LA COMPLESSITA' ASSISTENZIALE DELLA PERSONA CON DIABETE IN OSPEDALE E SUL TERRITORIO:
UPDATE SULLE PIÙ' RECENTI ACQUISIZIONI DI GOVERNO CLINICO E GESTIONE DELLA TERAPIA

Cento, 28 Maggio 2016

Nuove acquisizioni nella terapia antipertensiva e antiaggregante nel paziente diabetico

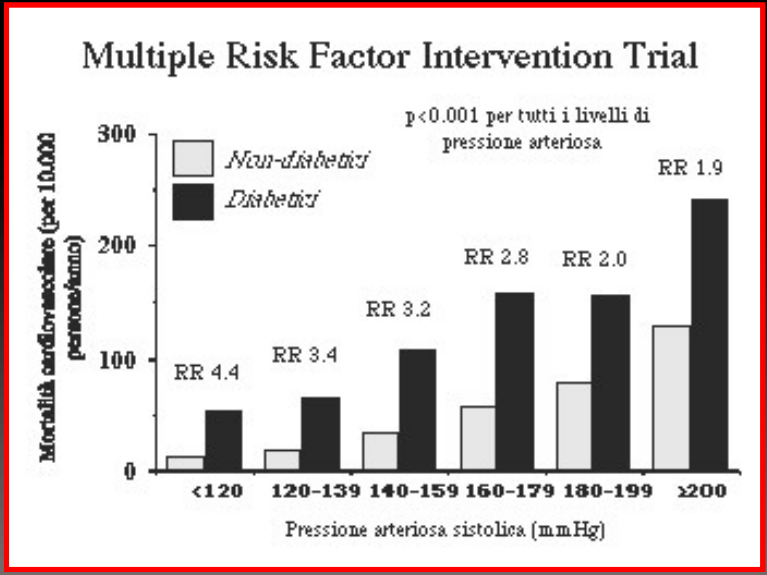
Dr. Federico Pacchioni

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO
BACKGROUND

• L'ipertensione arteriosa (HTN) è di frequente riscontro nei pazienti con diabete mellito (DM)

- T1DM: prevalenza fino al 49% [1]
- T2DM: prevalenza fino al 60% [2]

• HTN e DM sono entrambi riconosciuti fattori di rischio cardiovascolare (CV)
• DM raddoppia nell'uomo e triplica nella donna il rischio CV



[1] The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes 2006;55:3556–3565.

[2] Trends in blood pressure control in patients with type 2 diabetes: data from the Swedish National Diabetes Register (NDR). Blood Press 2011;20:
348–354.

[3] Diabetes, others risk factors and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial (MRFIT). Diabetes Care, Vol. 16, Number 2, February 1993; 434-444.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO
TRIALS

Popolazione con DM

- UKPDS (1997 -2007)
- ABCD (2000)
- CAPPP (2001)
- HDS (1998)
- BENEDICT (2004)
- ADVANCE (2008)
- ACCOMPLISH (2010)
- ACCORD (2010)
- ALTITUDE (2012)
- STENO TYPE 2
- STOP HTN 2 trial (2000)
- LIFE (2002)

Sottogruppi con DM

- SYST-EUR (1997)
- HOT (1998)
- ALLHAT (2002)
- ONTARGET (2008)
- SHEP (2000)
- FACET (1997)
- HOPE
- MIDAS
- EPESE

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DELLA TERAPIA

- Quali sono i valori di PA oltre i quali è indicato iniziare una terapia?
- Quali farmaci antipertensivi utilizzare e quali associazioni preferire?

GESTIONE DEL RISCHIO CLINICO

- Quali sono i valori di PA target per massimizzare il beneficio della terapia?
- Quali benefici clinici sono attesi dalla terapia antipertensiva nel DM?

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO
TRIALS

GESTIONE DELLA TERAPIA

Quali sono i valori di PA oltre i quali è indicato iniziare una terapia?

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J (2013) 34; 2159-2219.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO
TRIALS

GESTIONE DELLA TERAPIA

Quali sono i valori di PA oltre i quali è indicato iniziare una terapia?

- ABDC trial (470 pz.)
- Sottogruppi di HOPE e ADVANCE trial

Effect of Blood Pressure Control on Diabetic Microvascular Complications in Patients With Hypertension and Type 2 Diabetes

Raymond O. Estacio, MD
Barrett W. Jeffers, MSC
Nancy Gifford, RN
Robert W. Schrier, MD

Articles

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy

*Heart Outcomes Prevention Evaluation (HOPE) Study Investigators**

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DELLA TERAPIA

Quali farmaci antipertensivi utilizzare e quali associazioni preferire?

ORIGINAL INVESTIGATION

Effects of Different Blood Pressure–Lowering Regimens on Major Cardiovascular Events in Individuals With and Without Diabetes Mellitus

Results of Prospectively Designed Overviews of Randomized Trials

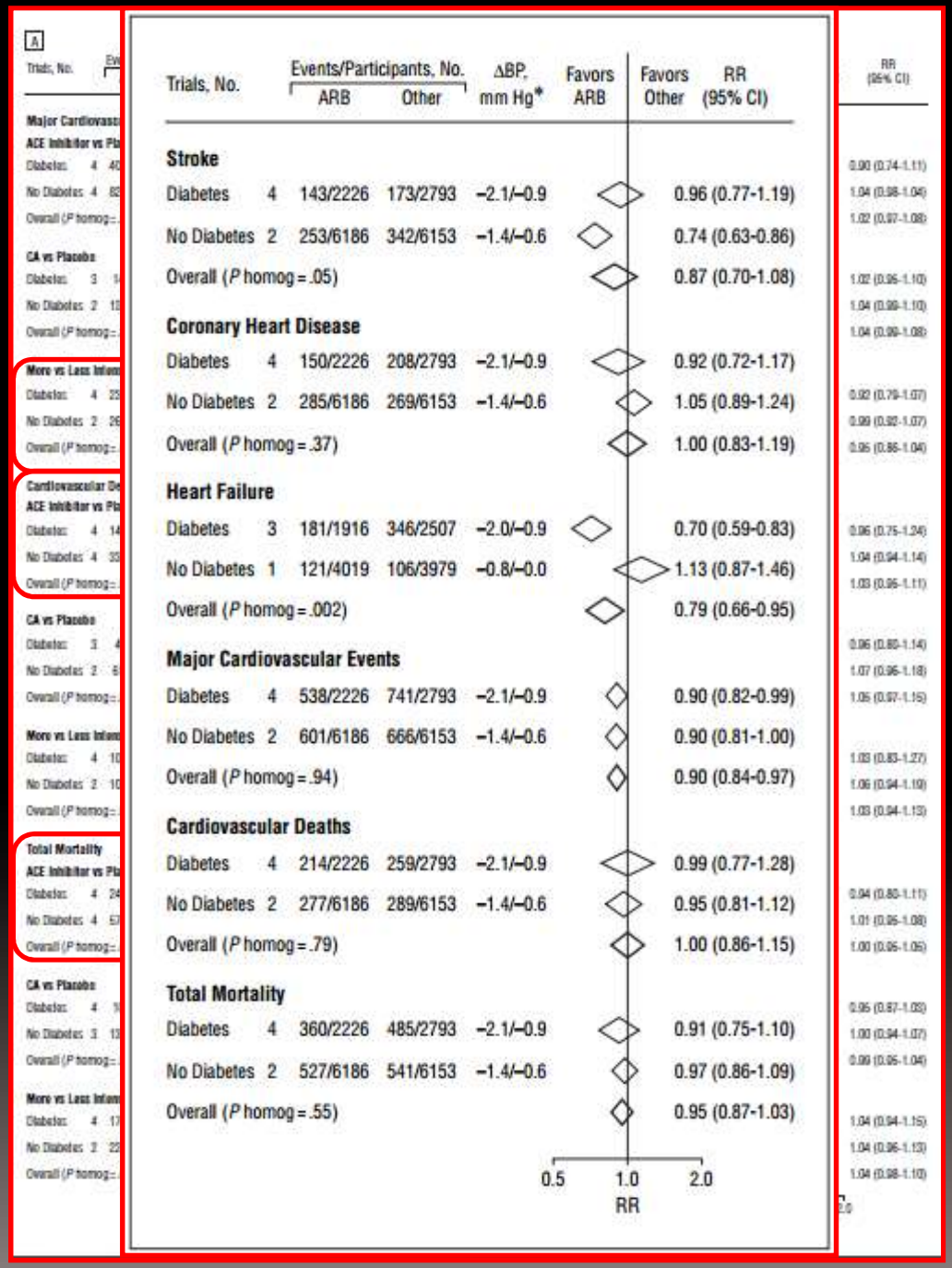
*Blood Pressure Lowering Treatment Trialists' Collaboration**

- 27 trials, 21% pz. Con DM
- Mean FU: 2,0 – 8,4 yrs

Table 2. Baseline Characteristics and Follow-up Blood Pressure Differences in Subgroups of Patients With and Without Diabetes Mellitus

