

IPERTENSIONE nel DIABETICO

QUALI FARMACI e PERCHE'



Roma,
9-11 novembre 2012

Quali target per il diabetico iperteso

Lino Furlani

Servizio di Endocrinologia

Ospedale Sacro Cuore – Don Calabria - Negrar (VR)



1° CORSO NAZIONALE DI AGGIORNAMENTO

Associazione Medici Endocrinologi

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Malattia cardiovascolare (CVD) e Diabete

- La malattia cardio – vascolare (CVD) è la principale causa di morbidità e di mortalità nei diabetici
 - 80 % mortalità per CVD di cui 75 % per CHD
- L'ipertensione arteriosa costituisce co-fattore di rischio per lo sviluppo di CVD nel Diabete
- Un adeguato controllo della PA riduce il rischio di progressione della nefropatia diabetica
- Il controllo e la prevenzione dei fattori di rischio di CVD individuali comporta evidenti benefici nei diabetici

Rischio CV

- Soggetti a **rischio elevato**

- Dislipidemia familiare
- **Diabete mellito (tipo 1 o tipo 2) non associato a fattori di rischio**
- Insufficienza renale moderata (eGFR 30–59 mL/min/1.73 m²)
- SCORE $\geq 5\% \leq 10\%$ secondo la tabella di rischio

- Soggetti a **rischio molto elevato**

- CVD documentata (coronarografia, imaging nucleare, ecostress)
- Ateromasi carotidea, anamnesi di IM o di procedure di rivascularizzazione, stroke, arteriopatia periferica.
- **Diabete mellito (tipo 1 o tipo 2) associato a uno o più fattori di rischio CV o a danno d'organo (per es microalbuminuria)**
- Insufficienza renale severa (eGFR < 30 mL/min/1.73 m²)
- SCORE $\geq 10\%$ secondo la tabella di rischio

Ipertensione e Diabete



- **diabete tipo 2**

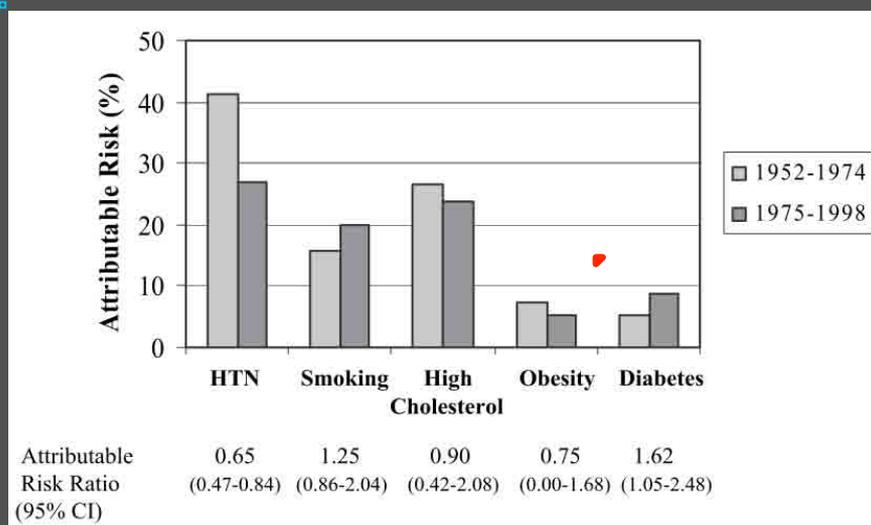
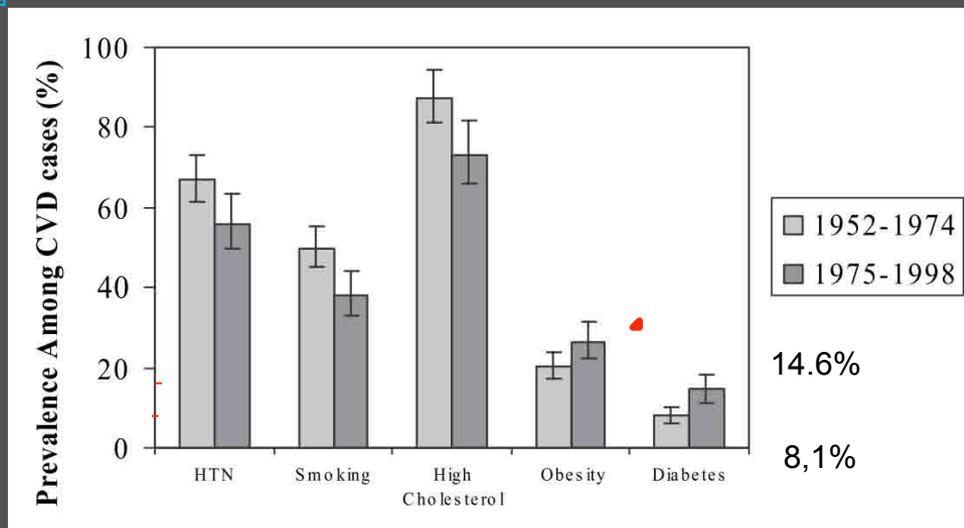
- si manifesta precocemente e spesso (specialmente negli obesi) precede lo sviluppo del diabete (a 45 anni il 40% e a 75 anni il 60% dei diabetici sono ipertesi)
- In almeno l'80% dei casi l'ipertensione o un anomalo profilo pressorio circadiano sono presenti al momento della diagnosi
- Ipertensione o anomalo profilo pressorio sono forti predittori di eventi CV
- il 35-75% delle complicanze cardiovascolari del diabete possono essere attribuite alla coesistenza di ipertensione.

- **Il rischio CVD nel diabete**

- aumenta di 2 - 4 volte per ogni livello di PAS
- è graduale e continuo per ogni livello di PA (anche pre-ipertensione)
- 2/3 muore per CHD o STROKE

Increasing Cardiovascular Disease Burden Due to Diabetes Mellitus : The Framingham Heart Study

Caroline S. Fox, Sean Coady, Paul D. Sorlie, Ralph B. D'Agostino, Sr, Michael J. Pencina, Ramachandran S. Vasan, James B. Meigs, Daniel Levy and Peter J. Savage



Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000

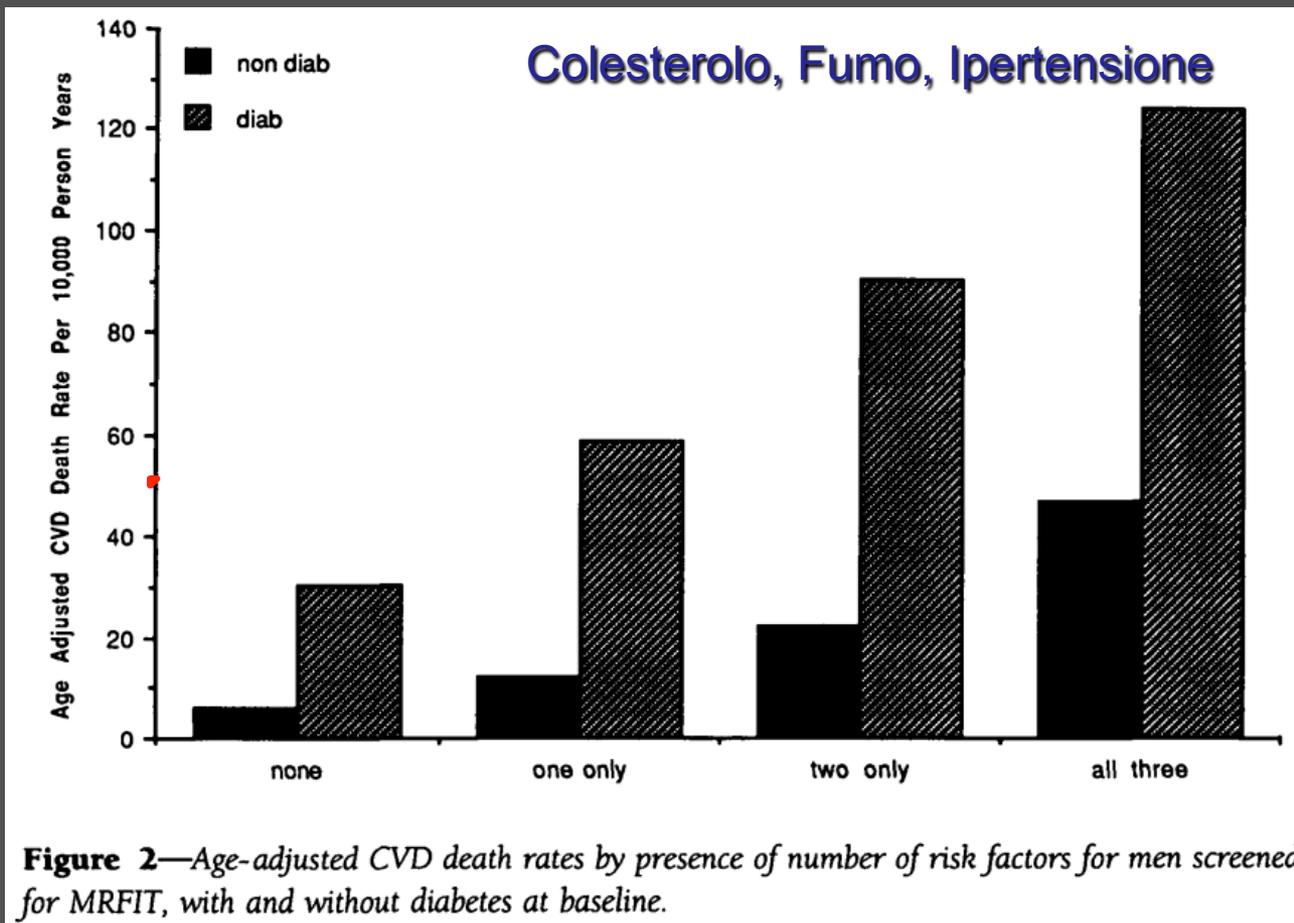
Belgin Unal, MD, MPH; Julia Alison Critchley, DPhil; Simon Capewell, MD

TABLE 2. Deaths Prevented or Postponed as a Result of Population Risk Factor Changes in England and Wales 1981–2000

Risk Factors	% Change in Risk Factor 1981–2000	β Coefficient	Deaths Prevented or Postponed (No.)			Proportion of Overall Deaths Prevented or Postponed, %, Best Estimate
			Best Estimate	Minimum Estimate	Maximum Estimate	
Smoking	–34.0	0.51	29 715	20 037	44 677	48.1
Population blood pressure	–7.7	1.67	5868	4246	15 469	9.5
Cholesterol	–4.2	2.46	7900	5284	16 692	9.6
		Relative Risk				
Deprivation	–6.6	1.24	2126	1063	3189	3.4
Physical activity	–30.6	0.50	–2662	–1491	–3460	–4.3
Obesity	+186.2	1.57	–2097	–1339	–2587	–3.4
Diabetes	+65.6	4.24	–2888	–2567	–4685	–4.7
Total risk factor effects	35 944	23 123	62 195	58.2

- annullano gli effetti favorevoli di astensione dal fumo, controllo pressorio e lipidico ottenuti nei 20 anni precedenti

Diabetes, Other Risk Factors, and 12-Yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial



