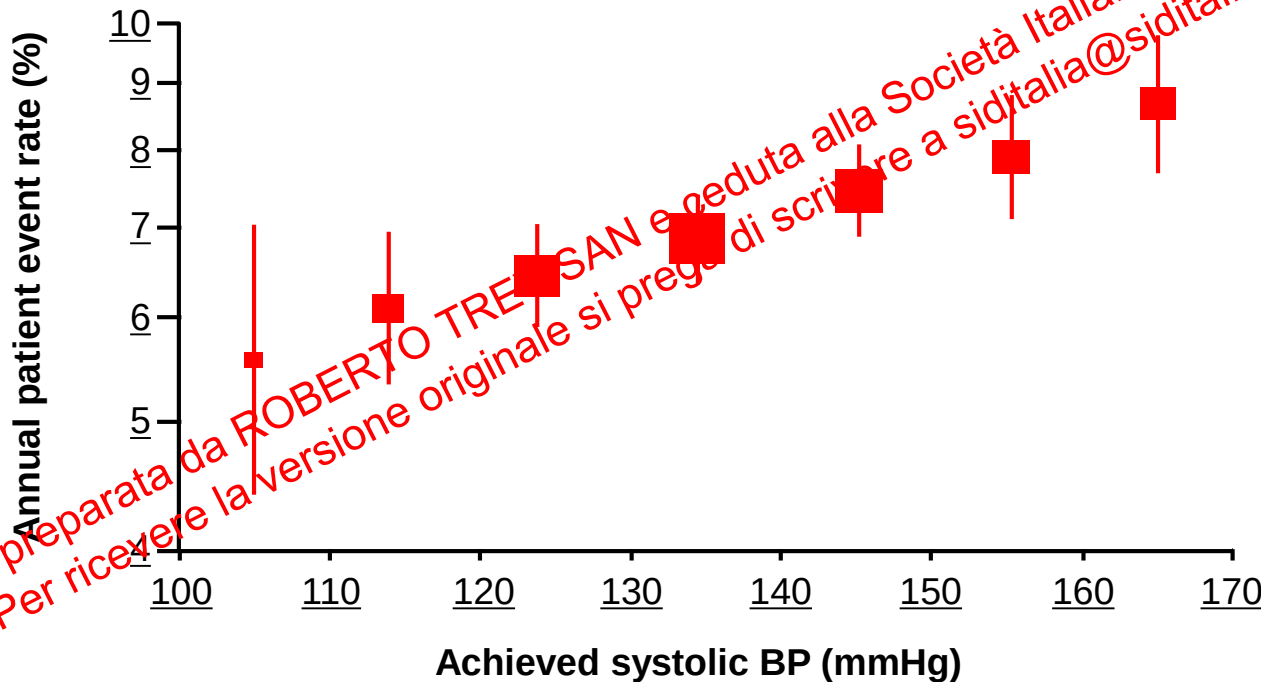
Figure 3. Adjusted Risk of All-Cause Mortality



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Lower blood pressure is associated with lower frequency of renal events in T2D

In the ADVANCE-BP study, rate of all renal events* significantly associated with achieved systolic BP levels ($p<0.0001$ for trend)



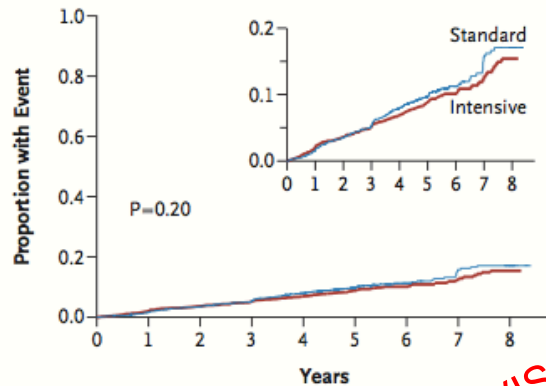
Median systolic BP (mmHg)	106	116	125	135	144	154	168
No. of person years	1431	4266	8974	11983	9138	4942	3470

*New-onset microalbuminuria or nephropathy, doubling of serum creatinine to $>200 \mu\text{mol/l}$, or ESRD
de Galan B et al. *J Am Soc Nephrol* 2009;20:883

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

- 4,733 persons with type 2 diabetes at high risk for cardiovascular events

A Primary Outcome



No. at Risk

Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108

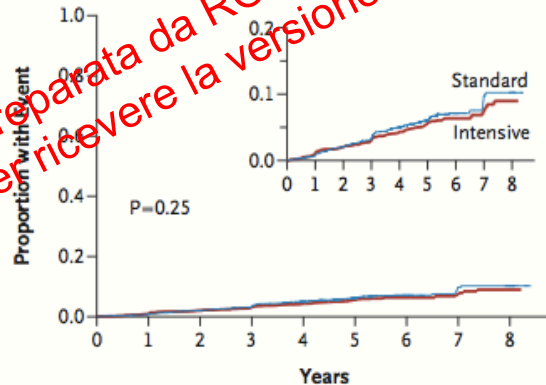
B Nonfatal Stroke



No. at Risk

Intensive	2362	2291	2223	2174	1841	1128	313	186	88
Standard	2371	2287	2235	2186	1879	1196	382	215	114