	Diabetes (n = 33 395)					No Diabetes (n = 125 314)				
Treatment Comparison	Participants, No.	Age, Mean, y	Baseline SBP/DBP, Mean, mm Hg	Difference in BP, Mean, mm Hg	Male, %	Participants, No.	Age, Mean, y	Baseline SBP/DBP, Mean, mm Hg	Difference in BP, Mean, mm Hg	Male, %
ACE inhibitor vs placebo	4714	64.9	143.0/80.8	−3.6/−1.9	66.3	13 515	64.7	141.0/81.6	−5.8/−2.7	81.4
CA vs placebo	1811	62.1	162.1/85.6	−5.9/−3.1	58.1	5671	68.1	167.4/85.0	−9.3/−3.9	40.1
More vs less intense	3599	59.6	161.7/97.8	−6.0/−4.6	55.3	18 383	60.6	167.9/104.5	−3.7/−3.3	53.5
ARB vs other	5019	63.9	162.7/88.1	−2.0/−0.9	56.5	12 339	70.0	171.4/95.4	−1.4/−0.6	42.4
ACE inhibitor vs D/BB	10 999	66.2	151.7/85.2	2.2/0.3	50.8	36 431	64.2	159.0/91.6	1.4/0.2	51.0
CA vs D/BB	14 826	66.5	153.1/86.6	0.7/−0.8	48.7	51 741	65.0	160.1/93.2	1.1/−0.4	48.1
ACE inhibitor vs CA	8323	66.4	149.6/84.6	1.6/1.2	51.4	17 433	68.4	157.0/88.1	1.3/0.9	51.3

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005;165:1410–1419.



TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DELLA TERAPIA

Quali farmaci antipertensivi utilizzare e quali associazioni preferire?

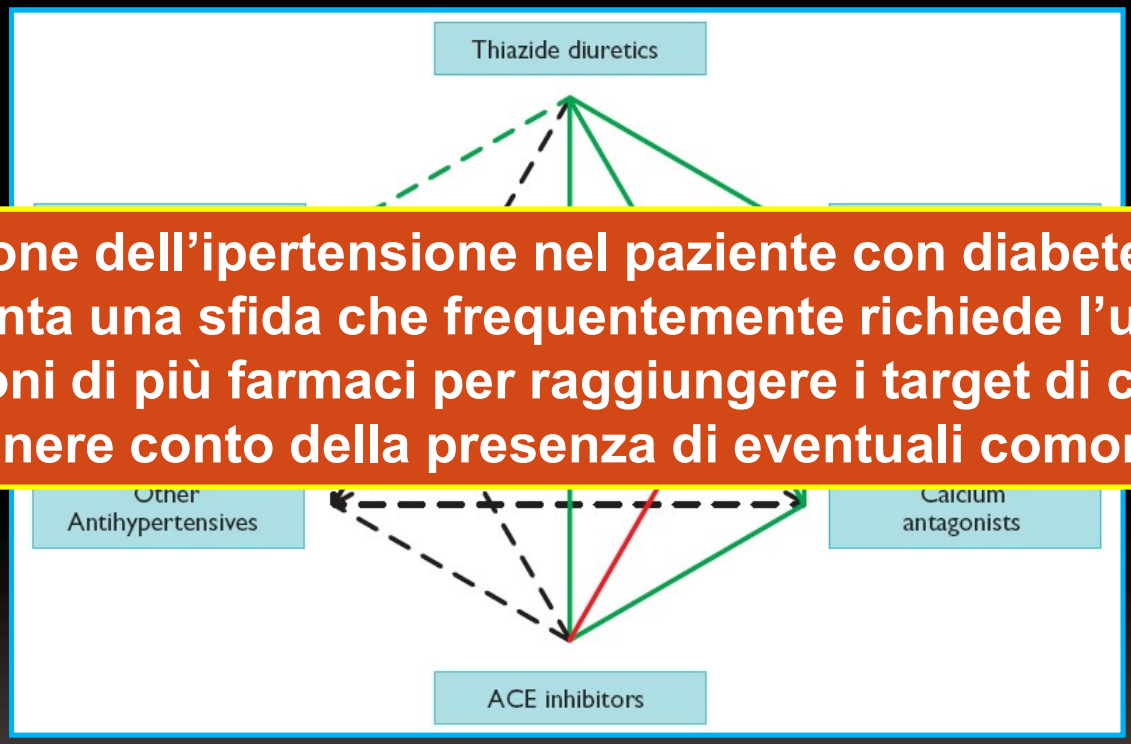
- Non differenze significative tra le varie classi di farmaci antipertensivi a confronto diretto in DM/ non DM.
- Modesto apparente effetto protettivo di ACE-inibitori su hard end-point vs placebo a favore dei pazienti con DM.

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005;165:1410–1419.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DELLA TERAPIA

Quali farmaci antipertensivi utilizzare e quali associazioni preferire?



La gestione dell'ipertensione nel paziente con diabete mellito rappresenta una sfida che frequentemente richiede l'utilizzo di associazioni di più farmaci per raggiungere i target di controllo e deve tenere conto della presenza di eventuali comorbidità.

ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J (2013) 34; 2159-2219.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DELLA TERAPIA

Quali farmaci antipertensivi utilizzare e quali associazioni preferire?

• Antagonisti RAAS sono efficaci nel ridurre gli eventi cardiovascolari maggiori (CAPPP, STOP HTN 2, LIFE, ACCOMPLISH).

•.

• ACE-I ritardano la comparsa di microalbuminuria in presenza di HTN e DM (BENEDICT).

• HCT, BB e la loro associazione possono aumentare il rischio di sviluppo di 2TDM, in particolare nella sindrome metabolica, pertanto andrebbero, almeno inizialmente, evitate.

• Il reale impatto negativo dell'uso di BB/HCT sull'assetto metabolico potrebbe essere inferiore al beneficio ottenuto dalla riduzione di PA (UKPDS).

• BB andrebbero evitati in prima scelta in assenza di cardiopatia ischemica (LIFE).

• L'associazione ACE-I + CB (amlodipina) appare superiore ad ACE-I + HCT nella riduzione degli eventi CV maggiori (ACCOMPLISH) a parità di riduzione pressoria.

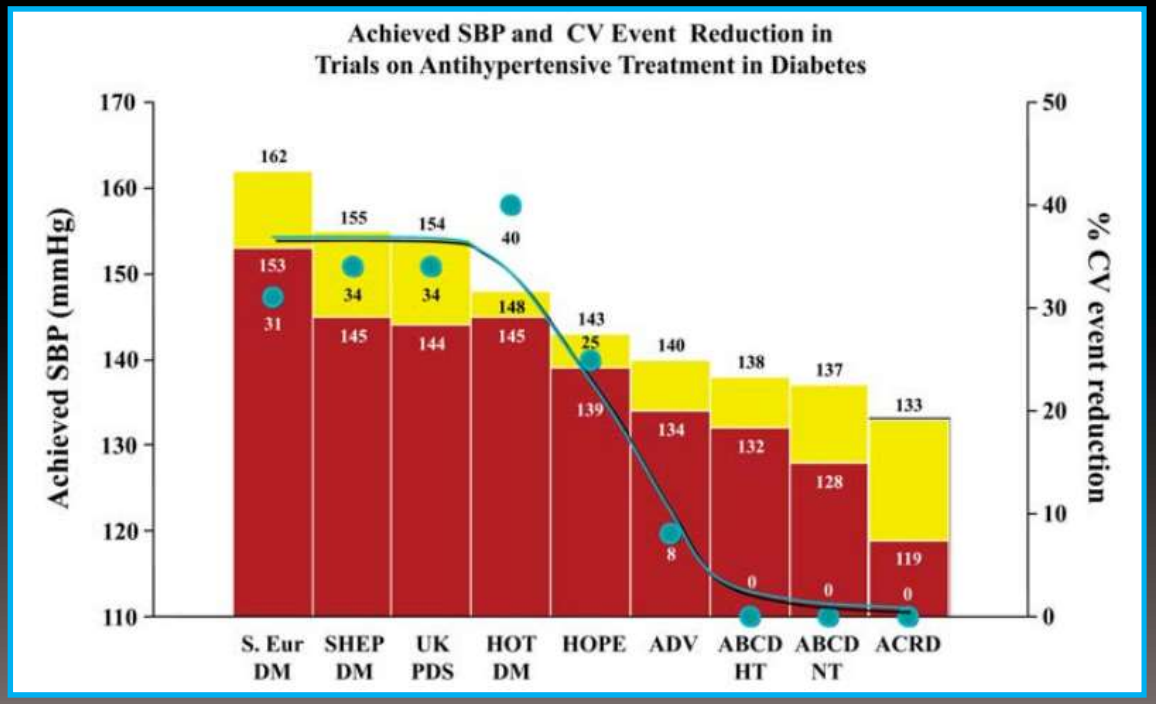
• L'associazione tra diversi antagonisti RAAS (ACE-I, ARB, aliskiren) non apporta benefici clinici e può essere dannosa (ONTARGET, ALTITUDE) in particolare nei pazienti anziani.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DEL RISCHIO CLINICO

Quali sono i valori di PA target per massimizzare il beneficio della terapia?