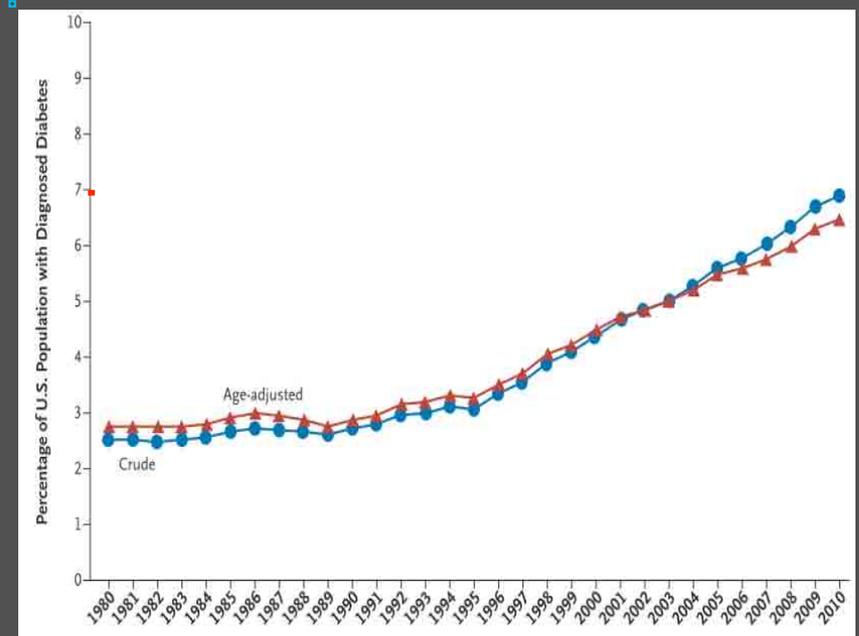
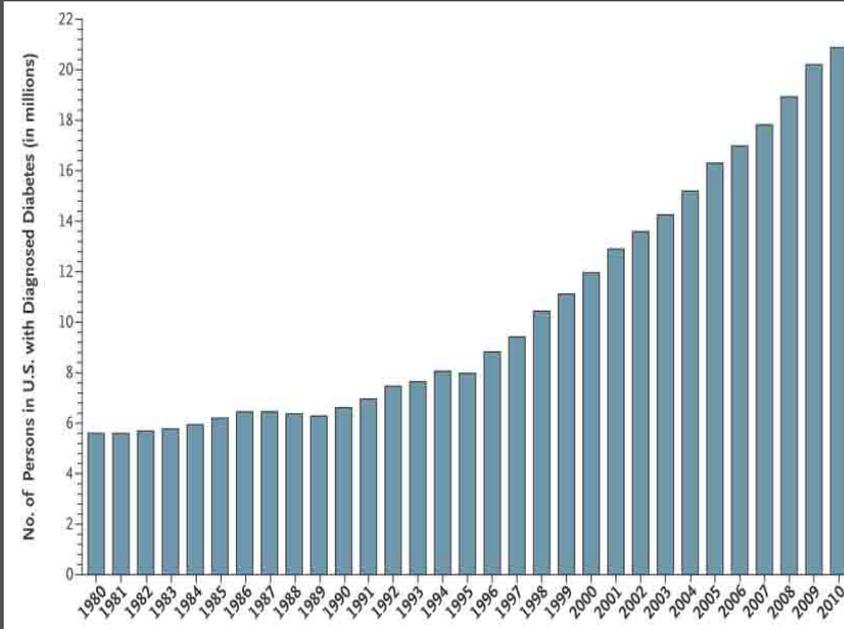


The Past 200 Years in Diabetes

Kenneth S. Polonsky, M.D.



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IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030

David R. Whiting ^{a,*}, Leonor Guariguata ^a, Clara Weil ^a, Jonathan Shaw ^b

^a International Diabetes Federation, Brussels, Belgium

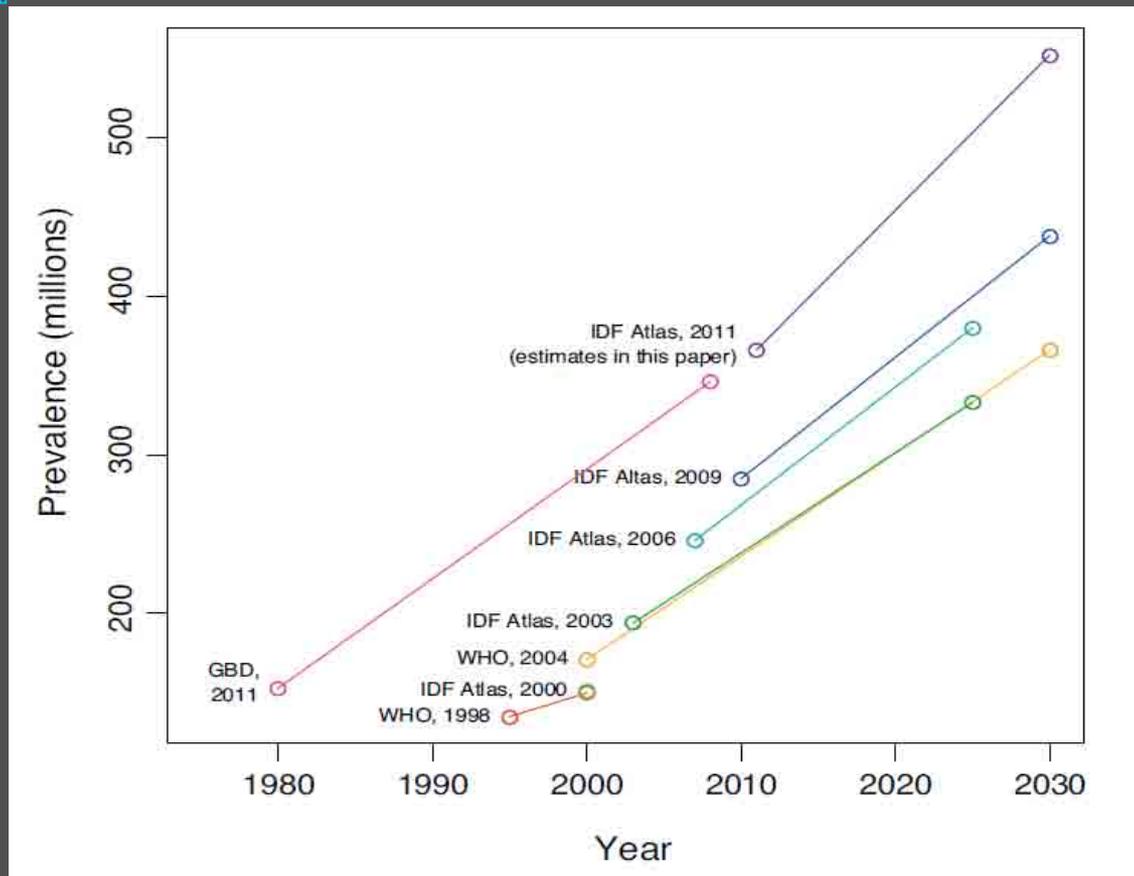
^b Baker IDI Heart and Diabetes Institute, Australia



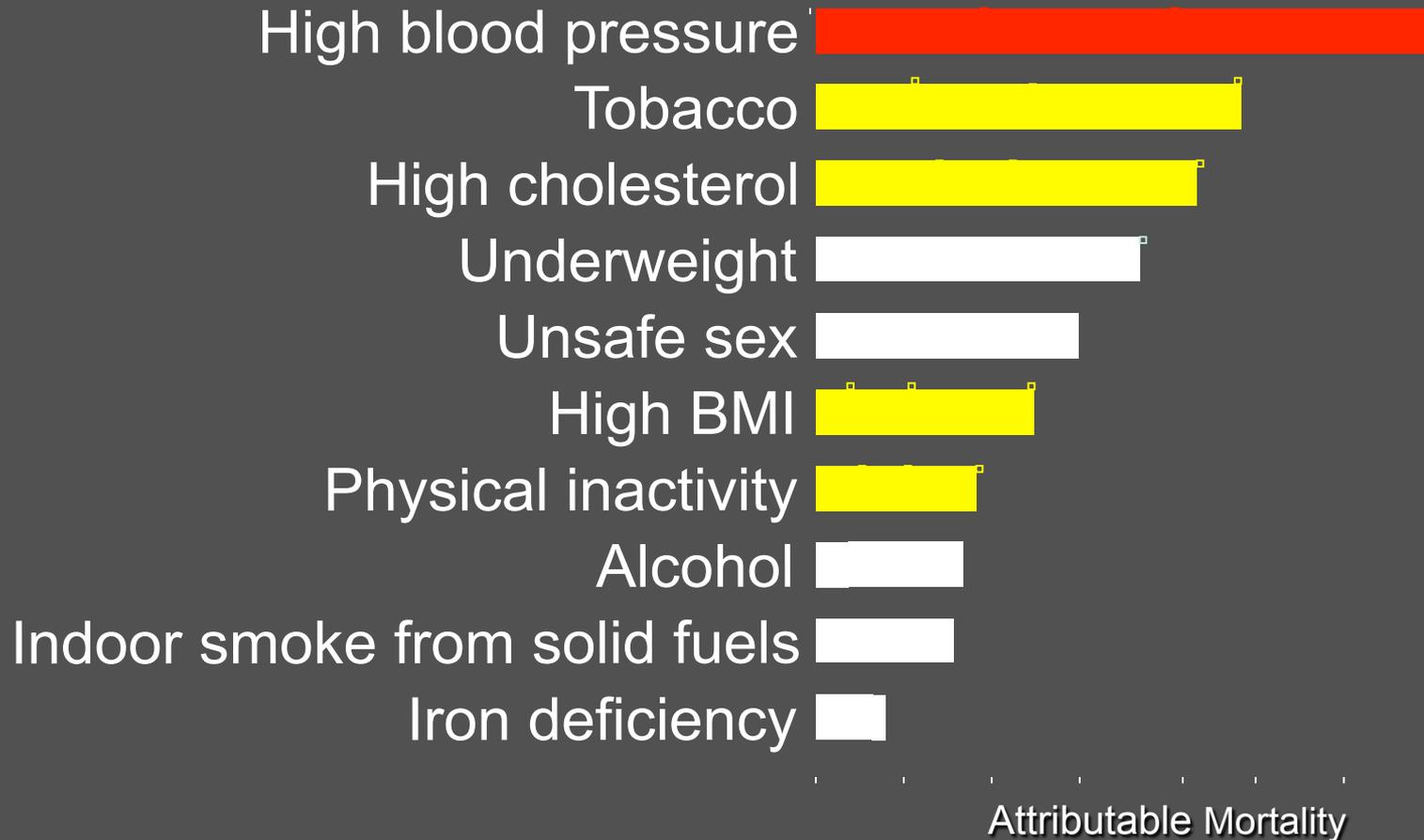
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in incremento in relazione al miglioramento delle condizioni economiche che ha portato a cambiare lo stile di vita



Decessi attribuibili ai principali fattori di rischio



L'ipertensione è il principale fattore di rischio per CHD, insufficienza di cuore, malattia cerebrovascolare, IR e FA.

Ipertensione

- Età < 60 anni (riducendo la PA di 10/5-6 mmHg)
 - Riduzione del rischio di stroke 42%
 - Riduzione di eventi CV 14%
- Età > 60 anni (riducendo la PA di 15/6 mmHg)
 - Riduzione della mortalità
 - per tutte le cause: 15%
 - per eventi CV. 36%
 - per Stroke: 35%
 - Per CHD: 18%



scuola:
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<http://unamelalchini.it>



Cardiovascular Outcomes in Framingham Participants With Diabetes : The Importance of Blood Pressure

Guanmin Chen, Finlay A. McAlister, Robin L. Walker, Brenda R. Hemmelgarn and Norm R.C. Campbell



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Table 3. Cardiovascular Events (and Rates per 1000 Person-Years) After Diagnosis of Diabetes Mellitus in Individuals Over Age 35 Years, Stratified by Hypertension Status at Time of Diabetes Mellitus Diagnosis

Subgroups	MI		Stroke		HF		Any MI, Stroke, or HF Event	
	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)
Total								
Normotensive (N=482)	43	22.3 (17.7 to 28.0)	14	10.5 (7.4 to 15.0)	10	7.3 (4.7 to 11.4)	67	30.8 (25.8 to 36.7)
Hypertensive (N=663)	77	34.5 (29.0 to 41.1)	32	20.8 (16.4 to 24.5)	28	18.6 (14.3 to 24.3)	137	51.7 (45.7 to 58.6)
Age <65 y								
Normotensive (N=328)	23	17.4 (13.0 to 20.3)	7	5.1 (3.6 to 6.6)	3	3.3 (1.6 to 5.0)	33	21.3 (16.7 to 26.1)
Hypertensive (N=337)	39	26.1 (23.4 to 33.4)	6	6.5 (3.8 to 10.2)	11	9.1 (7.7 to 14.6)	56	32.1 (27.2 to 39.4)
Age ≥65 y								
Normotensive (N=154)	20	40.4 (32.9 to 47.5)	7	26.5 (20.5 to 32.7)	7	20.9 (12.2 to 26.0)	34	62.6 (48.4 to 70.9)
Hypertensive (N=326)	38	51.5 (48.1 to 56.0)	26	44.5 (34.1 to 54.1)	17	35.1 (28.6 to 48.3)	81	81.9 (80.0 to 95.9)
Women								
Normotensive (N=203)	14	16.4 (10.8 to 24.9)	5	12.4 (10.7 to 13.9)	5	7.5 (3.9 to 13.4)	24	27.6 (20.8 to 36.6)
Hypertensive (N=309)	35	33.5 (25.8 to 41.4)	13	19.4 (15.5 to 23.7)	10	20.3 (18.9 to 29.6)	58	51.3 (42.7 to 61.7)
Men								
Normotensive (N=279)	29	26.4 (20.0 to 31.7)	9	8.9 (5.3 to 15.1)	5	7.2 (4.0 to 11.0)	43	33.2 (26.5 to 41.6)
Hypertensive (N=354)	42	35.4 (32.9 to 37.9)	19	22.2 (16.1 to 30.6)	18	17.3 (13.9 to 25.0)	79	52.1 (43.9 to 61.7)

CVD indicates cardiovascular disease; MI, myocardial infarction; HF, heart failure. Rates were adjusted for sex and age.