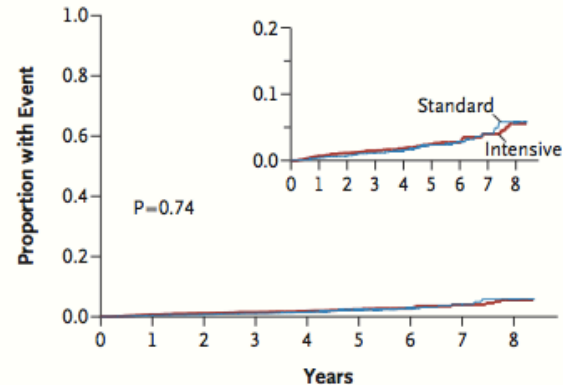
C Nonfatal Myocardial Infarction



No. at Risk

Intensive	2362	2278	2190	2133	1787	1087	299	177	82
Standard	2371	2278	2208	2141	1818	1145	365	201	112

D Death from Cardiovascular Disease



No. at Risk

Intensive	2362	2304	2252	2201	1870	1143	317	188	91
Standard	2371	2313	2268	2218	1922	1220	393	221	118

Adverse Events

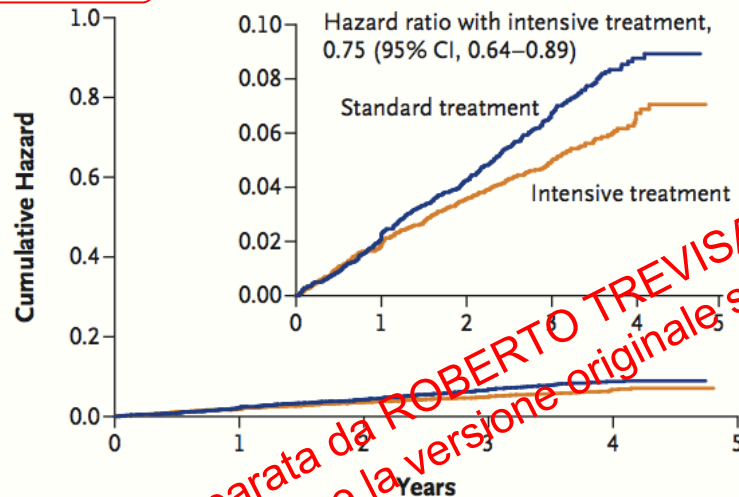
	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 ml/min/1.73m ²	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (2.5)	58 (2.4)	0.93
Dizziness on Standing†	217 (44)	188 (40)	0.36

† Symptom experienced over past 30 days from HRQL sample of N=969 participants assessed at 12, 36, and 48 months post-randomization

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

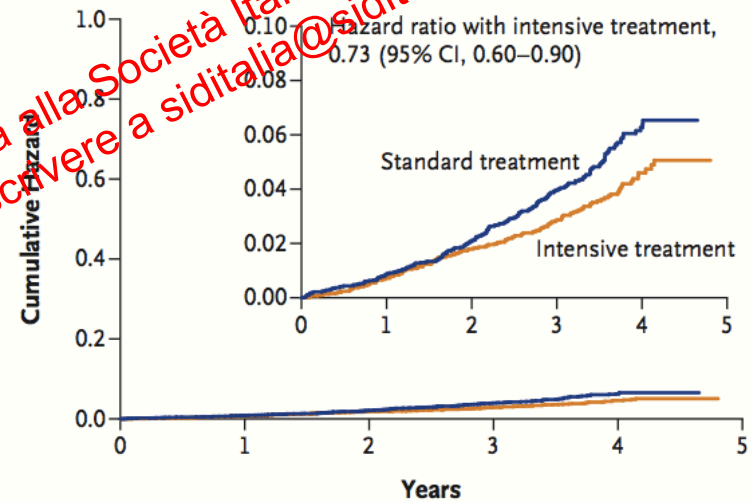
9,361 persons with a SBP of 130 mmHg or higher and increased cardiovascular risk, but without diabetes

A Primary Outcome



No. at Risk	0	1	2	3	4	5
Standard treatment	4683	4437	4228	2829	721	
Intensive treatment	4678	4436	4256	2900	779	

B Death from Any Cause



No. at Risk	0	1	2	3	4	5
Standard treatment	4683	4528	4383	2998	789	
Intensive treatment	4678	4516	4390	3016	807	