- E' indicato iniziare una terapia in presenza di HTN e DM con PAS > 140mmHg con target PAS < 140mmHg (FEVER, HOPE)
- E' indicato mantenere PAD nel range 80-85mmHg (HOT, UKPDS)
- La relazione tra le variazioni di PAS ed i benefici clinici conseguenti è sempre meno evidente all'avvicinarsi del limite inferiore di PAS nel range 130-140mmHg.



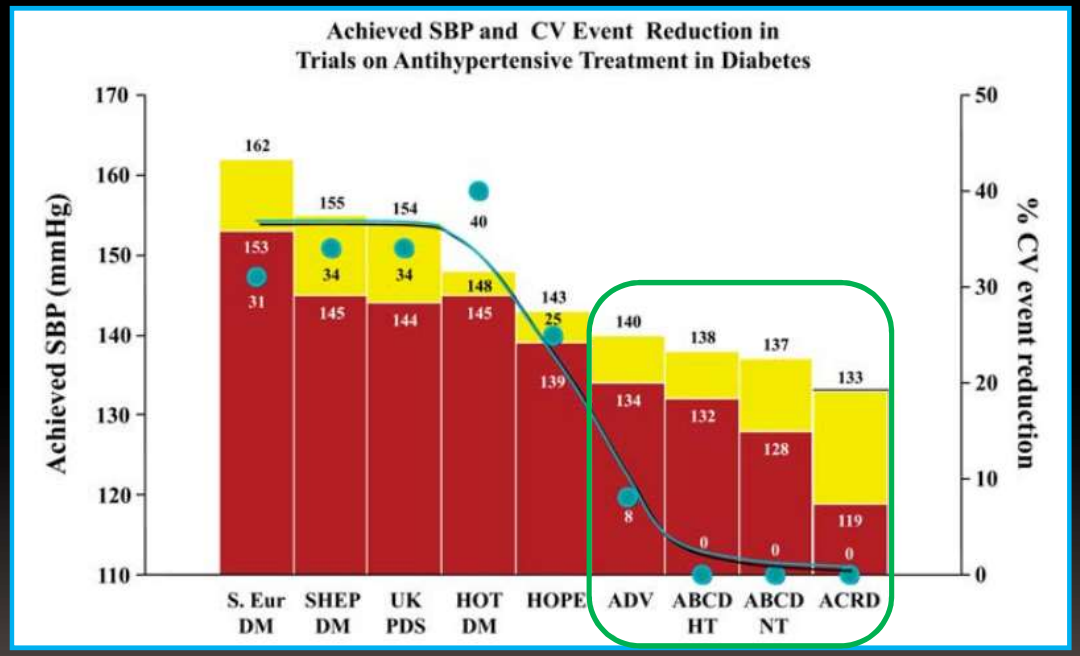
Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. Eur Heart J 2010;31:2837–2840.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

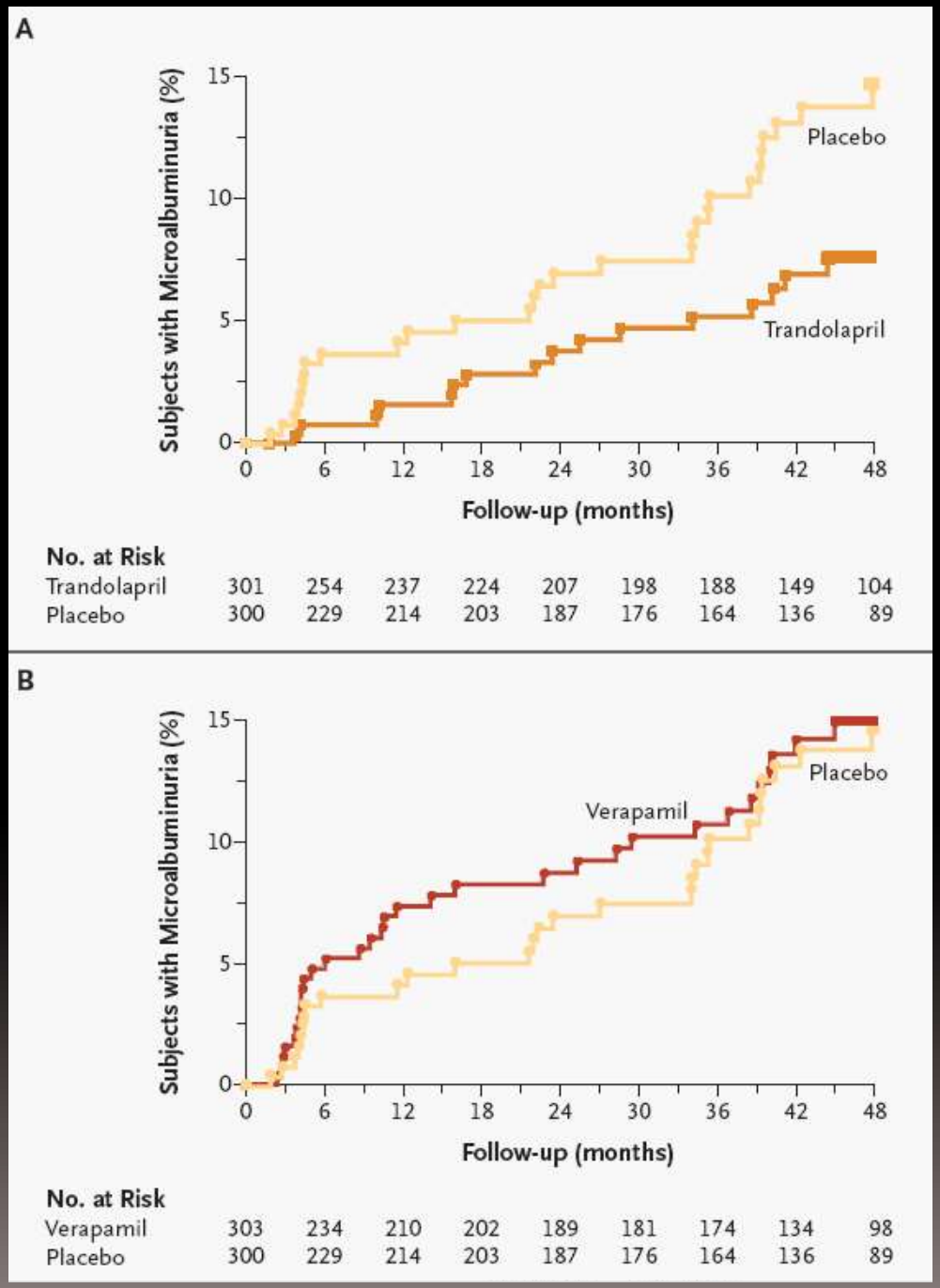
GESTIONE DEL RISCHIO CLINICO

Quali sono i valori di PA target per massimizzare il beneficio della terapia?

- Non emergono benefici clinici significativi per target PAS < 130mmHg.
- In pazienti con DM e proteinuria non vi è indicazione forte a perseguire target PAS < 130mmHg.



Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. Eur Heart J 2010;31:2837–2840.
Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensives patients with diabetes and coronary artery disease. JAMA 2010; 304:61–68.
Cederholm J, Gudbjornsdottir S, Eliasson B, Zethelius B, Eeg-Olofsson K,
Nilsson PM. Blood pressure and risk of cardiovascular disease in type 2 diabetes:further findings from the Swedish National Diabetes Register (NDR-BP-II). J Hypertens 2012;30:2020–2030.



TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DEL RISCHIO CLINICO

Quali benefici clinici sono attesi dalla terapia antipertensiva nel DM?

- Esiste evidenza da RCTs che la terapia antipertensiva, in particolare con ACE-I/ARB, riduce l'incidenza, l'entità e la progressione di proteinuria nella nefropatia diabetica.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 4, 2004 VOL. 351 NO. 19

Preventing Microalbuminuria in Type 2 Diabetes

Piero Ruggenenti, M.D., Anna Fassi, M.D., Anelja Parvanova Ilieva, M.D., Simona Bruno, M.D., Ilian Petrov Iliev, M.D., Varusca Brusegan, M.D., Nadia Rubis, R.N., Giulia Gherardi, R.N., Federica Arnoldi, R.N., Maria Ganeva, Stat.Sci.D., Bogdan Ene-Iordache, Eng.D., Flavio Gaspari, Ph.D., Annalisa Perna, Stat.Sci.D., Antonio Bossi, M.D., Roberto Trevisan, M.D., Alessandro R. Dodesini, M.D., and Giuseppe Remuzzi, M.D., for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators

Kunz R, Friedrich C,Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med 2008;148:30–48.