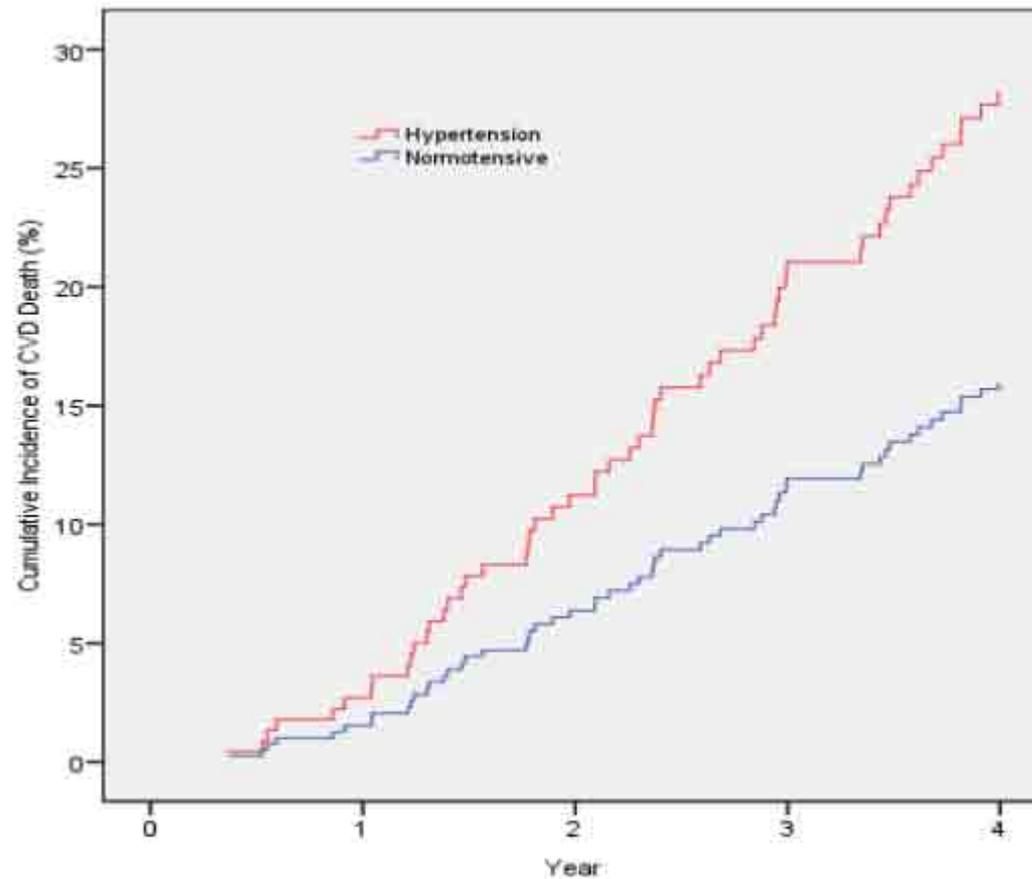
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CVD related death





Quale target ?



Prevenire le complicanze micro e macrovascolari

Diabetes, Other Risk Factors, and 12-Yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial

Table 2—Number of deaths by cause and age-adjusted death rate for men with (n = 5163) and without (n = 342,815) diabetes at initial screening for the MRFIT

CAUSE OF DEATH (ICD-9 CODE)	MEN WITH DIABETES		MEN WITHOUT DIABETES		ADJUSTED RR FOR DIABETIC/NONDIABETIC* (95% CI)
	DEATHS (N)	RATE (PER 10,000 PERSON-YR)	DEATHS (N)	RATE (PER 10,000 PERSON-YR)	
CVD (390–459)	603	85.13	8965	22.88	3.0 (2.8–3.3)
CHD (410–414, 429.2)	469	65.91	6681	17.05	3.2 (2.9–3.5)
STROKE (430–438)	48	6.72	685	1.75	2.8 (2.0–3.7)
OTHER CVD	86	12.49	1599	4.08	2.3 (1.8–2.9)
ALL DEATHS	1092	160.13	20,867	53.20	2.5 (2.4–2.7)

*Adjusted for age, race, income, serum cholesterol level, sBP, and number of cigarettes/day.

Table 5—Age-adjusted CVD death rates by sBP level for men with and without diabetes at initial screening for MRFIT

SBP LEVEL (MMHG)	MEN WITH DIABETES			MEN WITHOUT DIABETES			RR FOR DIABETIC/NONDIABETIC	ABSOLUTE EXCESS RISK FOR DIABETIC MINUS NONDIABETIC (PER 10,000 PERSON-YR)
	MEN (N)	CVD DEATHS (N)	RATE (PER 10,000 PERSON-YR)	MEN (N)	CVD DEATHS (N)	RATE (PER 10,000 PERSON-YR)		
<120	757	52	53.61	86,702	1112	12.19	4.40	41.42
120–139	2316	203	65.47	175,826	3745	19.07	3.43	46.40
140–159	1421	206	108.15	64,444	2794	34.18	3.16	73.97
160–179	494	102	158.71	12,827	952	56.47	2.81	102.24
180–199	131	27	155.65	2356	253	79.27	1.96	76.38
≥200	44	13	242.61	660	109	128.65	1.89	113.96
COEFFICIENT*	0.0172 ± 0.0019			0.0234 ± 0.0005				

* From proportional hazards regression model stratified by clinical center and with covariates corresponding to age, race, income, serum cholesterol level, sBP, and cigarettes/day.

	n	Duration (years)	Systolic BP goal (mm Hg)	Diastolic BP goal (mm Hg)	Mean BP, less intense (mm Hg)	Mean BP, more intense (mm Hg)
SHEP ⁷⁸	583	5	<148	None	155/72*	146/68*
Syst-Eur ⁷⁹	492	2	<150	None	162/82	153/78
HOT ^{80,81}	1501	3	None	<80	148/85	144/81
UKPDS ⁸²	1148	8-4	<150	<85	154/87	144/82
ABCD ⁸³	470	5-3	None	<75	138/86	132/78
ACCORD-BP ⁷²	4733	4-7	<120	None	134	119
INVEST	6400	3,5	< 130 tight;	130 – 140 less tight;	> 140 uncontrolled	

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

UK Prospective Diabetes Study Group



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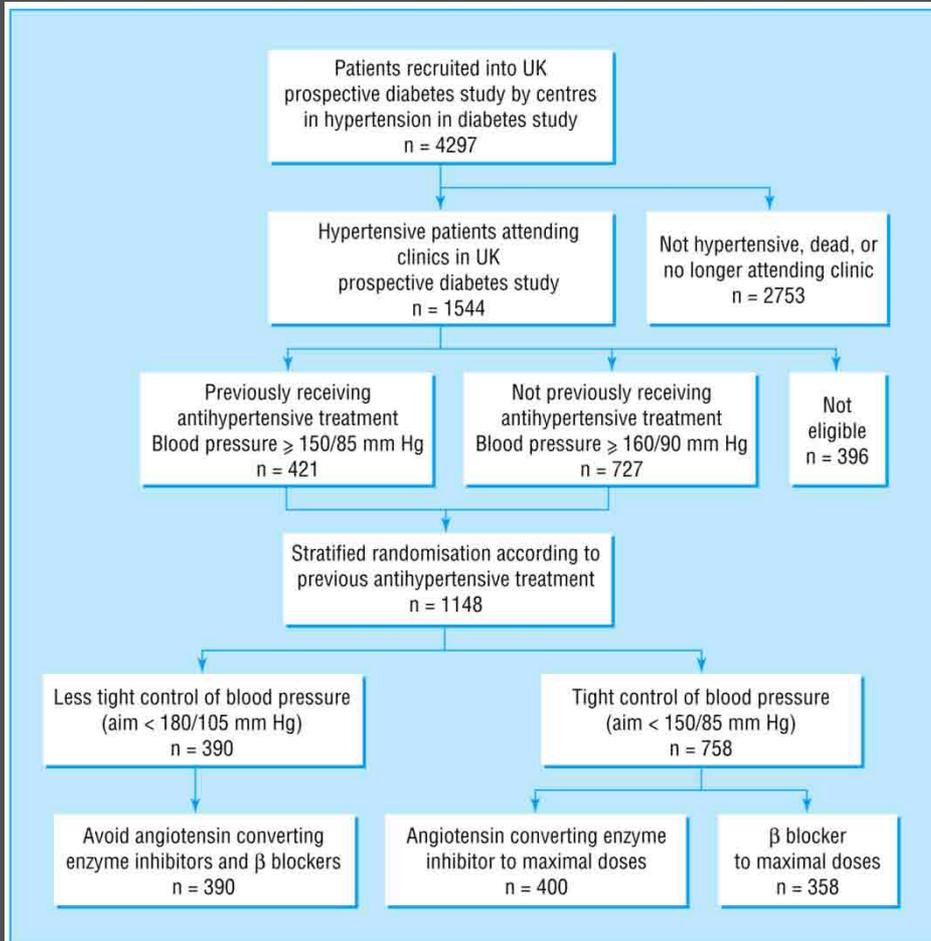
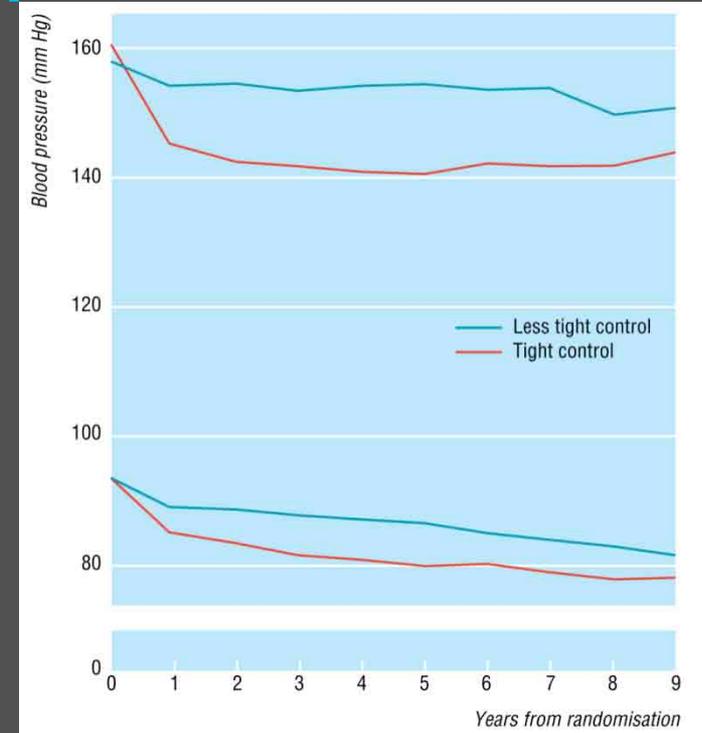


Fig 1 Selection and random allocation of patients to treatment in hypertension in diabetes study