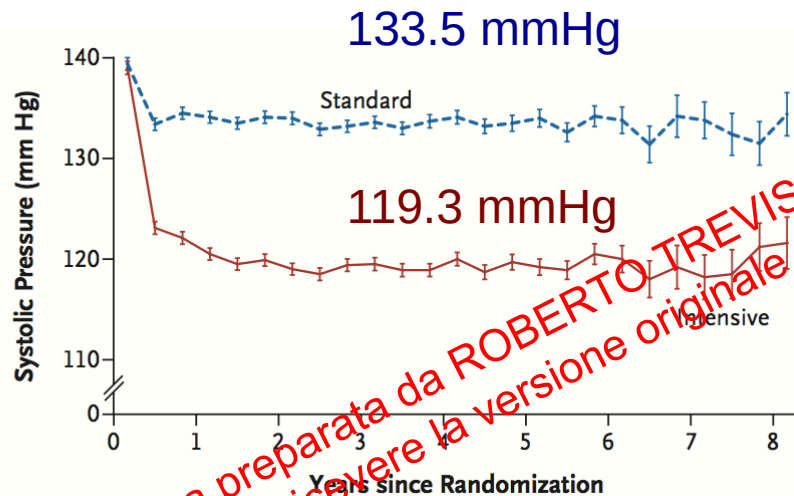
- HR 0.75; 95%CI 0.64-0.89, $p < 0.001$ (myocardial infarction, other ACS, stroke, HF, death from CVD)

- HR 0.73; 95%CI 0.60-0.90 $p = 0.003$

Effects of Intensive Blood-Pressure Control ACCORD and SPRINT

4,733 persons with type 2 diabetes at high risk for cardiovascular events

9,361 persons with a SBP of 130 mmHg or higher and increased cardiovascular risk, but without diabetes

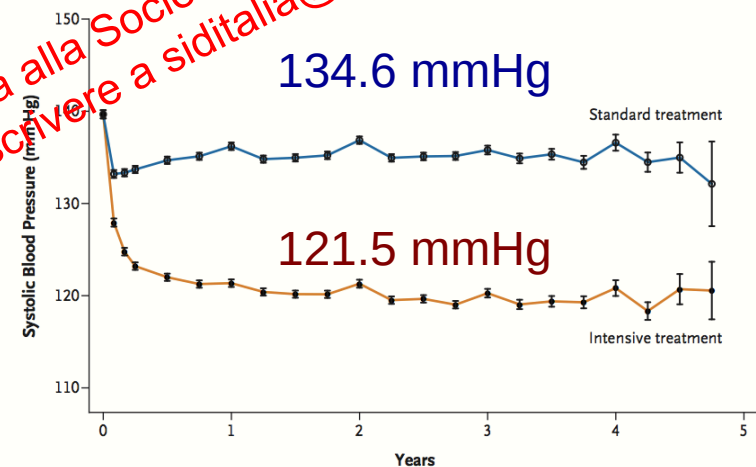


Mean No. of Medications Prescribed

	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Intensive	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
Standard								

No. of Patients

	2174	2071	1973	1792	1150	445	156	156
Intensive	2208	2136	2077	1860	1241	504	203	201
Standard								



No. with Data

	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Standard treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Intensive treatment										

Mean No. of Medications

	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Standard treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0
Intensive treatment										

The ACCORD Study Group, **N Engl J Med** 362: 1575-85, 2010

The SPRINT Research Group, **N Engl J Med** Nov 9, 2015

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

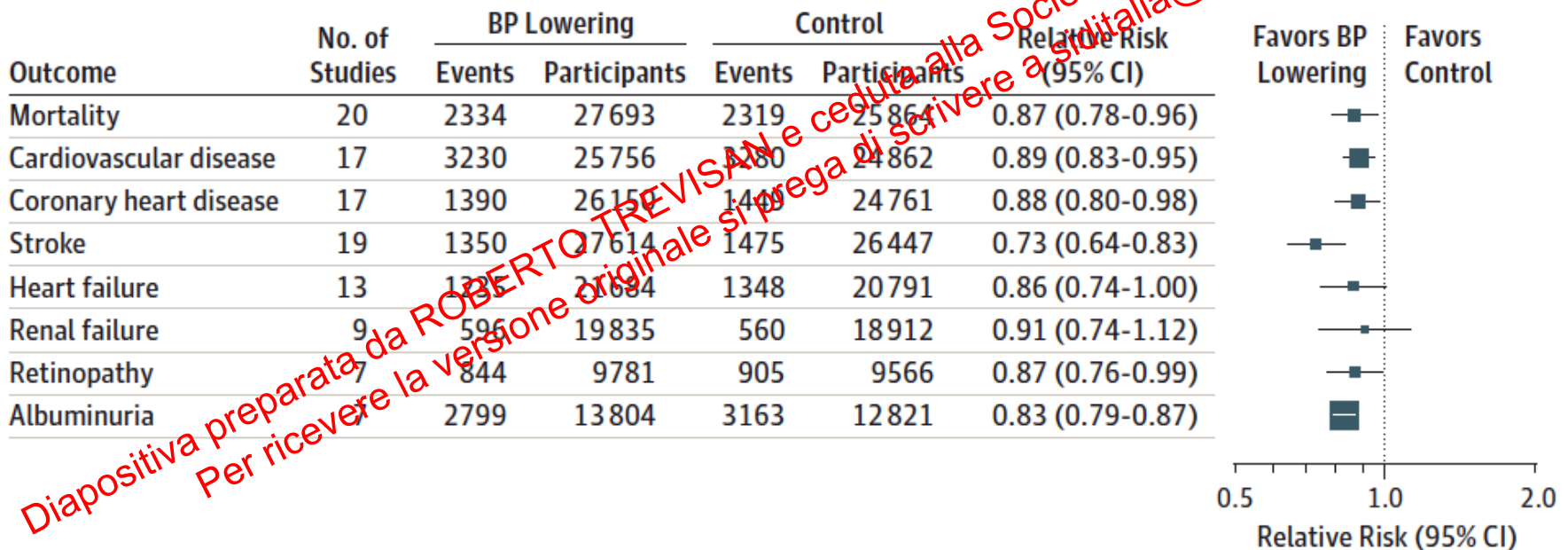
9,361 persons with a SBP of 130 mmHg or higher and increased cardiovascular risk, but without diabetes