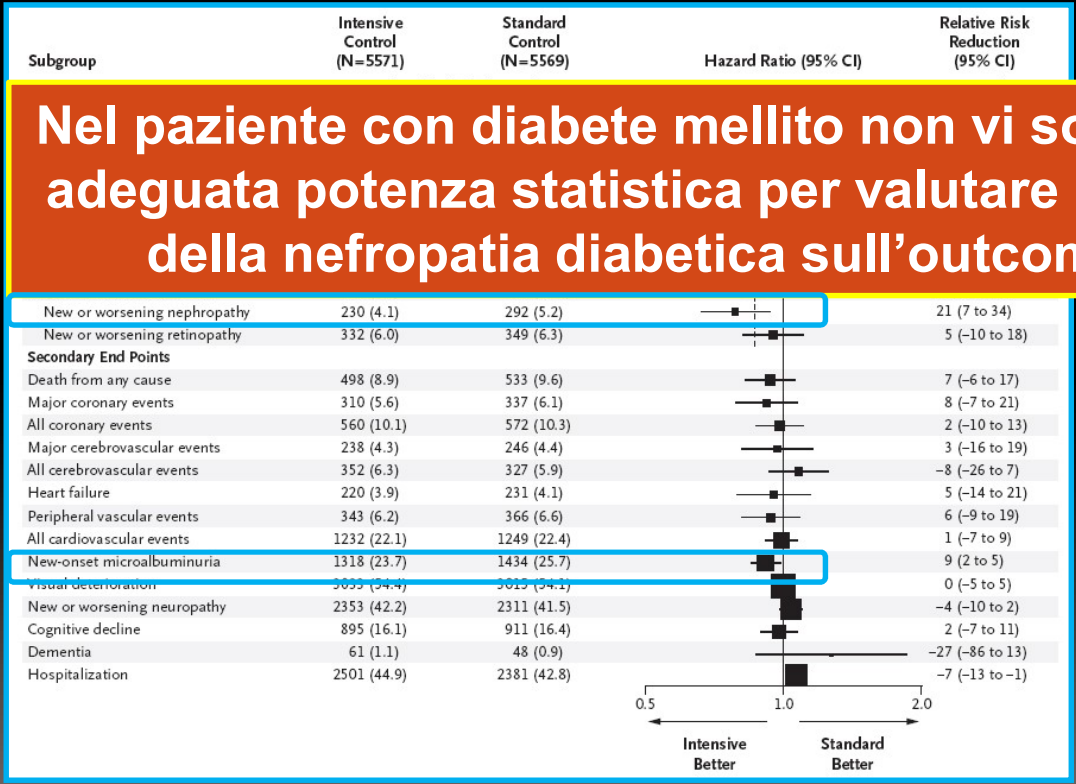
TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DEL RISCHIO CLINICO

Quali benefici clinici sono attesi dalla terapia antipertensiva nel DM?

- Non esiste dimostrazione che la riduzione della proteinuria in pazienti con nefropatia diabetica si traduca in riduzione significativa degli eventi macrovascolari.

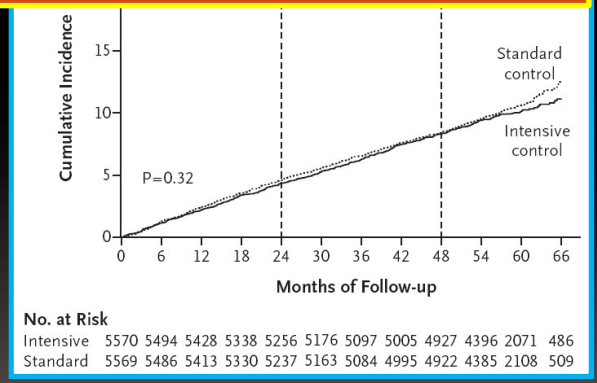
Nel paziente con diabete mellito non vi sono attualmente studi di adeguata potenza statistica per valutare l'impatto della gestione della nefropatia diabetica sull'outcome cardiovascolare.



Subgroup	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI)
New or worsening nephropathy	230 (4.1)	292 (5.2)		21 (7 to 34)
New or worsening retinopathy	332 (6.0)	349 (6.3)		5 (−10 to 18)
Secondary End Points				
Death from any cause	498 (8.9)	533 (9.6)		7 (−6 to 17)
Major coronary events	310 (5.6)	337 (6.1)		8 (−7 to 21)
All coronary events	560 (10.1)	572 (10.3)		2 (−10 to 13)
Major cerebrovascular events	238 (4.3)	246 (4.4)		3 (−16 to 19)
All cerebrovascular events	352 (6.3)	327 (5.9)		−8 (−26 to 7)
Heart failure	220 (3.9)	231 (4.1)		5 (−14 to 21)
Peripheral vascular events	343 (6.2)	366 (6.6)		6 (−9 to 19)
All cardiovascular events	1232 (22.1)	1249 (22.4)		1 (−7 to 9)
New-onset microalbuminuria	1318 (23.7)	1434 (25.7)		9 (2 to 5)
Visual deterioration	3033 (54.4)	3015 (54.1)		0 (−5 to 5)
New or worsening neuropathy	2353 (42.2)	2311 (41.5)		−4 (−10 to 2)
Cognitive decline	895 (16.1)	911 (16.4)		2 (−7 to 11)
Dementia	61 (1.1)	48 (0.9)		−27 (−86 to 13)
Hospitalization	2501 (44.9)	2381 (42.8)		−7 (−13 to −1)

0.5 1.0 2.0

Intensive Better Standard Better



No. at Risk

Intensive	5570	5494	5428	5338	5256	5176	5097	5005	4927	4396	2071	486
Standard	5569	5486	5413	5330	5237	5163	5084	4995	4922	4385	2108	509

ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370:829–840.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

Variable	Placebo	Perindopril–indapamide	*p* value	Standard glucose-lowering treatment	Intensive glucose-lowering treatment	*p* value
Progression of ≥2 steps in ETDRS classification						
Cases	103	84		99	88	
OR (95% CI)	1.0	0.78 (0.57–1.06)	0.12	1.0	0.84 (0.61–1.15)	0.27
Adjusted OR* (95% CI)	1.0	0.78 (0.57–1.06)	0.11	1.0	0.85 (0.62–1.16)	0.30
Progression of ≥1 steps in ETDRS classification						
Cases	135	132		137	130	
OR (95% CI)	1.0	0.96 (0.73–1.26)	0.77	1.0	0.90 (0.69–1.18)	0.44
Cases	81	92		95	78	
OR (95% CI)	1.0	1.14 (0.82–1.58)	0.43	1.0	0.76 (0.55–1.06)	0.10
Adjusted OR* (95% CI)	1.0	1.20 (0.85–1.69)	0.29	1.0	0.66 (0.47–0.94)	0.019
Macular oedema						
Cases	37	20		33	24	
OR (95% CI)	1.0	0.50 (0.29–0.88)	0.016	1.0	0.69 (0.40–1.18)	0.17
Adjusted OR* (95% CI)	1.0	0.50 (0.28–0.89)	0.018	1.0	0.59 (0.34–1.03)	0.065
Any retinal vascular lesion						
Cases	329	313		318	324	
OR (95% CI)	1.0	0.90 (0.72–1.12)	0.34	1.0	0.97 (0.78–1.22)	0.81
Adjusted OR* (95% CI)	1.0	0.92 (0.72–1.17)	0.48	1.0	0.87 (0.68–1.12)	0.28

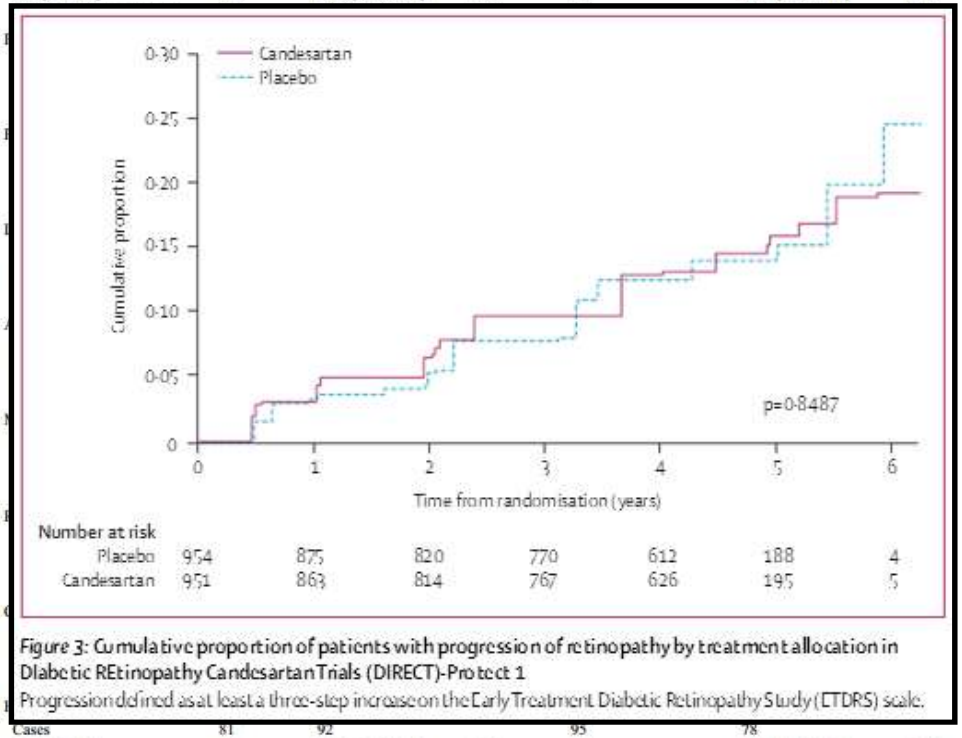


Figure 3: Cumulative proportion of patients with progression of retinopathy by treatment allocation in Diabetic REtinopathy CandesartanTrials (DIRECT)-Protect 1
Progression defined as at least a three-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

GESTIONE DEL RISCHIO CLINICO

Quali benefici clinici sono attesi dalla terapia antipertensiva nel DM?