Less tight	154 / 87 mm/Hg
Tight	144 / 82 mm/Hg
Delta	10 / 5 mm/Hg

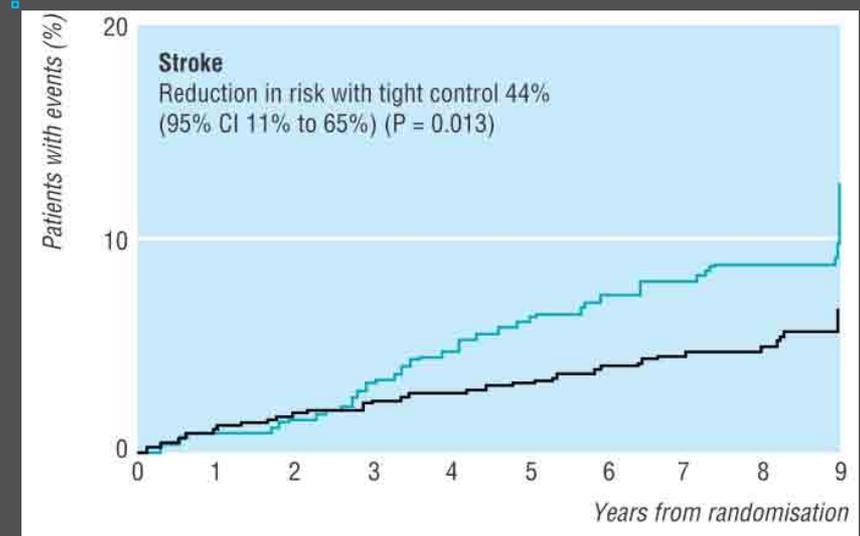
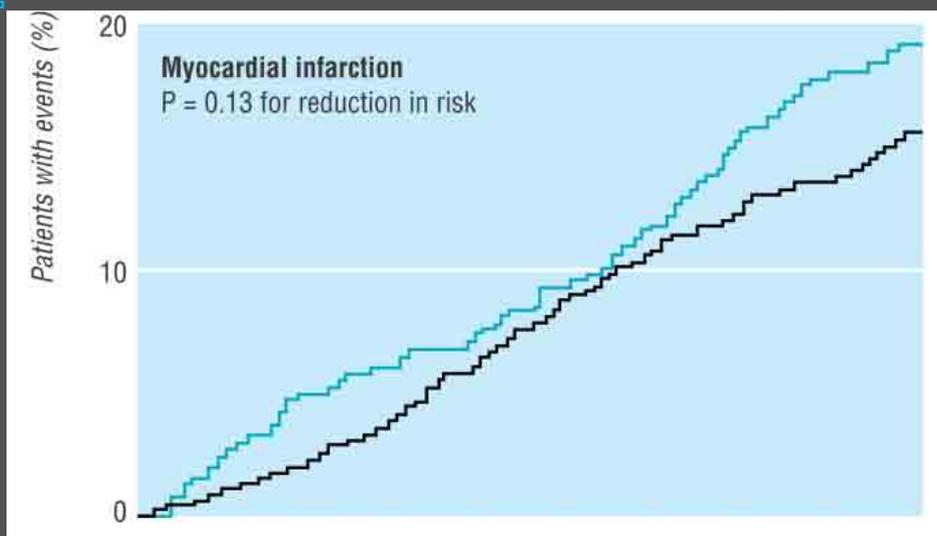
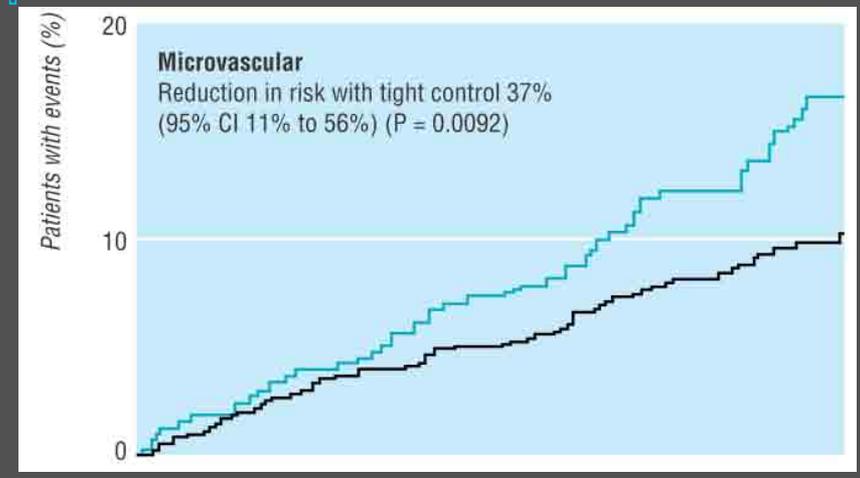
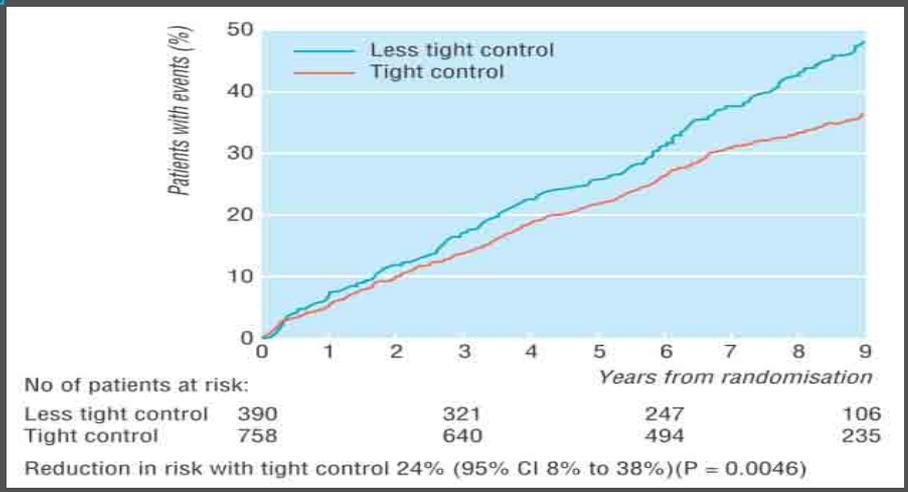


Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

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Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,
H. Andrew W. Neil, F.R.C.P., and David R. Matthews, F.R.C.P.



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UKPDS-PM

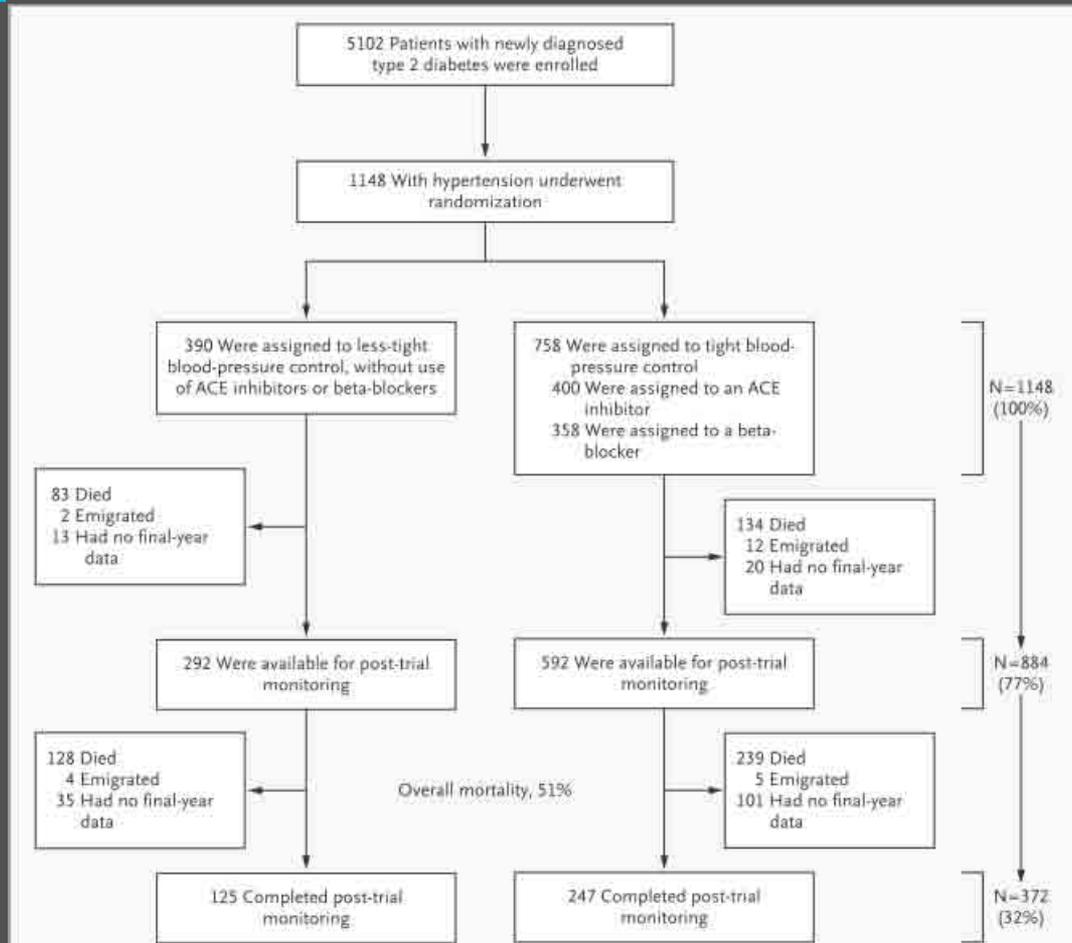


Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

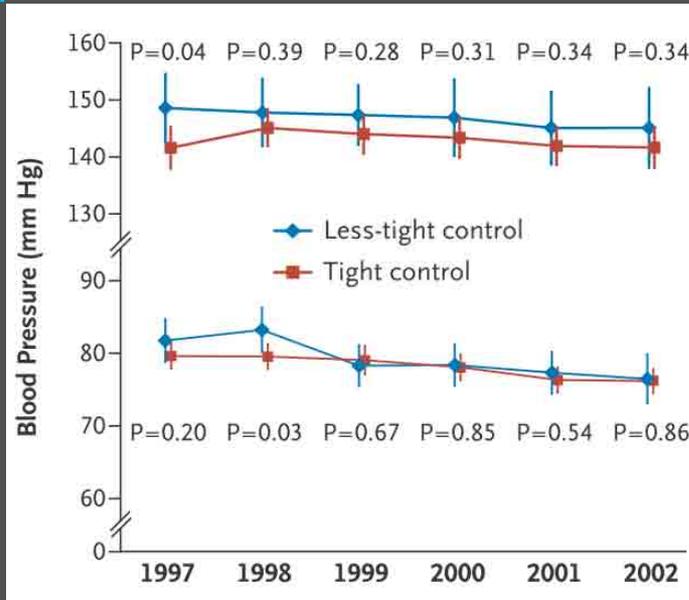
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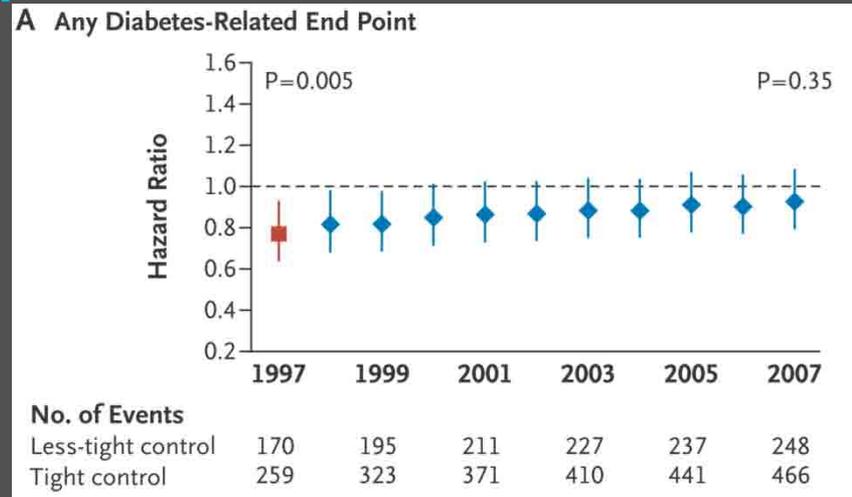
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UKPDS-PM



Differenze

- PAS perse dopo 1 anno
- PAD perse dopo 2 anni



Studio UKPDS

CONCLUSIONI:

Il trattamento con un ACEI o un β bloccante, con l'obiettivo di ridurre la pressione sanguigna a valori $<150 / 85$ mm Hg, riduce sostanzialmente il rischio di morte e di complicanze CV nel p. diabetico.

Il controllo della pressione arteriosa dovrebbe essere prioritario nel trattamento del diabete di tipo 2

UK Prospective Diabetes Study Group – BMJ, 1998; 317:703

L'ottimale controllo della pressione arteriosa è di fondamentale importanza per ridurre i rischi di malattia macrovascolare e microvascolare nei pazienti con diabete di tipo 2, ma deve essere mantenuta se si vogliono conservare questi benefici.

N Engl J Med 2008;359:1565-76

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

- Valutare la relazione fra eventi cardiovascolari maggiori e tre target di PAD (≤ 90 , ≤ 85 e ≤ 80 mmHg) in corso di terapia antiipertensiva
- valutare la relazione tra eventi cardiovascolari maggiori e la pressione diastolica raggiunta durante la terapia antiipertensiva
- valutare se bassi dosaggi di acido acetilsalicilico (ASA) in aggiunta alla terapia antiipertensiva riducono gli eventi cardiovascolari

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

	Diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Felodipine (%)	77	78	79
ACE inhibitors (%)	35	42	45
β-blockers (%)	25	28	32
Diuretics (%)	19	22	24

ACE=angiotensin converting enzyme.