- | BP was measured using an automated device when patients were sitting in a quiet room without an observer (not office BP)
- | This unobserved blood pressure is around 10-15 mmHg lower than office BP
- | 120 mmHg in SPRINT may equate 130-135 mmHg when using office BP
- | Further, goal BP <120 mmHg was only achieved in about 50% of the intensively treated individuals

Blood Pressure Lowering in Type 2 Diabetes

A Systematic Review and Meta-analysis

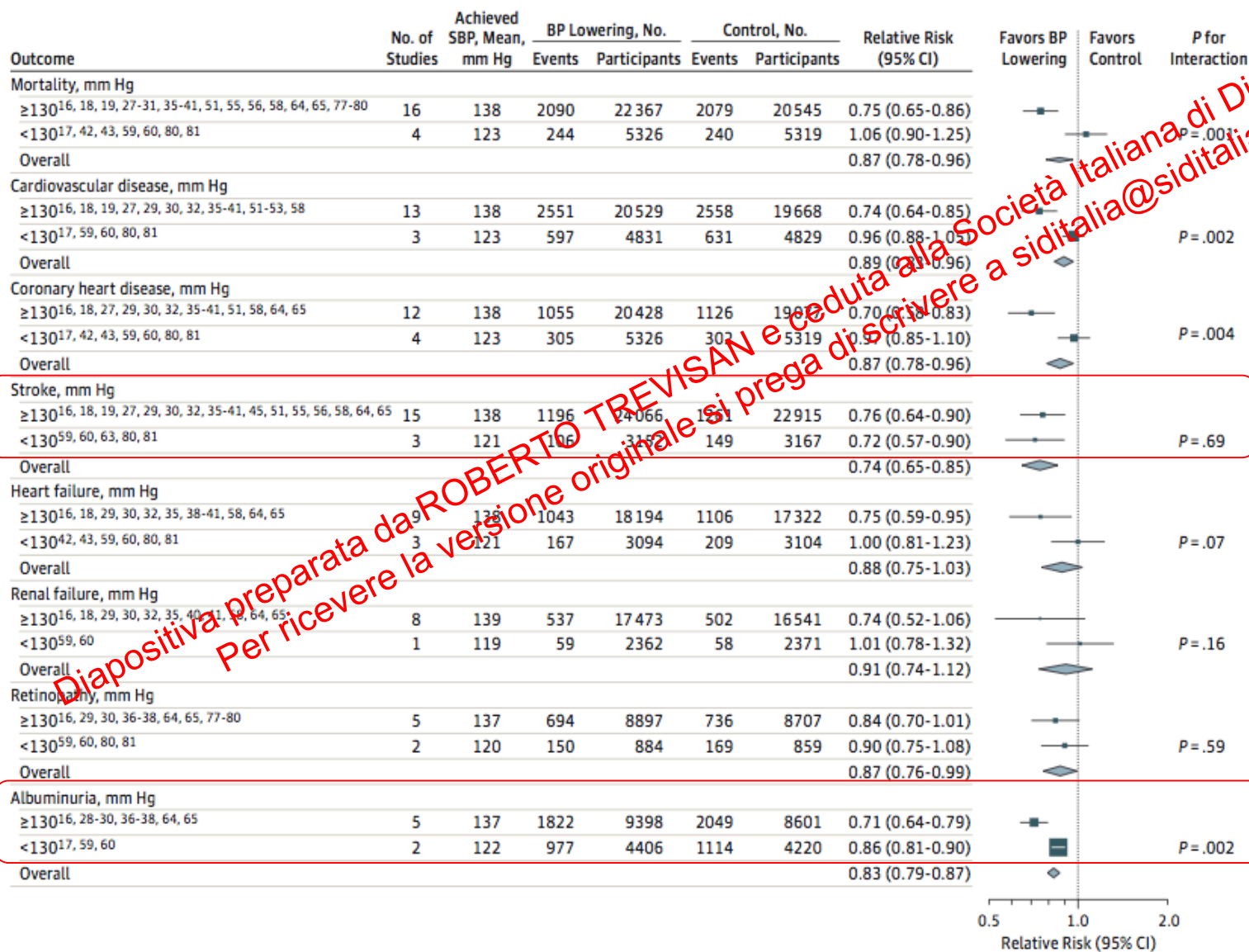
Figure 2. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients



Blood Pressure Lowering in Type 2 Diabetes

A Systematic Review and Meta-analysis

Figure 4. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes, Stratified by Mean Achieved Systolic BP in the Active Group of Each Trial



Stratification according to attained sBP

Key point

- Contrary to what was recommended by most guidelines until 2013, there is little or no additional benefit in lowering SBP below 130 mmHg in diabetes mellitus.