- Non esiste dimostrazione che il controllo pressorio in pazienti con DM si traduca in riduzione significativa dell'incidenza e progressione della retinopatia diabetica.

Beulens JW, Patel A, Vingerling JR, Cruickshank JK, Hughes AD, Stanton A, Lu J, McG Thom SA, Grobbee DE, Stolk RP. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. Diabetologia 2009;52: 2027–2036.

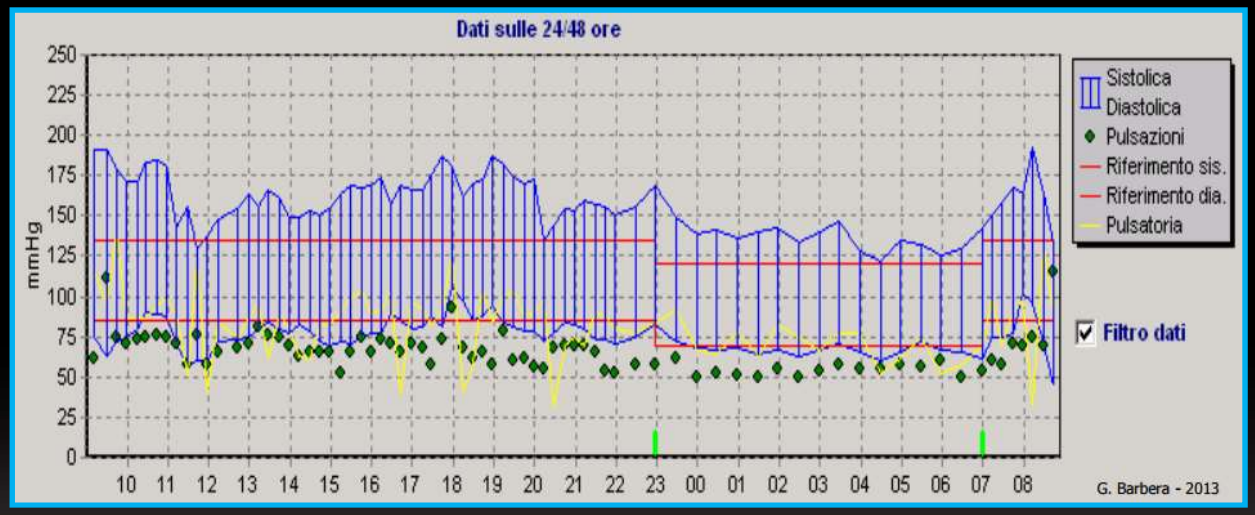
Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, Bilous R, Sjolie AK. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebocontrolled trials. Lancet 2008;372:1394–1402.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

GESTIONE DEL RISCHIO CLINICO

Quali benefici clinici sono attesi dalla terapia antipertensiva nel DM?

• Non esiste dimostrazione che il controllo pressorio farmacologico in pazienti con DM si traduca in riduzione significativa dell'incidenza e progressione della neuropatia diabetica.



• La presenza di ridotta variazione circadiana di PA (dipping ≤ 0%) predice con buona specificità ma ridotta sensibilità la presenza di NAD in pazienti con DM a conservata funzione renale e costituisce un fattore di rischio per eventi CV particolarmente nel DM.

TERAPIA ANTIPERTENSIVA E DIABETE MELLITO

Treatment strategies in patients with diabetes

Recommendations	Class [a]	Level [b]	Ref. [c]
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.	I	A	275, 276 290–293
A SBP goal <140 mmHg is recommended in patients with diabetes.	I	A	270,275, 276,295
The DBP target in patients with diabetes is recommended to be <85 mmHg.	I	A	290, 293
All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.	I	A	394,513
It is recommended that individual drug choice takes comorbidities into account.	I	C	-
Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.	III	B	433

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Blood pressure control in diabetes

Recommendations	Class [a]	Level [b]	Ref. [c]
Blood pressure control is recommended in patients with DM and hypertension to lower the risk of cardiovascular events.	I	A	189–191, 193–195
It is recommended that a patient with hypertension and DM is treated in an individualized manner, targeting a blood pressure of <140/85 mmHg.	I	A	191–193, 195
It is recommended that a combination of blood pressure lowering agents is used to achieve blood pressure control.	I	A	192–195, 205–207
A RAAS blocker (ACE-I or ARB) is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria.	I	A	200, 205–207
Simultaneous administration of two RAAS blockers should be avoided in patients with DM.	III	B	209, 210

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

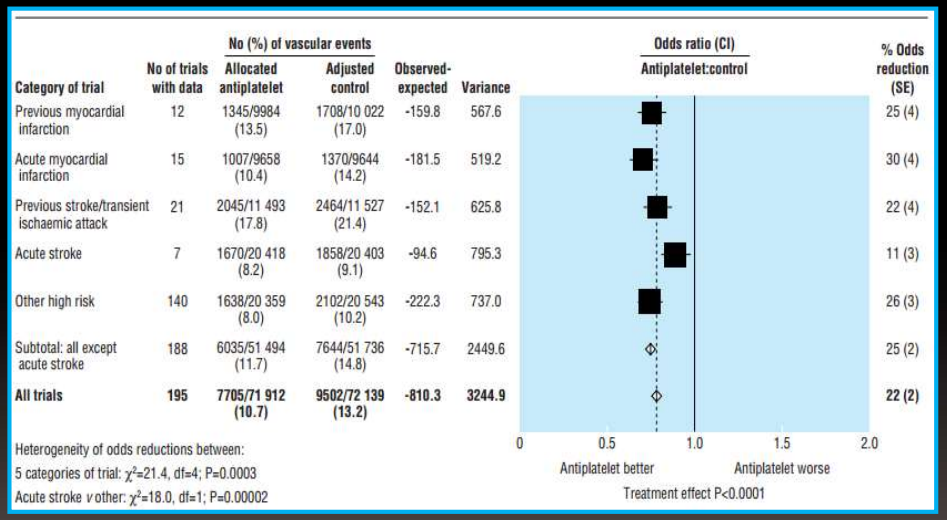
The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD).

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO
BACKGROUND

PREVENZIONE SECONDARIA

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration



Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**	**22 (2)**

Odds ratio (CI) Antiplatelet:control

0 0.5 1.0 1.5 2.0

Antiplatelet better Antiplatelet worse

Treatment effect P<0.0001

Heterogeneity of odds reductions between:

5 categories of trial: χ^2=21.4, df=4; P=0.0003

Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002

PREVENZIONE PRIMARIA

?

Collaborative overview of randomised trials of antiplatelet therapy I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO
BACKGROUND

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH AND WITHOUT TYPE 2 DIABETES

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEPPO LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D., AND MARKKU LAAKSO, M.D.