	Mean (SD) blood pressure by diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Systolic blood pressure (mm Hg)			
Baseline	169.8 (14.4)	169.5 (14.0)	169.7 (14.1)
Achieved*	143.7 (11.3)	141.4 (11.7)	139.7 (11.7)
Difference	26.2 (13.0)	28.0 (13.2)	29.9 (13.6)
Diastolic blood pressure (mm Hg)			
Baseline	105.4 (3.4)	105.4 (3.4)	105.4 (3.4)
Achieved*	85.2 (5.1)	83.2 (4.8)	81.1 (5.3)
Difference	20.3 (5.6)	22.3 (5.4)	24.3 (5.8)

*Mean of all blood pressures from 6 months of follow-up to end of study.

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

Event	Number of events	Events/1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
Major cardiovascular events					
≤90 mm Hg	232	9.9		90 vs 85	0.99 (0.83–1.19)
≤85 mm Hg	234	10.0		85 vs 80	1.08 (0.89–1.29)
≤80 mm Hg	217	9.3	0.50	90 vs 80	1.07 (0.89–1.28)
Major cardiovascular events, including silent myocardial infarction					
≤90 mm Hg	274	11.7		90 vs 85	0.99 (0.84–1.17)
≤85 mm Hg	276	11.8		85 vs 80	1.05 (0.88–1.24)
≤80 mm Hg	263	11.3	0.66	90 vs 80	1.04 (0.88–1.23)
All myocardial infarction					
≤90 mm Hg	84	3.6		90 vs 85	1.32 (0.95–1.82)
≤85 mm Hg	64	2.7		85 vs 80	1.05 (0.74–1.48)
≤80 mm Hg	61	2.6	0.05	90 vs 80	1.37 (0.99–1.91)
All myocardial infarction, including silent cases					
≤90 mm Hg	127	5.4		90 vs 85	1.19 (0.92–1.54)
≤85 mm Hg	107	4.6		85 vs 80	1.00 (0.76–1.30)
≤80 mm Hg	107	4.6	0.19	90 vs 80	1.19 (0.92–1.53)
All stroke					
≤90 mm Hg	94	4.0		90 vs 85	0.85 (0.64–1.11)
≤85 mm Hg	111	4.7		85 vs 80	1.24 (0.94–1.64)
≤80 mm Hg	89	3.8	0.74	90 vs 80	1.05 (0.79–1.41)
Cardiovascular mortality					
≤90 mm Hg	87	3.7		90 vs 85	0.97 (0.72–1.30)
≤85 mm Hg	90	3.8		85 vs 80	0.93 (0.70–1.24)
≤80 mm Hg	96	4.1	0.49	90 vs 80	0.90 (0.68–1.21)
Total mortality					
≤90 mm Hg	188	7.9		90 vs 85	0.97 (0.79–1.19)
≤85 mm Hg	194	8.2		85 vs 80	0.93 (0.77–1.14)
≤80 mm Hg	207	8.8	0.32	90 vs 80	0.91 (0.74–1.10)

Table 4: Events in relation to target blood pressure groups (n=6264, 6264, and 6262 in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively)

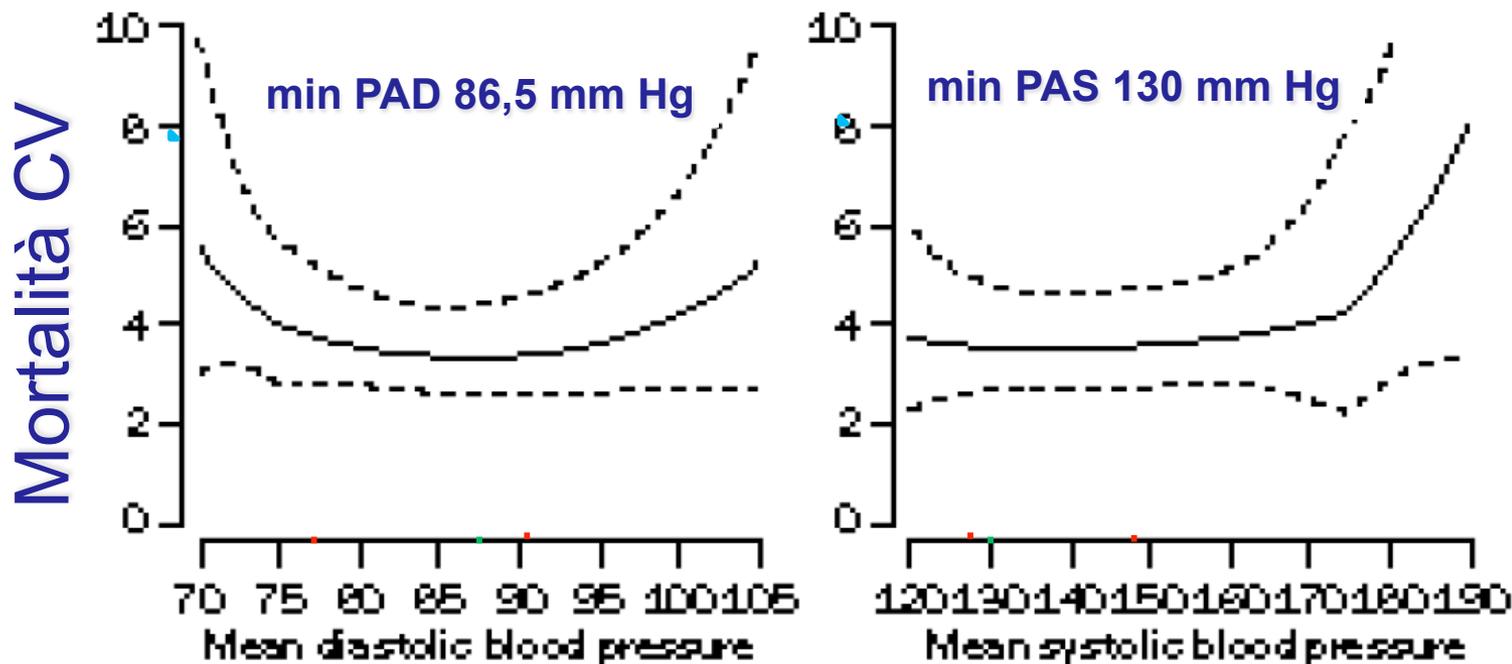
Event	Number of events	Events/1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
Major cardiovascular events					
≤90 mm Hg	45	24.4		90 vs 85	1.32 (0.84–2.06)
≤85 mm Hg	34	18.6		85 vs 80	1.56 (0.91–2.67)
≤80 mm Hg	22	11.9	0.005	90 vs 80	2.06 (1.24–3.44)
Major cardiovascular events, including silent myocardial infarction					
≤90 mm Hg	48	26.2		90 vs 85	1.13 (0.75–1.71)
≤85 mm Hg	42	23.3		85 vs 80	1.42 (0.89–2.26)
≤80 mm Hg	30	16.4	0.045	90 vs 80	1.60 (1.02–2.53)
All myocardial infarction					
≤90 mm Hg	14	7.5		90 vs 85	1.75 (0.73–4.17)
≤85 mm Hg	8	4.3		85 vs 80	1.14 (0.41–3.15)
≤80 mm Hg	7	3.7	0.11	90 vs 80	2.01 (0.81–4.97)
All myocardial infarction, including silent cases					
≤90 mm Hg	18	9.7		90 vs 85	1.12 (0.57–2.19)
≤85 mm Hg	16	8.7		85 vs 80	1.07 (0.53–2.16)
≤80 mm Hg	15	8.1	0.61	90 vs 80	1.20 (0.60–2.38)
All stroke					
≤90 mm Hg	17	9.1		90 vs 85	1.30 (0.63–2.67)
≤85 mm Hg	13	7.0		85 vs 80	1.10 (0.50–2.40)
≤80 mm Hg	12	6.4	0.34	90 vs 80	1.43 (0.68–2.99)
Cardiovascular mortality					
≤90 mm Hg	21	11.1		90 vs 85	0.99 (0.54–1.82)
≤85 mm Hg	21	11.2		85 vs 80	3.0 (1.29–7.13)
≤80 mm Hg	7	3.7	0.016	90 vs 80	3.0 (1.28–7.08)
Total mortality					
≤90 mm Hg	30	15.9		90 vs 85	1.03 (0.62–1.71)
≤85 mm Hg	29	15.5		85 vs 80	1.72 (0.95–3.14)
≤80 mm Hg	17	9.0	0.068	90 vs 80	1.77 (0.98–3.21)

Table 5: Events in patients with diabetes mellitus at baseline in relation to target blood pressure groups (n=501, 501, and 499 in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively)

* IM non fatale, stroke non fatale, morte CV

Hansson L. et al – Lancet, 1998; 351: 1755

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

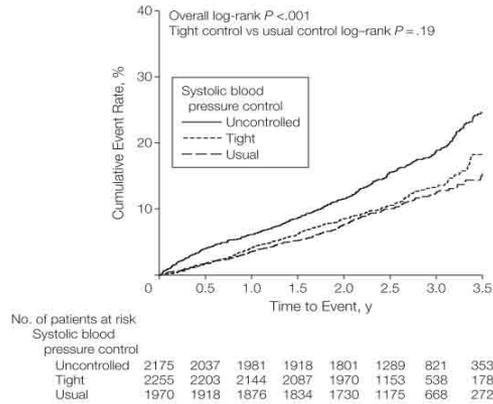


Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

- Nei pazienti ipertesi una riduzione significativa della PA ($\leq 140 / 85$ mm/Hg) si dimostra efficace nel ridurre il tasso di eventi CV maggiori
- Una riduzione della PA $\leq 120 / 70$ mm/Hg **non comporta significativi incrementi dei benefici ma non risulta nemmeno dannosa anche nel sottogruppo di pazienti con anamnesi di CI (incremento non significativo della mortalità)**
- i pazienti Diabetici beneficiano di una più stretta riduzione della PA

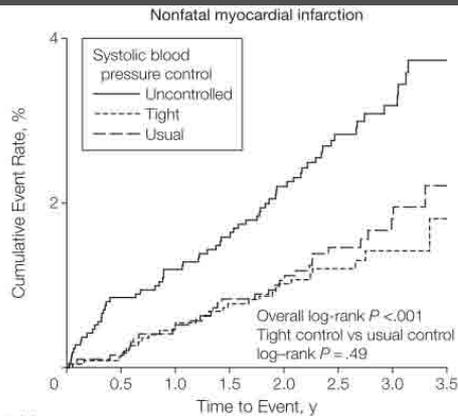
Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

Figure 1. Cumulative Event Rate for Primary Outcome

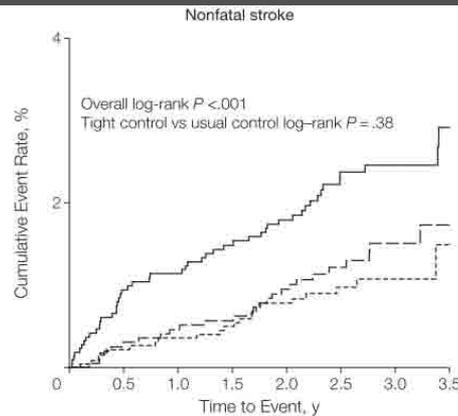


Primary outcomes are a composite of the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.