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Prevalence and comorbidities



BP thresholds for intervention



“J-curve hypothesis”, i.e. the marginal benefit of reducing BP to very low values and the target organ heterogeneity



Optimal BP target

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STANDARD DI CURA AMD-SID 2016

OBIETTIVI

- **PA < 140/90 mmHg** (Livello prova I, Forza raccomandazione A)
- **PA < 130/80 mmHg** in pz con recente diagnosi di ipertensione, giovani, elevato rischio di ictus, o con altri fattori di rischio CVD (Livello prova IV, Forza raccomandazione C)
- **PA < 130/80 mmHg** in pz con micro- o macroalbuminuria CVD (Livello prova III, Forza raccomandazione B)
- **PA < 150/90 mmHg** in pz anziani (Livello prova I, Forza raccomandazione A)

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“J-curve hypothesis”, i.e. the marginal benefit of reducing BP to very low values and the target organ heterogeneity



Optimal systolic BP target



BP lowering in older hypertensive patients

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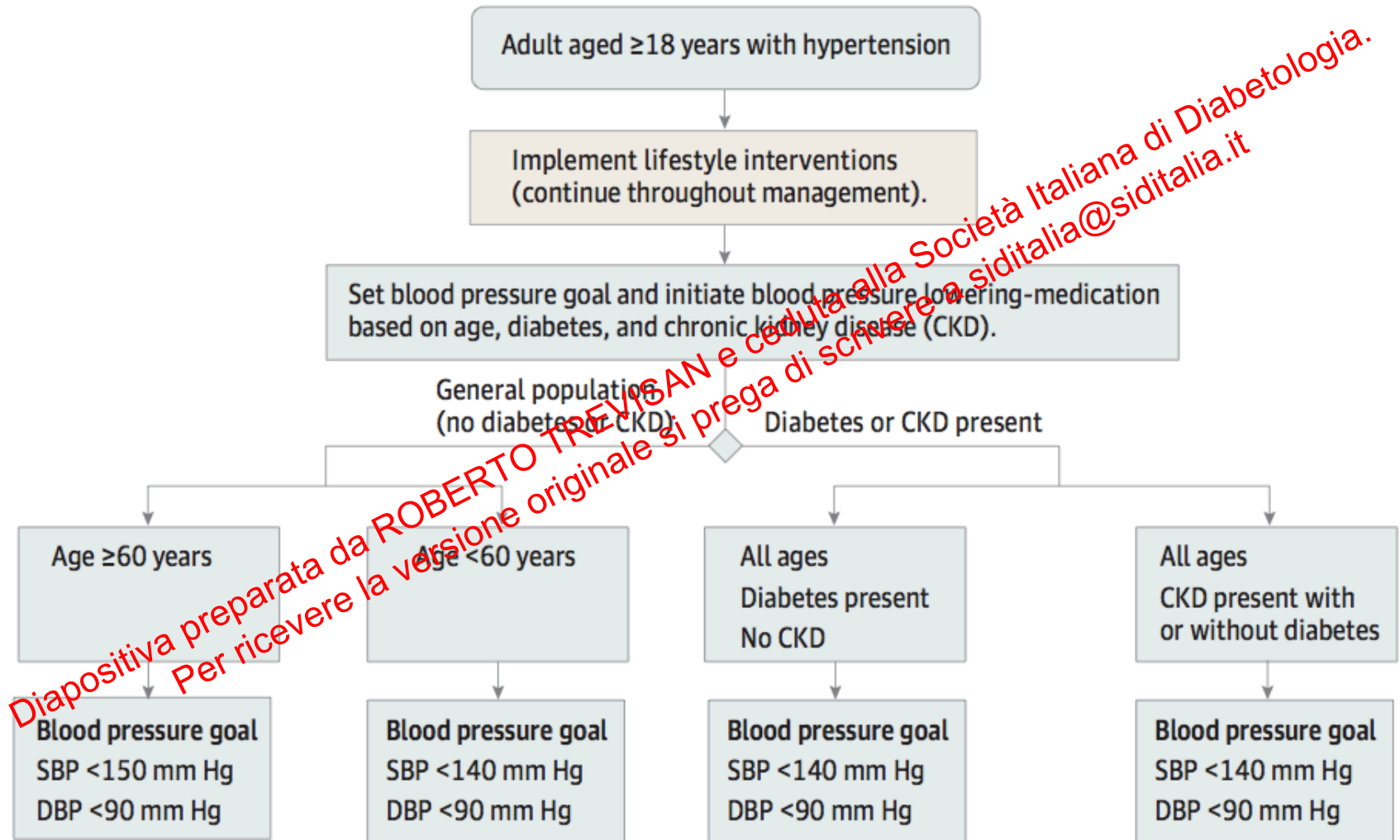
Blood Pressure Control in Patients with Diabetes