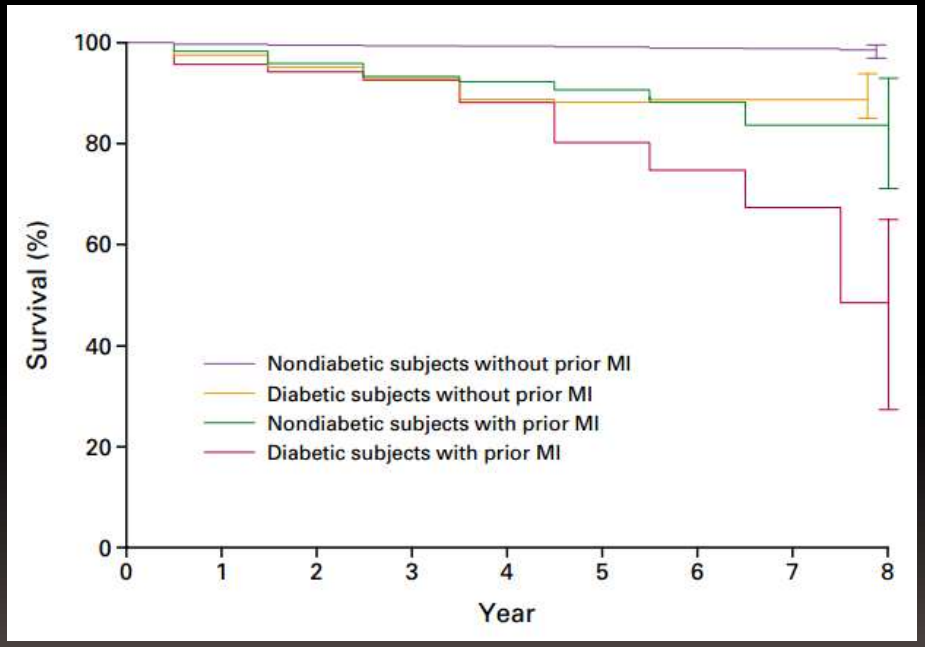


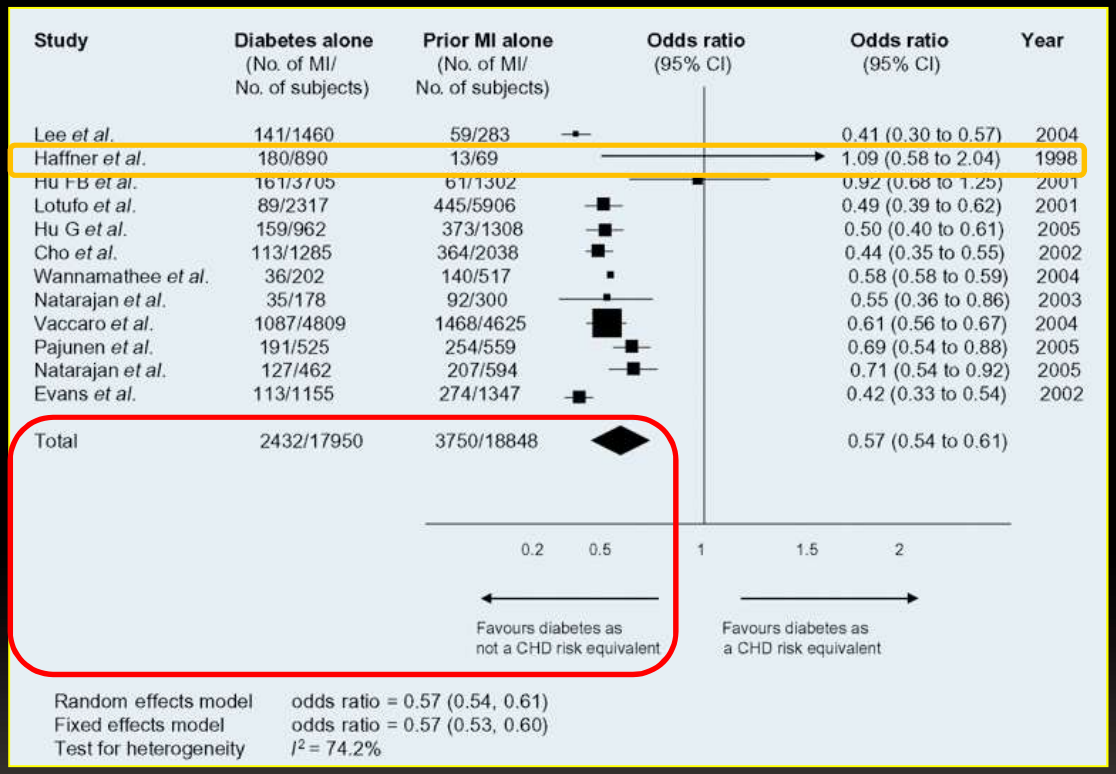
TABLE 3. RESULTS OF COX PROPORTIONAL-HAZARDS MODEL COMPARING MORTALITY FROM CORONARY HEART DISEASE IN 890 SUBJECTS WITH TYPE 2 DIABETES WITHOUT PRIOR MYOCARDIAL INFARCTION WITH THAT IN 69 NONDIABETIC SUBJECTS WITH PRIOR MYOCARDIAL INFARCTION DURING A SEVEN-YEAR FOLLOW-UP.*

VARIABLE	HAZARD RATIO FOR DIABETIC SUBJECTS (95% CI)	P VALUE
Adjusted for age, sex	1.4 (0.7–2.6)	0.4
Adjusted for age, sex, smoking status, hypertension, LDL cholesterol, HDL cholesterol, and triglycerides	1.2 (0.6–2.4)	0.5

*CI denotes confidence interval, LDL low-density lipoprotein, and HDL high-density lipoprotein.

Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO
BACKGROUND



Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009;26:142– 148

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO

No benefit

MI

Benefit in different end-points

Benefit? (underpowered)

Stroke

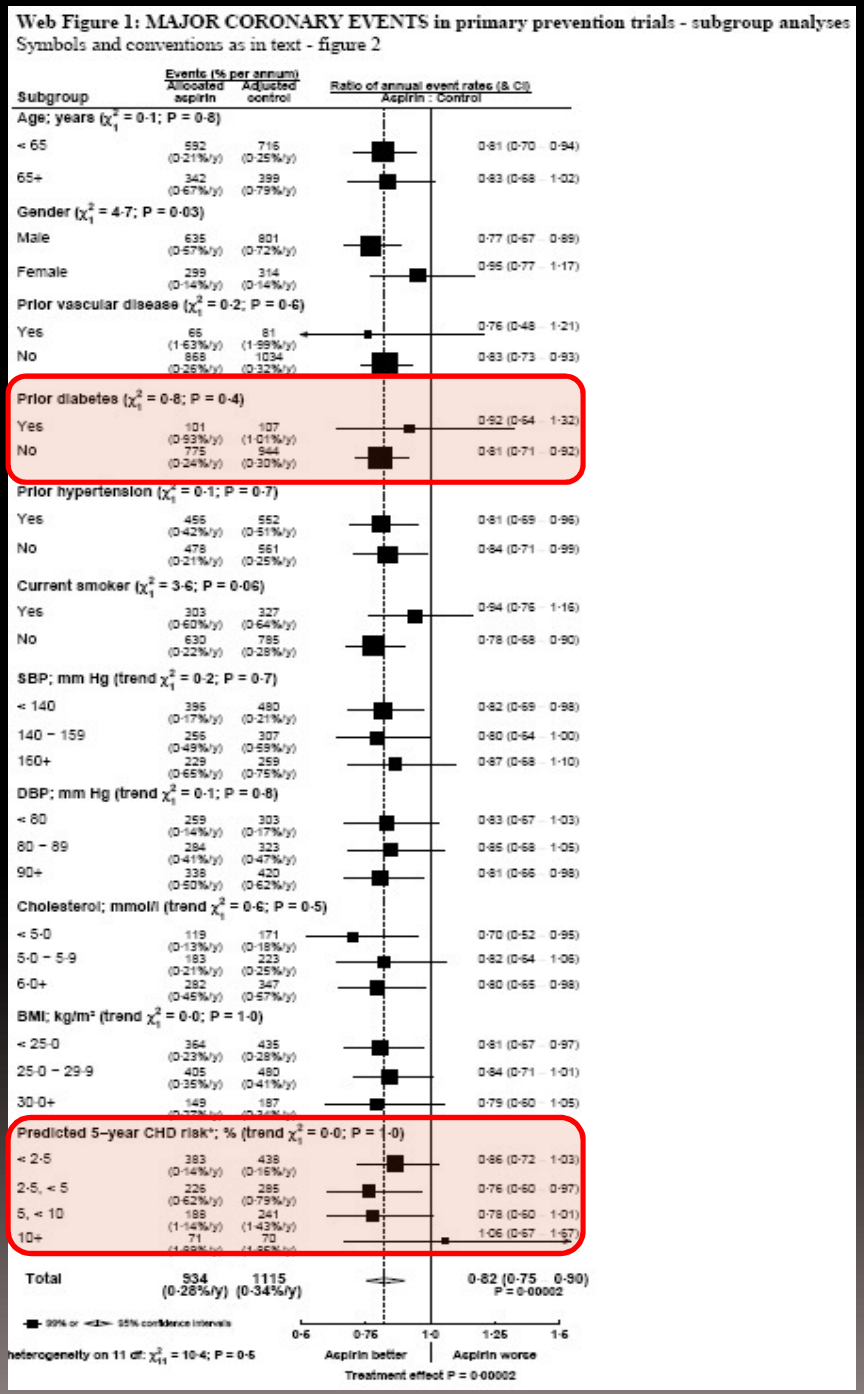
	Dates of recruitment	Participating countries	Year of main publication	Number of participants	Mean duration of follow-up (years)	Target population	Eligible age range (years) at entry	Aspirin regimen	Randomised factorial comparison	Placebo control
British Doctors' Study[10]	Nov 1978–Nov 1979	UK	1988	5139	5·6	Male doctors	19–90	500 mg daily	None	No
US Physicians' Health Study[11]	Aug 1981–Apr 1984	USA	1988	22071	5·0	Male doctors	45–73	325 mg alternate days	β carotene vs placebo	Yes
Thrombosis Prevention Trial[9]	Feb 1989–May 1994	UK	1998	5085	6·7	Men with risk factors for CHD	45–69	75 mg daily	Warfarin vs placebo	Yes
Hypertension Optimal Treatment Trial[12]	Oct 1992–May 1994	Europe, North and South America, Asia	1998	18790	3·8	Men and women with DBP 100–115 mm Hg	50–80	75 mg daily	Three blood pressure regimens	Yes
Primary Prevention Project[13]	June 1993–Apr 1998	Italy	2001	4495	3·7	Men and women with one or more risk factors for CHD	45–94	100 mg daily	Vitamin E vs open control	No
Women's Health Study[14]	Sep 1992–May 1995	USA	2005	39876	10·0	Female health professionals	≥45	100 mg alternate days	Vitamin E vs placebo	Yes