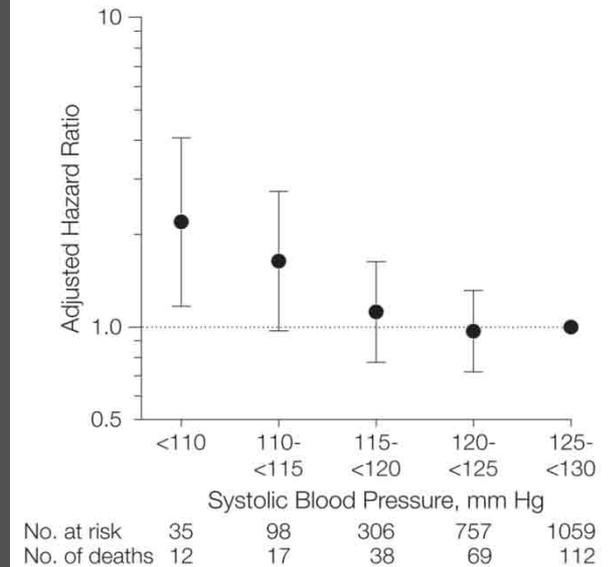
- 6400 pz diabetici
- Tight PAS < 130
- Usual PAS 130 – 140
- Uncontrolled PAS > 140



No. of patients at risk		Systolic blood pressure control							
		0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Uncontrolled	2175	2058	2006	1950	1836	1320	841	363	
Tight	2255	2209	2155	2102	1985	1171	547	181	
Usual	1970	1925	1886	1844	1744	1189	680	280	



No. of patients at risk		Systolic blood pressure control							
		0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Uncontrolled	2175	2055	2006	1947	1840	1325	849	365	
Tight	2255	2207	2154	2103	1988	1171	551	185	
Usual	1970	1922	1886	1848	1746	1190	680	280	

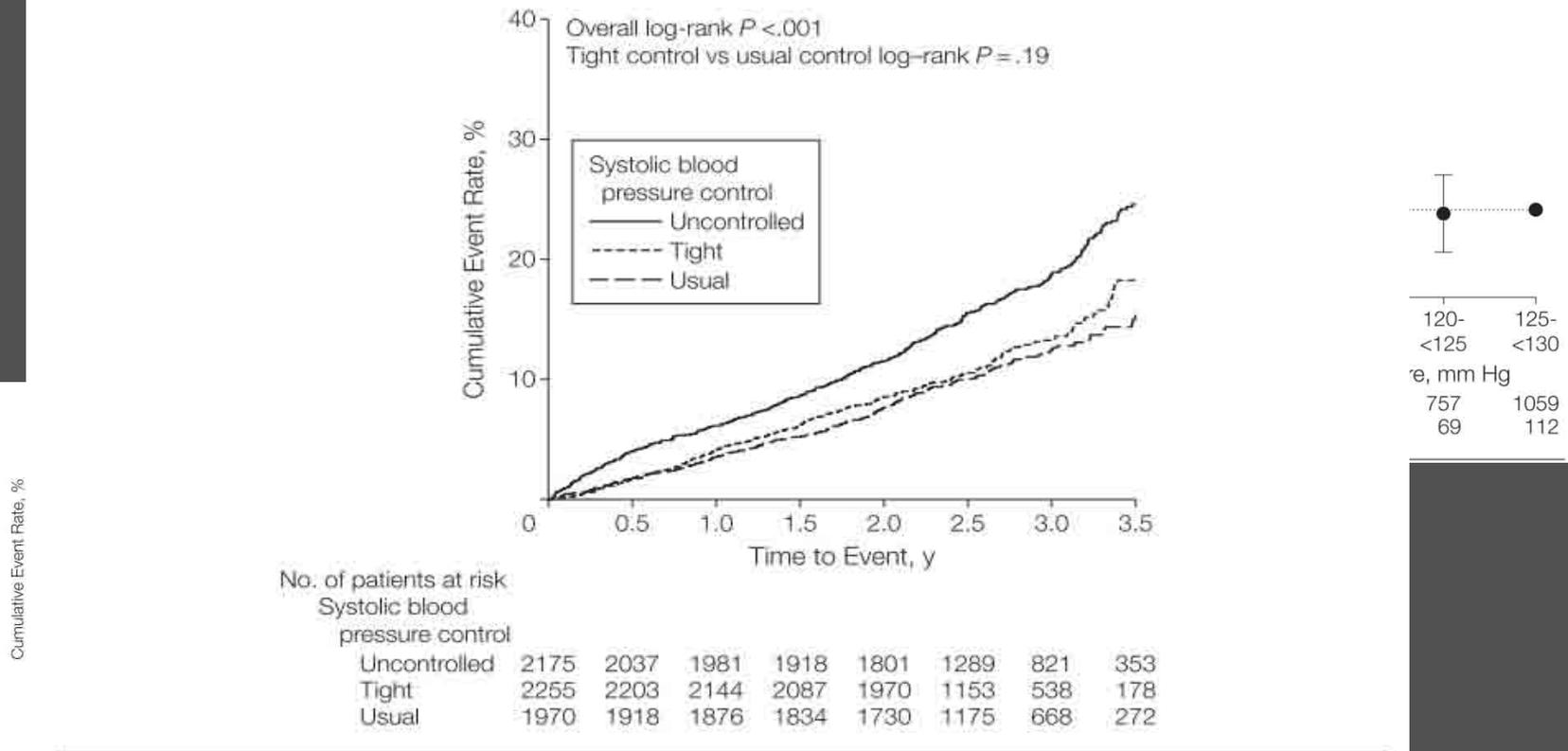


Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease



INVEST

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.

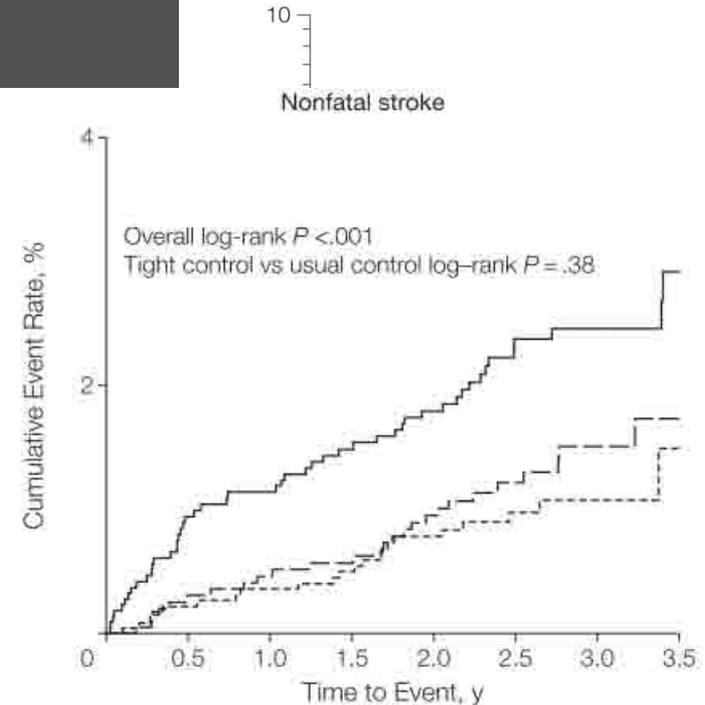
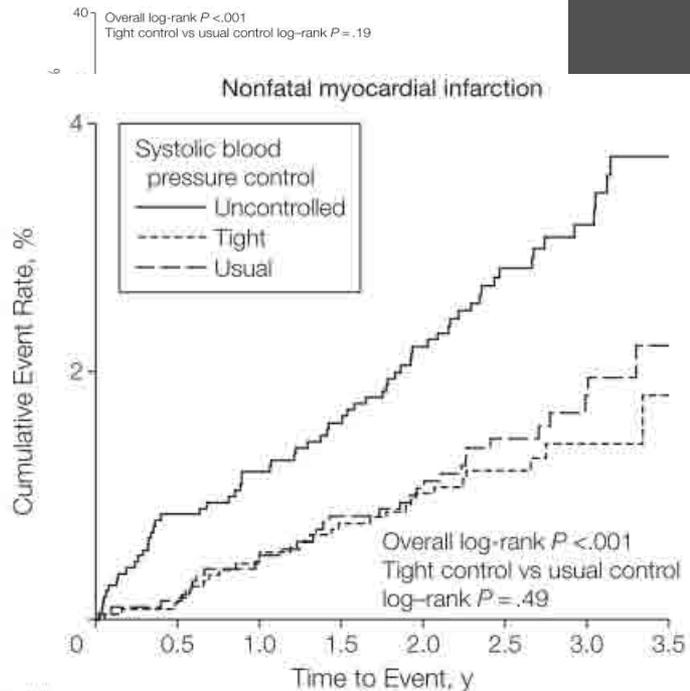
Systolic blood pressure control	No. of patients at risk								No. of patients at risk							
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Uncontrolled	2255	2209	2155	2102	1985	1171	547	181	2255	2207	2154	2103	1988	1171	551	185
Tight	1970	1925	1886	1844	1744	1189	680	280	1970	1922	1886	1848	1746	1190	680	280
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Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease



INVEST

Figure 1. Cumulative Event Rate for Primary Outcome



No. of patients at risk
Systolic blood pressure control

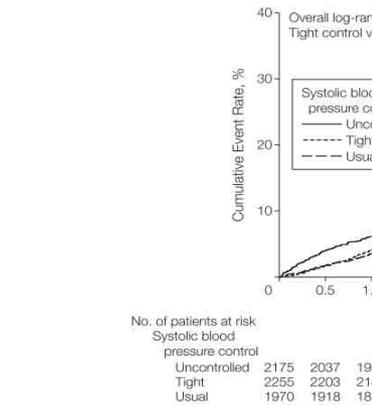
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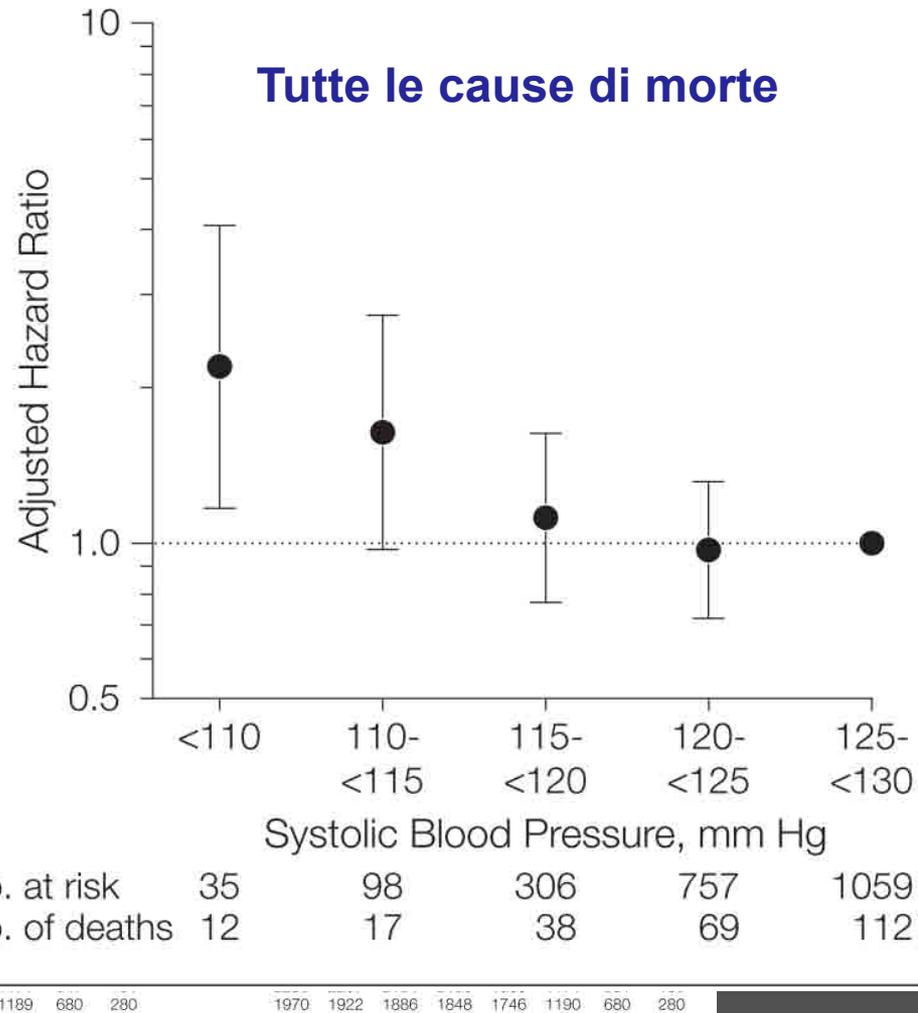
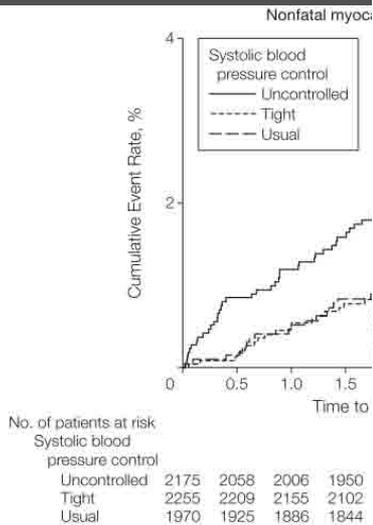
Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease



Figure 1. Cumulative Event Rate for Primary Outcome



Primary outcomes are a composite of the first occurred nonfatal stroke.



- **Il controllo pressorio intensivo nel DM**
 - non riduce significativamente gli outcomes CV rispetto al controllo pressorio usuale
 - Al momento non esistono evidenze sicure che provino un beneficio derivante dalla riduzione della PAS < 130 mm Hg
 - opportuno mantenere la PAS fra 130 e 139 mm Hg, focalizzare l'attenzione su un adeguato stile di vita e correggere altri fattori di rischio CV

Studio ACCORD



- n. 4733 Partecipanti randomizzati
 - 1° gruppo: target PAS < 120 mm/Hg
 - 2° gruppo: target PAS < 140 mm/Hg
- Inclusi tutti i regimi terapeutici di provata efficacia nel ridurre il rischio CV nel DM (lo scopo non era validare le classi di farmaci ma ottenere la riduzione della PA secondo i target stabiliti)

Studio ACCORD

Table 3. Primary and Secondary Outcomes.