	<60 years of age	<60 years of age + DM	<60 years of age + CKD	Elderly >60 years or 60-80 years	Elderly >80 years
ESC/ESH ESC/EASD 2013 ¹	<140/90	<140/85	<140/90 (<130/90)	SBP 140-150	SBP <160
JNC8 2014 ²	<140/90	<140/90	<140/90	<150/90	<150/90
ASH/ISH 2014 ³	<140/90	<140/90 (<130/80)	<140/90 (<130/80)		<150/90 (<140/90 if DM and CKD)
AHA/ACC 2015 ⁴	<140/90 in CAD, ACS, HF *				<150/90
NICE 2016 ³	<140/90				<150/90

* <130/80 in previous MI/stroke/TIA or CAD-risk equivalents (AAA, PAD and carotid artery disease) can be considered

The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). **European Heart Journal** 34: 3035-3087, **2013**. Eight Joint National Committee (JNC 8). **JAMA** 311: 507-520, **2014**. Weber MA et al. Clinical Practice Guidelines for the management of Hypertension in the Community. A statement by the ASH and the ISH. **J Clin Hypertens**, **2015**. Rosendorff C et al., Treatment of Hypertension in Patients With Coronary Artery Disease A Scientific Statement From the American Heart Association, American College of Cardiology, and American Society of Hypertension. **Hypertension**, **2015**.

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults



Benefits and Harms of Intensive Blood Pressure Treatment in Adults aged 60 years or older

RRs for death, stroke, and cardiac events in trials in which the intervention group had a target of SBP ≤ 150 mmHg or DBP ≤ 90 mmHg

High-strenght evidence

	Trials	Treatment Events, n/N	Control Events, n/N	RR	95%CI
Mortality	9 Trials (SBP ≥ 160)	1024/26328	1119/20122	0.90	0.83-0.98
	4 Trials (SBP < 160)	825/17450	976/17495	0.85	0.72-0.99
Stroke	9 Trials (SBP ≥ 160)	413/26328	543/20122	0.74	0.65-0.84
	4 Trials (SBP < 160)	490/17450	601/17495	0.80	0.62-1.01
Cardiac Events	9 Trials (SBP ≥ 160)	546/26328	669/20122	0.77	0.68-0.89
	4 Trials (SBP < 160)	708/17450	828/17495	0.86	0.72-0.96

Benefits and Harms of Intensive Blood Pressure Treatment in Adults aged 60 years or older

RRs for death, stroke, and cardiac events in trials in which the intervention group had a target of SBP ≤ 140 mmHg or DBP ≤ 85 mmHg

Low-strenght to moderate-strenght evidence

	Trials	Treatment Events, n/N	Control Events, n/N	RR	95%CI
Mortality	6 Trials	388/23880	427/17611	0.86	0.69-1.06
Stroke	6 Trials	195/23880	230/17611	0.79	0.59-0.99
Cardiac Events	6 Trials	442/23880	491/17611	0.82	0.64-1.00

- | No evidence that age (<75 vs 75 or older) modifies treatment effect
- | Diabetic individuals are at least as likely to benefit from BP lowering
- | Patients frailty dose not seem to modify treatment effects

Outcomes of Intensive Blood Pressure Lowering in Older Hypertensive Patients

4 high-quality trials involving 10,857 older hypertensive patients with a mean follow-up of 3.1 years

CENTRAL ILLUSTRATION Intensive BP Lowering and Cardiovascular and Safety Outcomes in Older Hypertensive Patients

Effects of Intensive BP-lowering in Older (≥ 65 Years) Hypertensive Patients



Beneficial effects

29% reduction in major adverse cardiovascular (CV) events (MACE)

33% reduction in CV mortality

37% reduction in heart failure



Drawbacks/concerns

Patients use an increased number of anti-hypertensive medications

Possible increase in renal failure

Possible increase in serious adverse events

Possible increase in hypotension, syncope and other adverse effects



Prevalence and comorbidities



BP thresholds for intervention



“J-curve hypothesis”, i.e. the marginal benefit of reducing BP to very low values and the target organ heterogeneity



Optimal systolic BP target



BP lowering in older hypertensive patients



Older individuals with diabetes

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American Diabetes Association

Older Adults

Treatment of hypertension to individualized target levels is indicated in most older adults

Patients characteristics	Health Status	Rationale	BP (mmHg)
Healthy	Few coexisting chronic illnesses, intact cognitive and functional status	Longer remaining life expectancy	<140/90
Complex/intermediate	Multiple coexisting chronic illnesses* or 2+ instrumental activity of daily life impairments or mild-to-moderate cognitive impairment	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<140/90

*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By “multiple,” we mean at least three, but many patients may have five or more.

