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Creazione dell'interazione

DIABETOLOGO e CARDIOLOGO nel paziente con diabete mellito di tipo 2

con multipli fattori di rischio cardiovascolare
o malattia cardiovascolare conclamata

10 luglio 2020

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Il ruolo della diagnostica di laboratorio nella valutazione del rischio cardiovascolare nel paziente con diabete tipo 2

Prof. Alberto Margonato

Responsabile dell'Unità Operativa di Cardiologia Clinica all'IRCCS Ospedale San Raffaele di Milano

Professore ordinario di Cardiologia all'Università Vita-Salute San Raffaele.

Hazard ratios (HRs) for vascular outcomes in people with versus without diabetes at baseline, based on analyses of 530 083 patients

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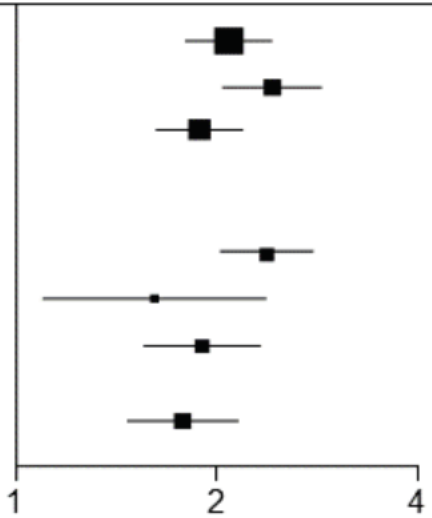
	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26 505	2.00 (1.83–2.19)	64 (54–71)
Coronary death	11 556	2.31 (2.05–2.60)	41 (24–54)
Non-fatal myocardial infarction	14 741	1.82 (1.64–2.03)	37 (19–51)
Stroke subtypes*			
Ischaemic stroke	3 799	2.27 (1.95–2.65)	1 (0–20)
Haemorrhagic stroke	1 183	1.56 (1.19–2.05)	0 (0–26)
Unclassified stroke	4 973	1.84 (1.59–2.13)	33 (12–48)
Other vascular deaths	3 826	1.73 (1.51–1.98)	0 (0–26)



CI = confidence interval. *Includes both fatal and non-fatal events

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Recommendations for glycaemic control in individuals with DM

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Recommendations	Class	Level
It is recommended to apply tight glucose control, targeting a near-normal HbA1c (<7.0% or <53 mmol/mol), to decrease microvascular complications in DM.	I	A
It is recommended that HbA1c targets are individualized according to duration of DM, comorbidities, and age.	I	C
Avoidance of hypoglycaemia is recommended.	I	C
The use of structured self-monitoring of blood glucose and/or continuous glucose monitoring should be considered to facilitate optimal glycaemic control.	IIa	A
An HbA1c target of <7.0% (or <53 mmol/mol) should be considered for the prevention of macrovascular complications in individuals with DM.	IIa	C

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Recommendations for the treatment of dyslipidaemias in diabetes mellitus

Recommendations	Class[a]	Level[b]
In patients with T2DM at very-high risk[c], an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.[34,418,432]	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.[418]	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c] [427]	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.[33,299]	IIa	B
Statin therapy is not recommended in premenopausal patients with diabetes who are considering pregnancy or are not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, as long as pregnancy is not being planned.	IIb	C

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ESC Guidelines 2019 for management of dyslipidaemias

Clinical assessment of cardiovascular damage in DM

- The addition of circulating biomarkers for CV risk assessment has “limited” clinical value
- **C-reactive protein** or **fibrinogen**
- **hs-TnT**
- N-terminal *pro-B-type natriuretic peptide* (**NT-proBNP**)
- **Albuminuria**

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Clinical assessment of cardiovascular damage in DM

▪C-reactive protein or fibrinogen

- In patients with DM without known CVD, measurement of **C-reactive protein** or **fibrinogen**

(inflammatory markers) provides minor incremental value to current risk assessment