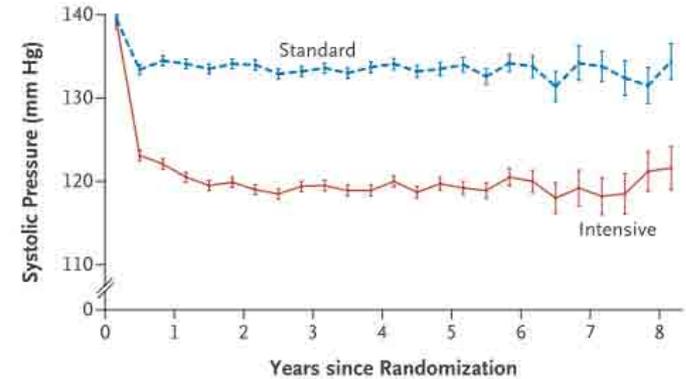
Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	no. of events	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)[†]			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Symptoms affecting quality of life — no./total no. (%)[‡]			
Hives or swelling	44/501 (8.8)	41/468 (8.8)	1.00
Dizziness when standing	217/501 (44.3)	188/467 (40.3)	0.36
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m ²	99 (4.2)	52 (2.2)	<0.001
Clinical measures[§]			
Glycated hemoglobin — %	7.6±1.3	7.5±1.2	0.13
Fasting plasma glucose — mg/dl	147.1±56.6	148.1±57.5	0.58
Plasma LDL cholesterol — mg/dl	98.7±40.3	96.8±37.8	0.10
Plasma HDL cholesterol — mg/dl	46.7±14.0	47.8±14.9	0.02
Plasma triglycerides — mg/dl			0.001
Median	138	131	
Interquartile range	97–210	92–197	
Potassium — mg/dl	4.3±0.5	4.4±0.5	0.17
Serum creatinine — mg/dl	1.1±0.4	1.0±0.5	<0.001
Estimated GFR — ml/min/1.73 m ²	74.8±25.0	80.6±24.8	<0.001
Ratio of urinary albumin (mg) to creatinine (g)			<0.001
Median	12.6	14.9	
Interquartile range	6.4–41.7	7.0–56.8	
Microalbuminuria — no./total no. (%)	656/2174 (30.2)	712/2205 (32.3)	0.13
Macroalbuminuria — no./total no. (%)	143/2174 (6.6)	192/2205 (8.7)	0.009
Weight — kg	93.3±21.2	92.5±20.2	0.20



Mean No. of Medications Prescribed

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

No. of Patients

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

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.

I bars indicate 95% confidence intervals.

- **Il regime terapeutico intensivo nel DM**
 - non riduce significativamente gli outcomes CV primari e/o il tasso di mortalità per ogni causa
 - Non significativi benefici per la maggior parte degli outcome secondari: solo stroke (totale degli eventi e non fatale)
 - Eventi avversi seri nel gruppo trattato in modo intensivo



Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose : Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials

Sripal Bangalore, Sunil Kumar, Iryna Lobach and Franz H. Messerli

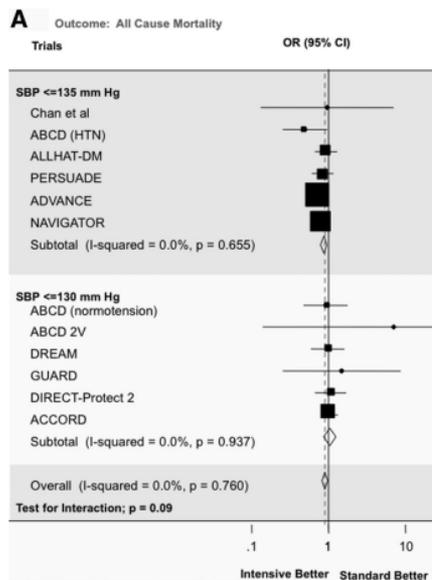
Table 1. Baseline Characteristics of Included Trials

Study	Year	n	Comparison	Follow-Up, mo	Mean Age, y	Men, %	Hemoglobin A _{1c}	Final Systolic BP, mm Hg	Final Diastolic BP, mm Hg
ABCD (hypertension) ²⁹	2007	470	Intensive vs standard BP lowering	60	58	58	11.5	133 vs 139	78 vs 86
ABCD (normotension) ²⁹	2007	480	Intensive vs standard BP lowering	60	59	55	11.5	128 vs 137	75 vs 81
ABCD-2V ²⁴	2006	129	Intensive vs standard BP lowering	23	56.1	67	8.2	118 vs 124	75 vs 80
ACCORD ^{5,22}	2010	4733	Intensive vs standard BP lowering	60	62.2	52.3	8.3	119.3 vs 133.5	64.4 vs 70.5
ADVANCE ²⁸	2007	11140	Perindopril-indapamide vs placebo	52	66	57	7.5	135 vs 140	74 vs 76
ALLHAT (New Diabetic) ¹⁸	2004	1690	Doxazosine vs chlorthalidone	38	67	60	NA	139 vs 134	77 vs 75
Chan et al ²¹	1992	102	Enalapril vs nifedipine	66	58	NA	7.5	137 vs 132.2	72.1 vs 72.6
DIRECT Protect 2 ¹⁹	2009	1905	Candesartan vs placebo	58	57	50	8.2	119.4 vs 123	73.2 vs 76
DREAM ²⁰	2006	5269	Ramipril vs placebo	36	55	41	NA	127.9 vs 132.2	78 vs 80.4
Fogari et al ²⁵	2002	207	Fosinopril/amlodipine vs amlodipine	48	62	57	7	132.4 vs 140.4	82.3 vs 86.5
GUARD ¹⁷	2008	304	Benazepril/amlodipine vs benazepril/hydrochlorothiazide	77	58	65.4	NA	129.5 vs 132.2	88.4 vs 87.2
NAVIGATOR ²⁷	2010	9306	Valsartan vs placebo	78	64	49.3	NA	133.1 vs 136.1	78.1 vs 79.6
PERSUADE ²³	2005	1502	Perindopril vs placebo	52	62	82	NA	132 vs 136.6	76.5 vs 78.3
SANDS ²⁶	2008	499	Intensive vs standard BP lowering	36	56	34.5	8.1	117 vs 129	67 vs 73

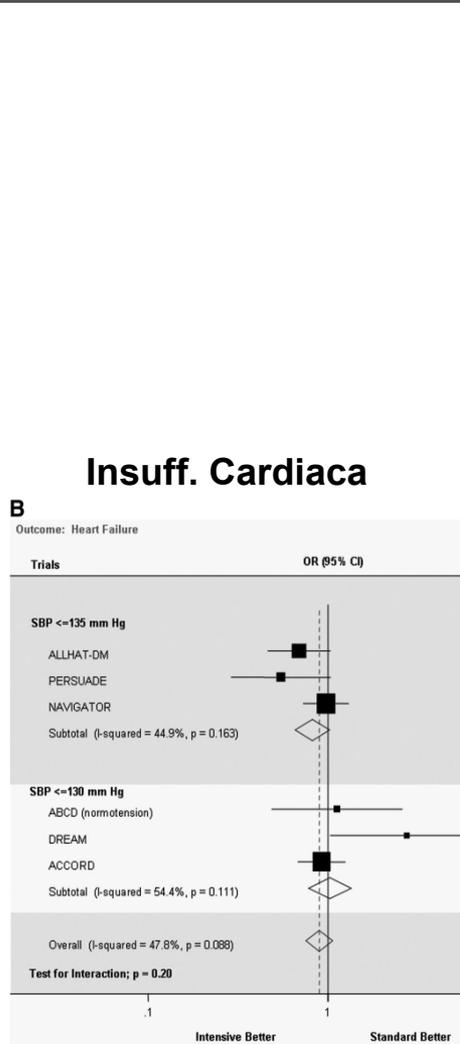
BP indicates blood pressure; ABCD, Appropriate Blood Pressure Control in Diabetes; ABCD-2V, ABCD-2 Valsartan; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DIRECT, Diabetic Retinopathy Candesartan Trials; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; GUARD, Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; PERSUADE, Perindopril Substudy in Coronary Artery Disease and Diabetes; and SANDS, Stop Atherosclerosis in Native Diabetics Study.

Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose : Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials

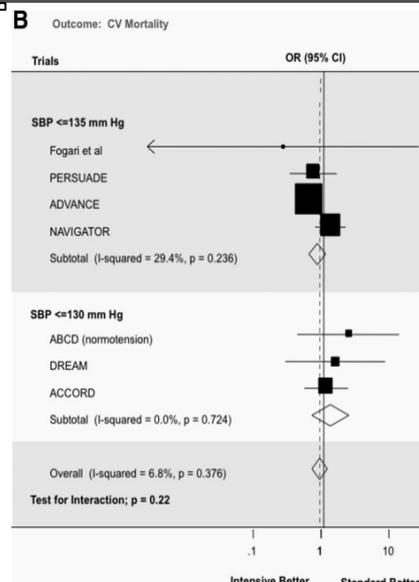
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Tutte cause mortalità

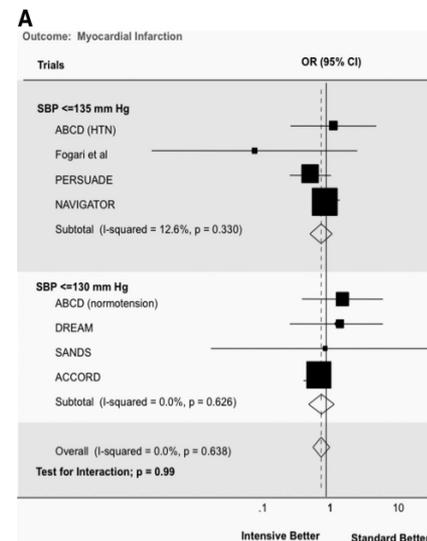


Insuff. Cardiaca



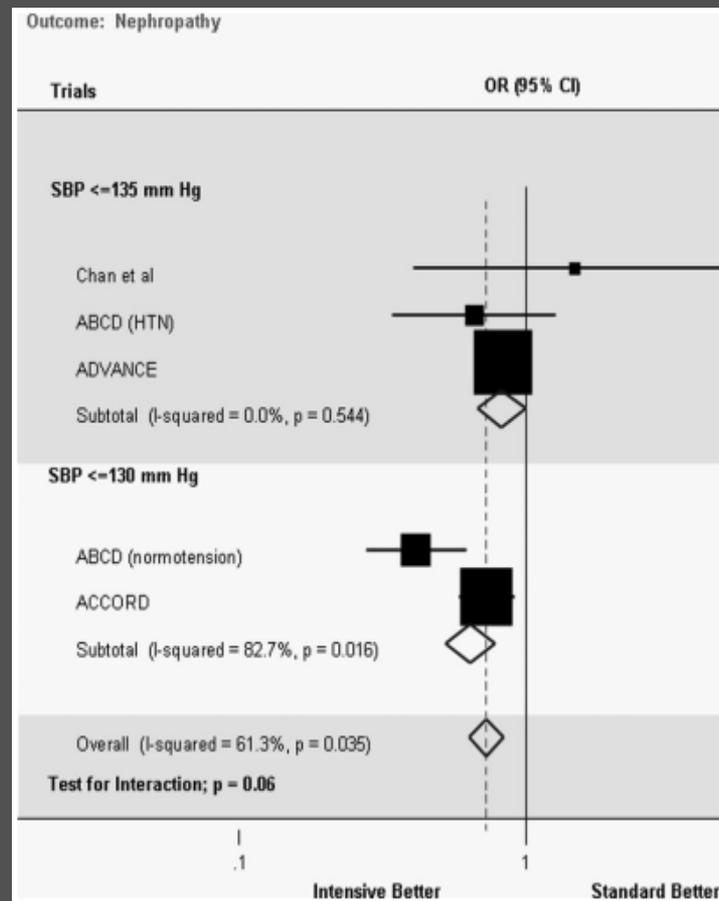
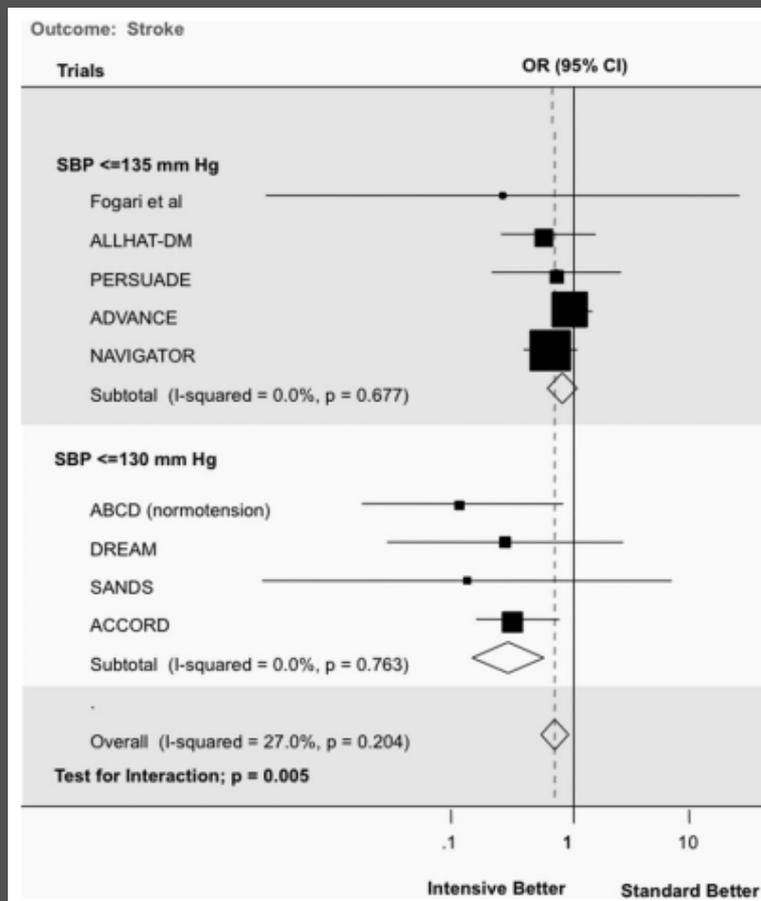
Mortalità CV