American Diabetes Association

Older Adults

Treatment of hypertension to individualized target levels is indicated in most older adults

Patients characteristics	Health Status	Rationale	BP (mmHg)
Very complex/poor health	LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ activity of daily life dependencies	Limited remaining life expectancy makes benefit uncertain	<150/90

** The presence of a single end-stage chronic illness, such as stage 3-4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

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

Older Adults (Aged ≥ 65 years)

Specific observations	
1.	Diabetes is itself associated with an increase in arterial stiffness , leading to a greater age-related increase in SBP (and decreased DBP).
2.	Older adults with diabetes and hypertension (mainly systolic) typically present with high risk for CV events and other age-related diseases, difficulties achieving blood pressure targets also due to arterial stiffness.
3.	Older adults with diabetes and hypertension (mainly systolic) have polypharmacy and high risk of iatrogenic complications , including hypoglycemia, hypotension and volume depletion.

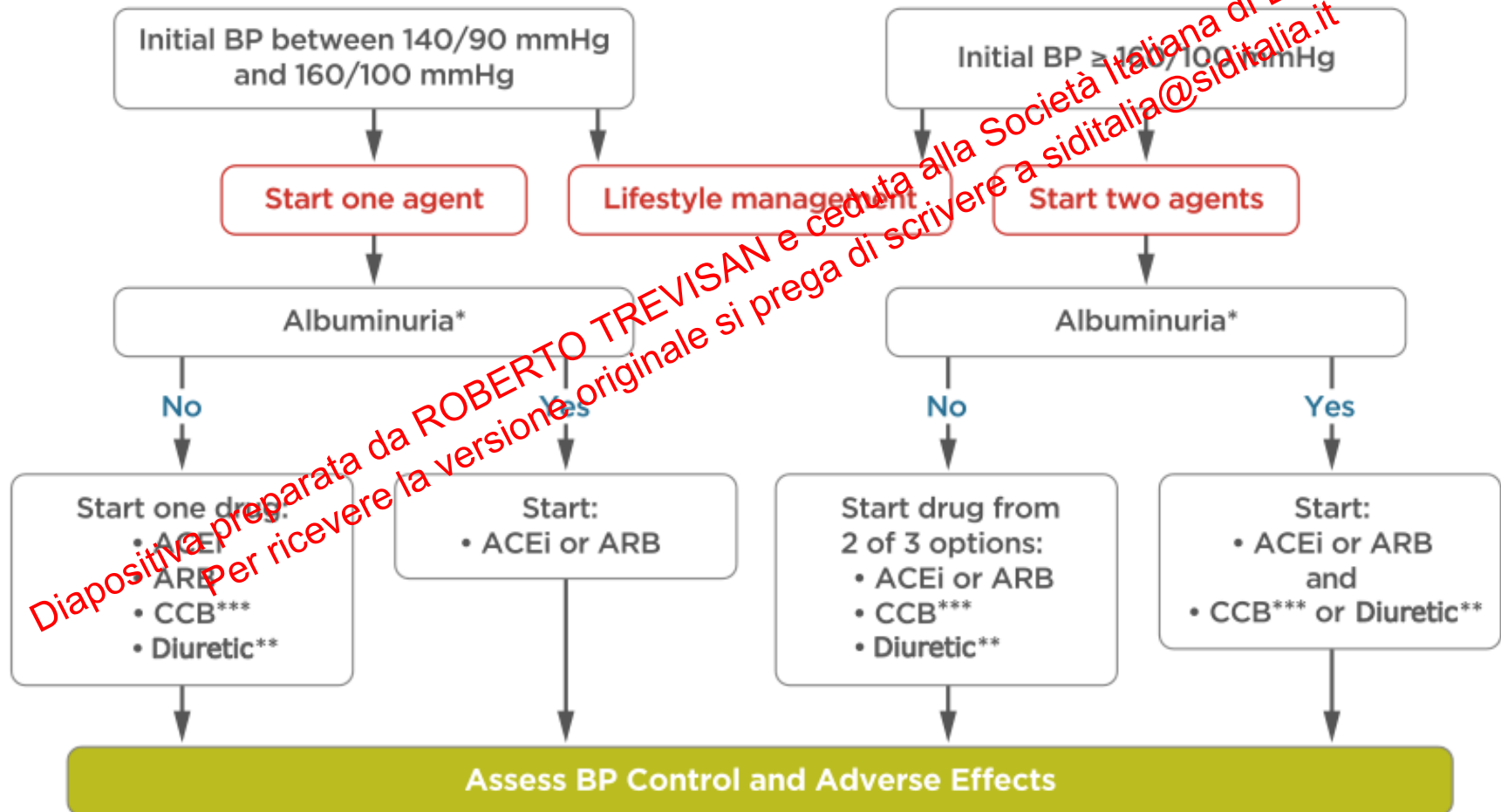
Diabetes and Hypertension: A Position Statement by the American Diabetes Association

Older Adults (Aged ≥ 65 years)

Specific observations	
4.	SBP should be the main target of treatment.
5.	In fitter patients, a therapeutic strategy similar to that used in younger individuals may be used.
3.	In older adults with impaired vascular compliance, as indicated by a difference >60 mmHg between SBP and DPB (pulse pressure), attempt to reach a target SBP must be balanced against the risk of lowering DBP <65 -70 mmHg.