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction

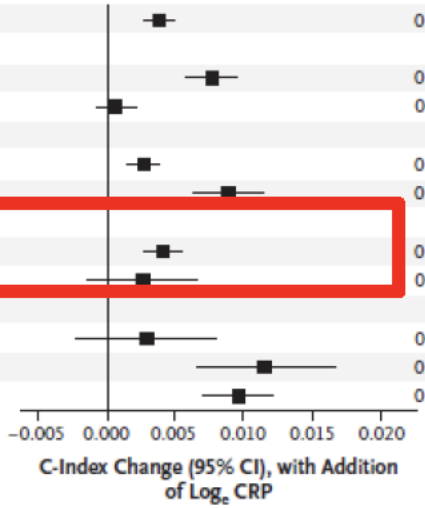
The Emerging Risk Factors Collaboration*

NEJM 2012

ABSTRACT

A C-Reactive Protein

Subgroup	CVD Cases	C-Index Change (95% CI)	P Value for Heterogeneity
Overall	13,568	0.0039 (0.0028 to 0.0050)	NA
Sex			<0.001
Male	5,755	0.0077 (0.0058 to 0.0096)	
Female	4,535	0.0007 (−0.0007 to 0.0021)	
Smoking status			<0.001
Not current	8,880	0.0027 (0.0015 to 0.0039)	
Current	4,688	0.0089 (0.0064 to 0.0115)	
History of diabetes			0.48
No	11,418	0.0042 (0.0029 to 0.0055)	
Yes	1,580	0.0026 (−0.0015 to 0.0067)	
Predicted 10-yr CVD risk			0.04
<10%	1,602	0.0029 (−0.0023 to 0.0081)	
10% to <20%	3,903	0.0116 (0.0065 to 0.0166)	
≥20%	7,417	0.0095 (0.0070 to 0.0121)	



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction

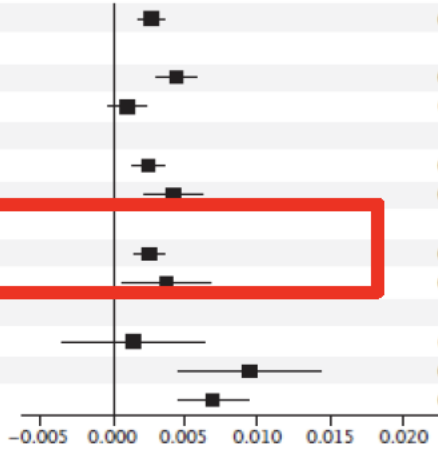
The Emerging Risk Factors Collaboration*

NEJM 2012

ABSTRACT

B Fibrinogen

Subgroup	CVD Cases	C-Index Change (95% CI)	P Value for Heterogeneity
Overall	12,021	0.0027 (0.0018 to 0.0036)	NA
Sex			0.001
Male	4,438	0.0043 (0.0029 to 0.0057)	
Female	3,368	0.0011 (–0.0004 to 0.0025)	
Smoking status			0.15
Not current	7,819	0.0024 (0.0013 to 0.0036)	
Current	4,202	0.0041 (0.0021 to 0.0061)	
History of diabetes			0.50
No	10,142	0.0026 (0.0015 to 0.0037)	
Yes	1,868	0.0037 (0.0007 to 0.0068)	
Predicted 10-yr CVD risk			0.07
<10%	1,509	0.0015 (–0.0034 to 0.0064)	
10% to <20%	3,301	0.0094 (0.0045 to 0.0144)	
≥20%	6,233	0.0068 (0.0044 to 0.0093)	