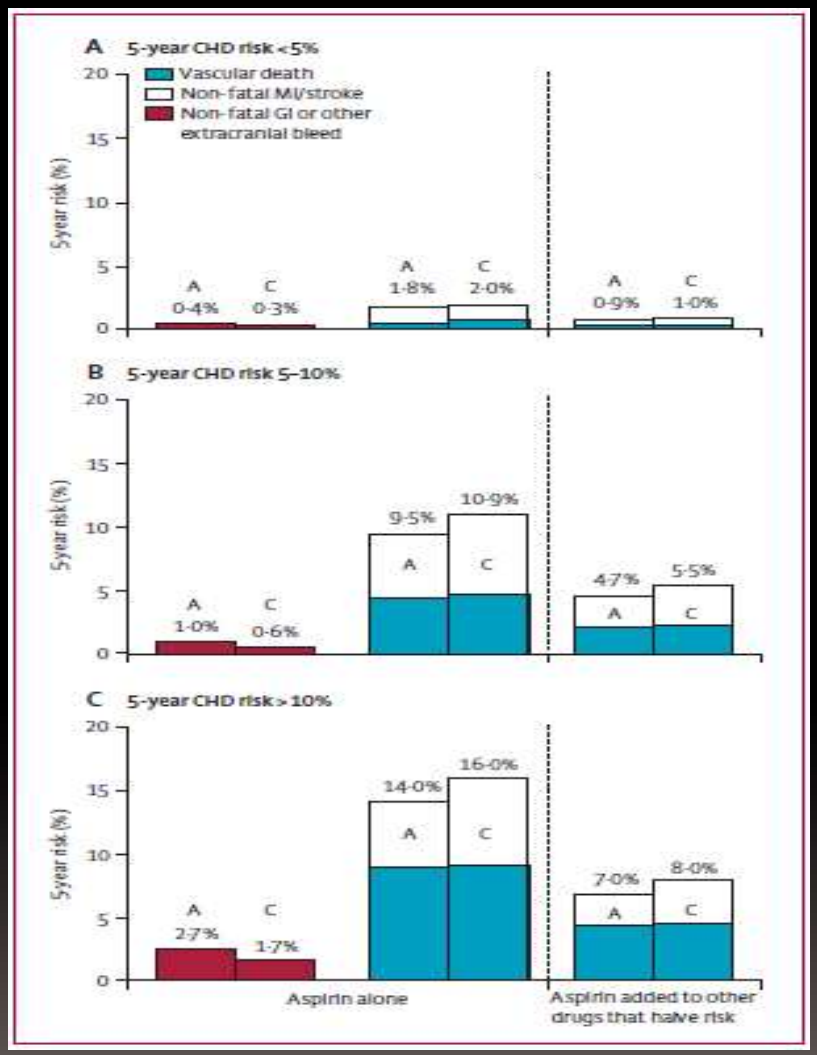
CHD=coronary heart disease. DBP=diastolic blood pressure.

Table 1: Design and eligibility criteria of primary prevention trials

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials Antithrombotic Trialists' (ATT) Collaboration* Lancet 2009; 373: 1849–60.

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO





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Lancet 2009; 373: 1849–60

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO

POPADAD
(2008; DM1/2)

JPAD
(2008; DM2)

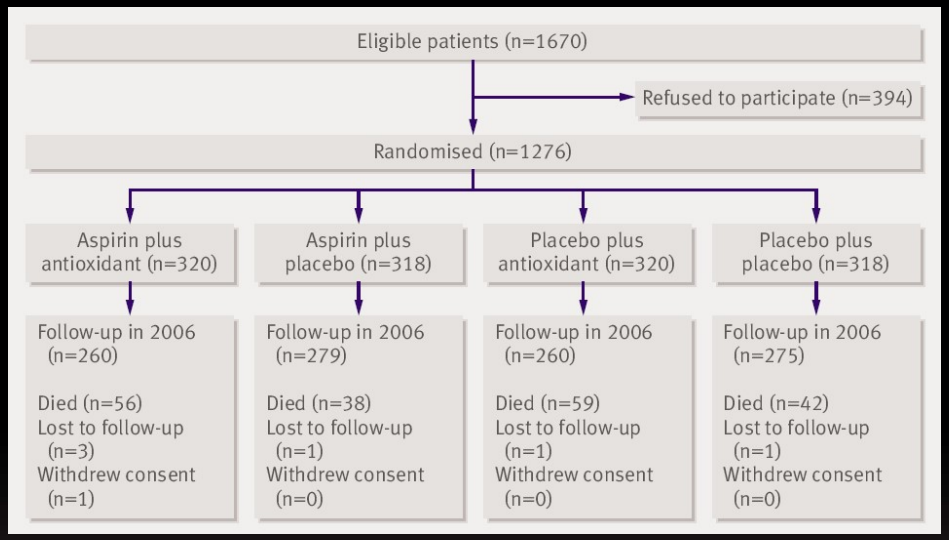
Prevenzione primaria di CVD in pz. con DM 1/2, età > 40 anni

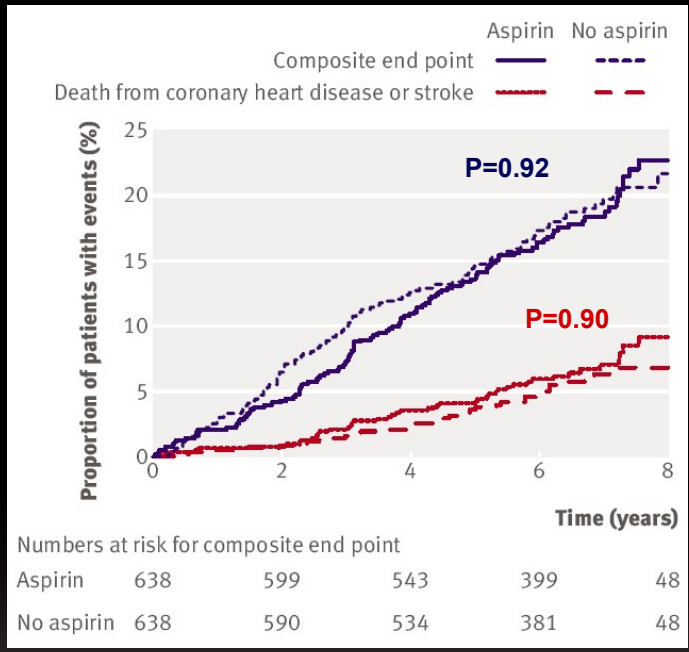
ASCEND
(**on-going**)

ACCEPT-D
(**ongoing**)