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

Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes *

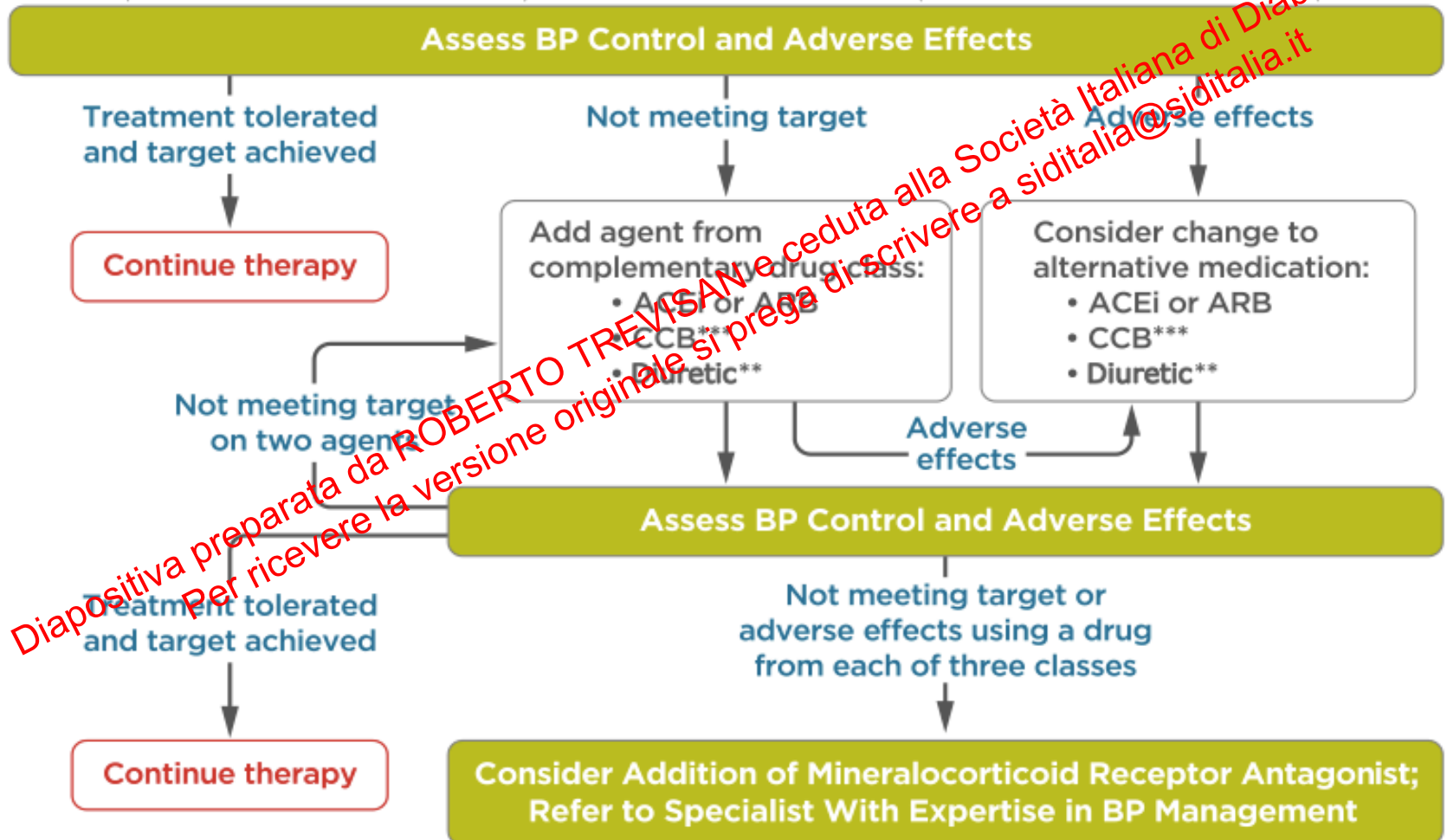


* Irrespective of age

De Boer IH et al., **Diabetes Care** 40: 1273-1284, 2017

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

Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes *



* Irrespective of age

De Boer IH et al., **Diabetes Care** 40: 1273-1284, 2017

Tolerability of antihypertensive medications in older adults

Choice of antihypertensive medication in older adults:
is there an ideal agent?

Specific observations	
1.	All drug classes are effective and work.
2.	Similar BP reduction irrespective of the drug resulted in similar lowering of risk.
3.	Drug efficacy is similar in young and old (aged over 65 years).
4.	BP variability, white coat hypertension, postural hypotension, widened pulse pressure deserve consideration in older adults.



Grazie per la vostra attenzione