Infarto miocardico



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Conclusioni: nel paziente con DM-2

- Il trattamento intensivo ($PAS \leq 135$ mm Hg) riduce il rischio macrovascolare (stroke, morte)
- Un target di PAS compreso fra 130 e 135 mm Hg è pertanto accettabile
- Un trattamento più intensivo ($PAS 120$ mm Hg) può essere considerato nei pazienti
 - Ad elevato rischio per stroke e/o nefropatia
- Considerare che i benefici attesi da un trattamento che miri ad ottenere una $PAS < 130$ mm Hg è controbilanciato da un aumentato rischio di effetti collaterali maggiori senza significativi benefici sugli outcomes cardiaci e sulla retinopatia

Conclusioni - 1

- Nel paziente diabetico:
 - Non v'è dubbio che la prevenzione degli eventi CV richiede un controllo più stringente della PA rispetto ai non diabetici
 - Vi è generale accordo nell'individuare il target pressorio $\leq 130 / 80$ mm Hg per iniziare la terapia farmacologica o per potenziarla nei pazienti già in trattamento
 - Solitamente sono necessari più farmaci antiipertensivi per ottenere un adeguato controllo della PA
 - I livelli di PA da raggiungere vanno individualizzati secondo età, presenza di co-fattori di rischio e anamnesi per patologia CV
 - Non va dimenticato di porre attenzione allo stile di vita

Altri interventi

Intervention	Targeted change	Expected BP change
Sodium reduction	< 1500 mg/day	-5 / -3
Weight loss	BMI < 25 kg/m ²	-7 / -6
Alcohol reduction	< 2 drinks/day	-5 / -2
Exercise	4+ times/week	-5 / -4
Dietary Approaches to Stop Hypertension	DASH diet	-11 / -6

Conclusioni - 2

- Non vi sono ancora sufficienti evidenze per raccomandare un controllo più “stringente” della PA (< 120/70 mm Hg)
 - Per raggiungere questo obiettivo è necessario associare più farmaci → rischio effetti avversi severi
 - Compliance ? Costo / beneficio ?

TABLE 3 Traditional Meta-Analysis of Dosing Frequency Analyses of Taking, Regimen, and Timing Adherence^a

Frequency of Dosing	N (%) Groups [N of Patients] in Taking Adherence Analysis	Taking Adherence ^b (95% CI)	N (%) Groups [N of Patients] in Regimen Adherence Analysis	Regimen Adherence ^c (95% CI)	N (%) Groups [N of Patients] in Timing Adherence Analysis	Timing Adherence ^d (95% CI)
Once daily	33 (50.8) [n=2,006]	93.0 (91.2-94.7)	35 (46.1) [n=2,118]	81.8 (77.9-85.7)	20 (42.6) [n=936]	76.9 (72.5-81.3)
Twice daily	22 (33.8) [n=1,259]	85.6 (82.5-88.8)	24 (31.6) [n=826]	74.2 (70.0-78.5)	16 (34.0) [n=650]	59.3 (40.6-58.0)
Three times daily	9 (13.8) [n=362]	80.1 (72.0-88.2)	13 (17.1) [n=321]	62.8 (55.4-70.1)	8 (17.0) [n=343]	35.9 (21.8-50.1)
Four times daily	1 (1.5) [n=57]	84.4 (78.5-90.3)	4 (5.3) [n=86]	68.2 (48.9-87.4)	3 (6.4) [n=109]	18.8 (10.1-27.5)

^aWeighted by the inverse of the variance of medication adherence.

^bTaking adherence was defined as the number of openings divided by the prescribed number of doses.

^cRegimen adherence was defined as the percentage of days with the appropriate number of doses taken.

^dTiming adherence was defined as the percentage of near optimal interadministration intervals.

CI=confidence interval.

TARGET

	normale	normale alta	grado 1	grado 2	grado 3
Altri fattori di rischio o DOSC o malattia	SP 120 - 129 DP 80 - 84	SP 130 - 139 DP 85 - 89	SP 140 - 159 DP 90 - 99	SP 160 - 179 DP 100 - 109	SP ≥ 180 DP ≥ 110
No altri fattori di rischio	nessuna terapia	nessuna terapia	stile di vita; se dopo qualche mese non migliora, terapia	stile di vita; se dopo qualche settimana non migliora, terapia	stile di vita + terapia immediata
1 - 2 fattori di rischio	stile di vita	stile di vita	stile di vita; se dopo qualche settimana non migliora, terapia	stile di vita; se dopo qualche settimana non migliora, terapia	stile di vita + terapia immediata
≥ 3 fattori di rischio / DOSC / malattia	stile di vita	stile di vita e considerare terapia	stile di vita + terapia	stile di vita + terapia	stile di vita + terapia immediata
DIABETE	stile di vita	stile di vita + terapia	stile di vita + terapia	stile di vita + terapia	stile di vita + terapia immediata
CV o danno renale	stile di vita + terapia immediata	stile di vita + terapia immediata	stile di vita + terapia immediata	stile di vita + terapia immediata	stile di vita + terapia immediata

Il meglio può anche essere un nemico del bene, ma la perfezione è sicuramente un nemico mortale di entrambi.

Zygmunt Bauman



scuola:
AME



Roma,
9-11 novembre 2012



Grazie per l'attenzione



scuola:
fondazione
AME



Roma,
9-11 novembre 2012

Quesiti ECM

a) qual è il target pressorio da perseguire nei pazienti diabetici ?

- **PA \leq 130/80, da adattare al singolo paziente in relazione alle sue condizioni cliniche**
- PA \leq 140/90, perché valori inferiori non hanno evidenziato un sicuro beneficio in termini di riduzione degli eventi cardiovascolari maggiori e non espone al rischio di ipotensione e sincope
- PA \leq 120/70, perché è stata dimostrata una riduzione di tutti gli eventi avversi cardiovascolari rispetto al target 130/80
- PA \leq 130/90, perché non espone il paziente diabetico al rischio di ipotensione e sincope

a) il diabete tipo 2

- costituisce per sé fattore di rischio indipendente per lo sviluppo di CVD
- **costituisce per sé fattore di rischio indipendente per lo sviluppo di CVD, aggravato dalla coesistenza di insulino-resistenza, obesità, dislipidemia e Ipertensione arteriosa**
- si complica con CVD a causa della insulino-resistenza, obesità e dislipidemia
- si complica con CVD a causa della insulino-resistenza, obesità e dislipidemia e Ipertensione arteriosa

- Le evidenze scientifiche più solide suggeriscono di mirare ad un target pressorio $< 150/80 - 85$ mm Hg nel paziente diabetico
- Numerosi studi concordano nel ritenere ragionevole un target pressorio $< 140/85$ mm Hg nel diabetico iperteso

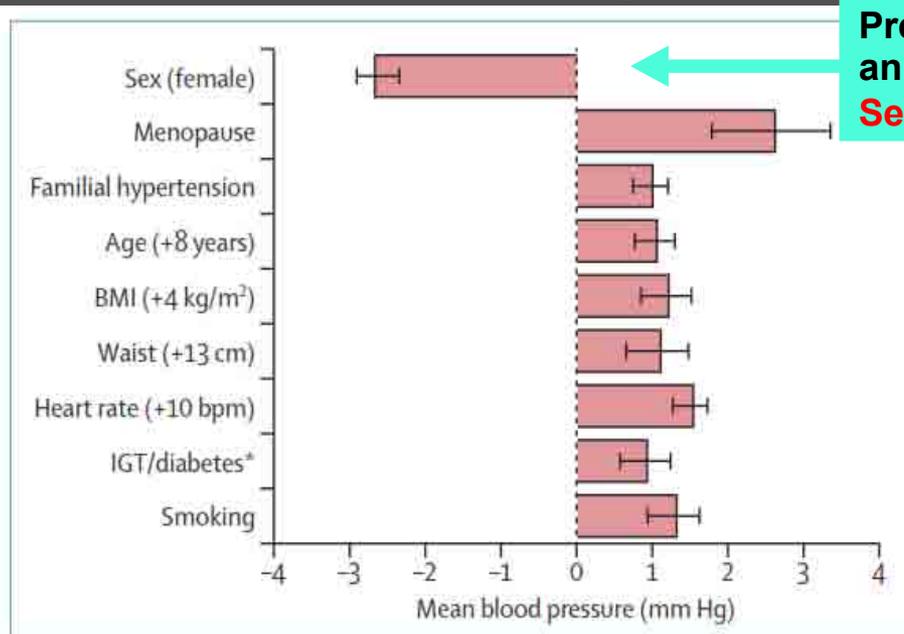


Figure 1: Phenotypic characteristics associated with blood pressure in people without hypertension or diabetes

Prevalenza di donne ipertese non diabetiche 55 - 64 anni = maschi
Se diabete 45 - 54 anni (1)

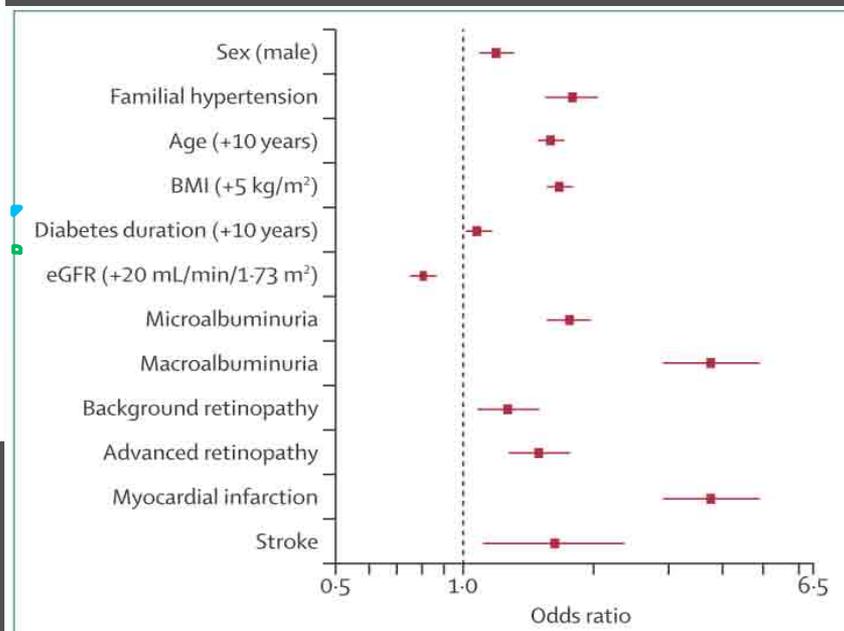


Figure 2: Phenotypic characteristics associated with hypertension in patients with type 2 diabetes