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO

POPADAD





Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840

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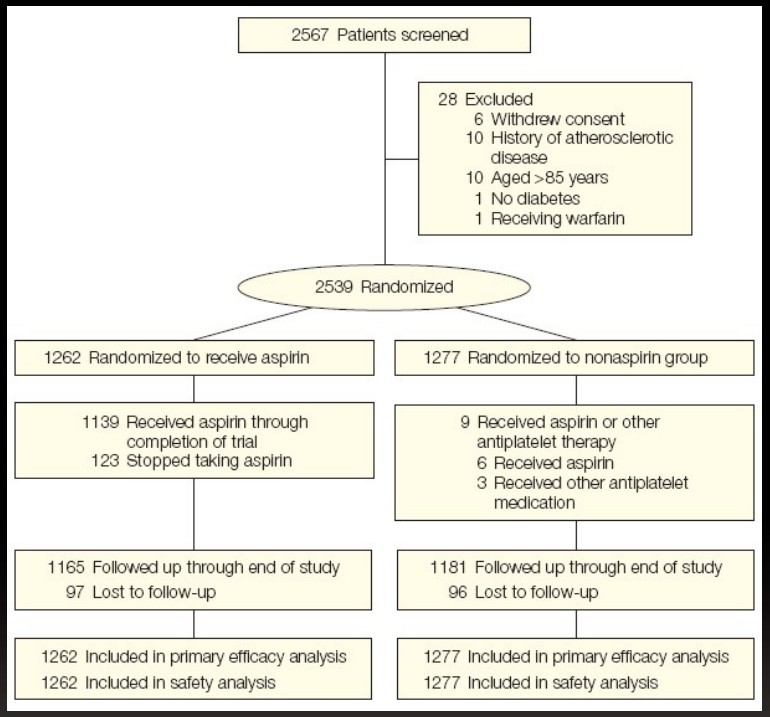
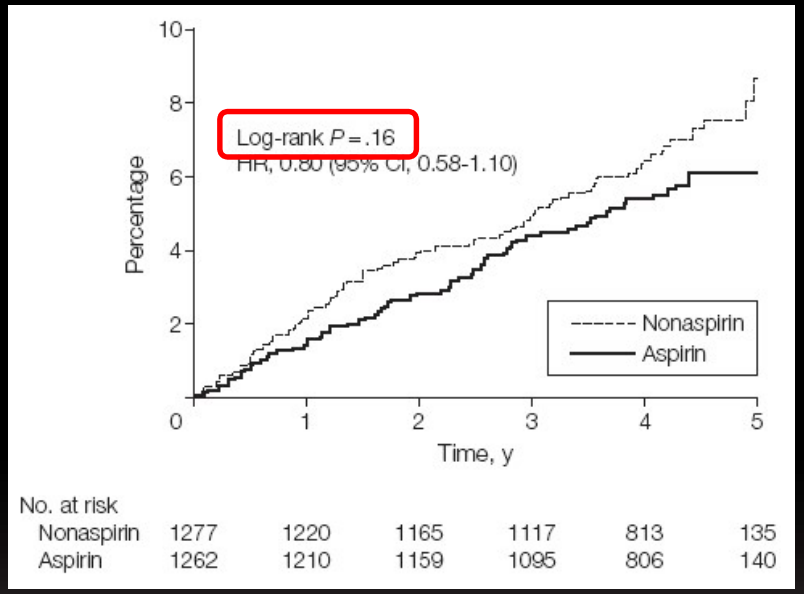
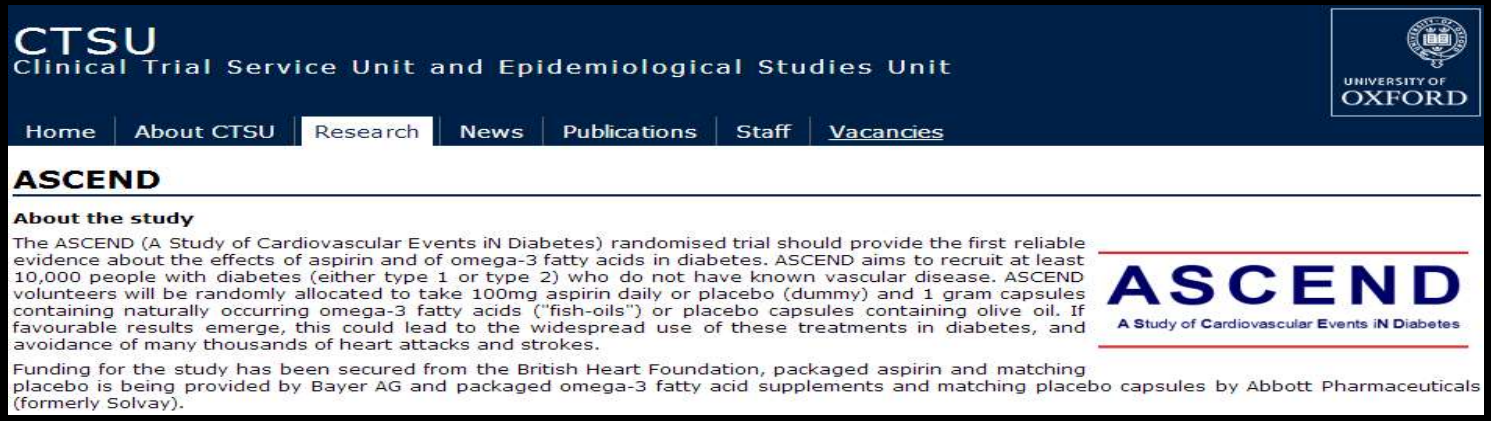
JPAD





Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO



CTSU
Clinical Trial Service Unit and Epidemiological Studies Unit

UNIVERSITY OF OXFORD

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ASCEND

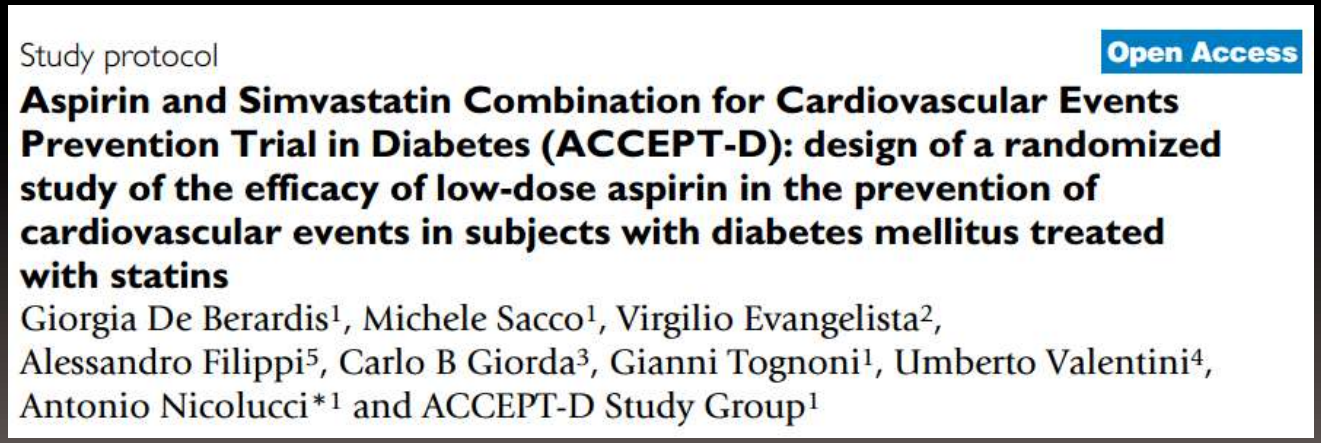
About the study

The ASCEND (A Study of Cardiovascular Events iN Diabetes) randomised trial should provide the first reliable evidence about the effects of aspirin and of omega-3 fatty acids in diabetes. ASCEND aims to recruit at least 10,000 people with diabetes (either type 1 or type 2) who do not have known vascular disease. ASCEND volunteers will be randomly allocated to take 100mg aspirin daily or placebo (dummy) and 1 gram capsules containing naturally occurring omega-3 fatty acids ("fish-oils") or placebo capsules containing olive oil. If favourable results emerge, this could lead to the widespread use of these treatments in diabetes, and avoidance of many thousands of heart attacks and strokes.

ASCEND
A Study of Cardiovascular Events iN Diabetes

Funding for the study has been secured from the British Heart Foundation, packaged aspirin and matching placebo is being provided by Bayer AG and packaged omega-3 fatty acid supplements and matching placebo capsules by Abbott Pharmaceuticals (formerly Solvay).

UK; 10.000 pts; estimated primary completion date: Sept. 2017; DM 1/2)



Study protocol

Open Access

Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins

Giorgia De Berardis[1], Michele Sacco[1], Virgilio Evangelista[2], Alessandro Filippi[5], Carlo B Giorda[3], Gianni Tognoni[1], Umberto Valentini[4], Antonio Nicolucci*[1] and ACCEPT-D Study Group[1]

IT; 5.000 pts; overall trial end date: Apr. 2015; DM 1/2)

TERAPIA ANTIAGGREGANTE PIASTRINICA E DIABETE MELLITO

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk (10-year risk >10%). This includes most men or women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria) and are not at increased risk of bleeding. C
- Aspirin should not be recommended for atherosclerotic cardiovascular disease prevention for adults with diabetes at low atherosclerotic cardiovascular disease risk (10-year atherosclerotic cardiovascular disease risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. C
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. A
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. B

Antiplatelet therapy in patients with diabetes

Recommendations	Class [a]	Level [b]	Ref. [c]
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A	272–274
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C	-
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in DM.	I	A	270
A $P2Y_{12}$ receptor blocker is recommended in patients with DM and ACS for 1 year and in those subjected to PCI (duration depending on stent type). In patients with PCI for ACS preferably prasugrel or ticagrelor should be given.	I	A	276, 277, 280, 282, 284
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B	280, 285

SUPPLEMENT 1

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2016

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

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).