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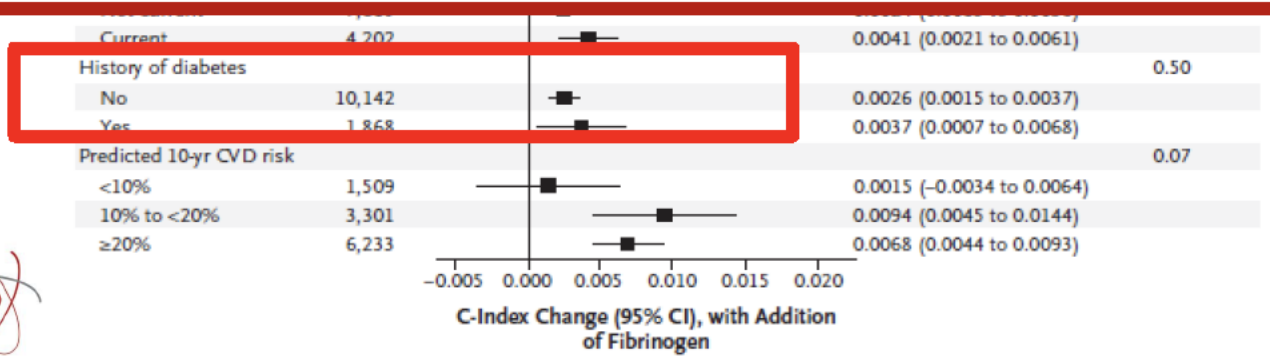
The Emerging Risk Factors Collaboration*

CONCLUSIONS

In a study of people without known cardiovascular disease, we estimated that under current treatment guidelines, assessment of the CRP or fibrinogen level in people at intermediate risk for a cardiovascular event could help prevent one additional event over a period of 10 years for every 400 to 500 people screened. (Funded by the British Heart Foundation and others.)



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Clinical assessment of cardiovascular damage in DM

- The addition of **hs-TnT** to conventional risk factors has shown incremental discriminative power.

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ESC 2019 Guidelines

Atherosclerosis 264 (2017) 67–73

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Comparison of non-traditional biomarkers, and combinations of biomarkers, for vascular risk prediction in people with type 2 diabetes: The Edinburgh Type 2 Diabetes Study

Anna H. Price [a, *], Christopher J. Weir [a, b], Paul Welsh [c], Stela McLachlan [a], Mark W.J. Strachan [d], Naveed Sattar [c], Jackie F. Price [a, **]

[a] Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK
[b] Edinburgh Clinical Trials Unit, University of Edinburgh, Scotland, UK
[c] Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK
[d] Metabolic Unit, Western General Hospital, Edinburgh, Scotland, UK

The Edinburg Type 2 diabetes study

Adding biomarkers to the basic model (all columns refer to total population with complete case analysis, n = 989[a], except for final column which gives c-statistics for sub-population with no CVD at baseline).

Predictors in the model, additional to conventional risk factors[b]	OR for a one SD increase in biomarker (95% CI)	C statistic (95% CI)	*p*-value for comparison with basic model	NR –event[c](%)	NR –no event[c] (%)	NRI	Goodness of fit (Hosmer-Lemeshow *p* value)	C statistic (95% CI) for sub-population with no baseline CVD
Basic model	–	0.722 (0.681, 0.763)					0.97	0.685 (0.623, 0.747)
ABI	0.86 (0.73, 1.00)	0.725 (0.684, 0.766)	0.44	−2.2	2.0	0.015	0.83	0.691 (0.628, 0.753)
NT-proBNP	1.23 (1.02, 1.49)	0.726 (0.685, 0.767)	0.39	−2.2	1.5	−0.007	0.81	0.684 (0.623, 0.745)
hs-cTnT	1.35 (1.13, 1.61)	0.732 (0.690, 0.774)	0.19	−1.6	2.2	0.006	0.09	0.685 (0.623, 0.747)
Gamma-GT	1.16 (0.98, 1.37)	0.726 (0.685, 0.766)	0.40	−2.7	1.1	−0.016	0.40	0.689 (0.626, 0.751)
g	1.07 (0.90, 1.27)	0.724 (0.683, 0.765)	0.29	0.5	1.2	0.018	0.90	0.693 (0.631, 0.755)
Top five models chosen (all-subsets regression)								
ABI, hs-cTnT, GGT	–	0.740 (0.699, 0.781)	0.04	−1.1	4.4	0.033	0.15	0.700 (0.637, 0.762)
ABI, hs-cTnT, GGT, proBNP	–	0.740 (0.699, 0.780)	0.06	−2.7	3.5	0.008	0.34	0.701 (0.640, 0.763)
hs-cTnT, GGT, proBNP	–	0.738 (0.697, 0.779)	0.07	−1.6	5.1	0.035	0.47	0.696 (0.634, 0.758)
ABI, hs-cTnT	–	0.735 (0.694, 0.776)	0.12	−3.2	5.4	0.021	0.35	0.695 (0.633, 0.756)
hs-cTnT, GGT	–	0.738 (0.697, 0.778)	0.06	−1.1	3.9	0.028	0.21	0.694 (0.632, 0.756)
Full model								
ABI, hs-cTnT, GGT, proBNP, *g*	–	0.740 (0.699, 0.781)	0.06	−1.6	5.2	0.036	0.39	0.706 (0.644, 0.767)

[a] A complete case analysis was carried out, n = 989 (n = 643, events = 83 for subpopulation with no CVD at baseline).

[b] Conventional risk factors: age, sex, smoking, atrial fibrillation, chronic kidney disease, arthritis, hypertension, BMI, sBP, total:HDL cholesterol, social status, baseline CVD status (MI, angina, TIA and stroke) and lipid lowering medication.

[c] n = 186 for event, n = 803 for no event.

The Edinburg Type 2 diabetes study

Conclusions: Individually, hs-cTnT appeared to be the most promising biomarker in terms of improving vascular risk prediction in people with type 2 diabetes, over and above traditional risk factors incorporated in the QRISK2 score. Combining several non-traditional biomarkers added further predictive value, and this approach merits further investigation when developing cost effective risk prediction tools for use in clinical practice.

Adding biomarkers to the basic model (all columns refer to total population with complete case analysis, n = 989[a], except for final column which gives c-statistics for subpopulation with no CVD at b

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Clinical assessment of cardiovascular damage in DM

- The prognostic value of N-terminal *pro-B-type natriuretic peptide* (**NT-proBNP**) in an unselected cohort of people with DM (including known CVD) showed that **patients with low levels of NT-proBNP have an excellent short-term prognosis**

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ESC 2019 Guidelines

European Heart Journal (2008) **29**, 2259–2264
doi:10.1093/eurheartj/ehn334

CLINICAL RESEARCH
Prevention and epidemiology

NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus

Martin Huelsmann[1†], Stephanie Neuhold[1†], Guido Strunk[2], Deddo Moertl[1], Rudolf Berger[1], Rudolf Prager[3], Heidemarie Abrahamian[3], Michaela Riedl[4], Richard Pacher[1*], Anton Luger[4], and Martin Clodi[4]

[1]Department of Cardiology, Medical University Vienna, Vienna, Austria; [2]Research Institute for Health Care Management and Economics, University of Economics and Business Administration, Vienna, Austria; [3]Third Department of Medicine, Hietzing Hospital, Vienna, Austria; and [4]Department of Endocrinology, Medical University, Vienna, Austria

Received 24 January 2008; revised 24 June 2008; accepted 27 June 2008; online publish-ahead-of-print 23 July 2008

Table 1 Baseline clinical and laboratory characteristics

Number of unplanned cardiovascular hospitalization or death %	44 (7.00%)
Age (years)	58.70 ± 13.86
Gender (female), *n* (%)	282 (44.70)
Body mass index (kg/m^2)	30.21 ± 11.80
History of any cardiac disease (%)	144 (22.82)
History of ischaemic heart disease (%)	108 (17.12)
History of hypertension (%)	513 (81.30)
History of smoking (%)	274 (56.57)
RR sys (mmHg)	142.52 ± 22.34
HbA_{1c} (%)	8.00 ± 1.63
LDL-cholesterol (mg/dL)	112.16 ± 37.93
Serum-creatinine (mg/dL)	1.05 ± .45
GFR (mL/min)	92.73 ± 39.98
NT-proBNP (pg/mL)	285.55 ± 489.43
NYHA-class (I/II/III/IV) (%)	428(67.8)/145 (23.00)/ 55(8.7)/3 (0.5)
MLHFQ (0–100)	11.22 ± 11.01
Dyspnoe score (1–10)	1.39 ± 6.60
Duration of diabetes (years)	9.28 ± 10.13
Serum-creatinine (log)	1.67E-3 ± .29
NT-proBNP (log)	4.95 ± 1.03

Baseline clinical and laboratory characteristics of 631 diabetic patients with and without an unplanned cardiovascular hospitalization or death.

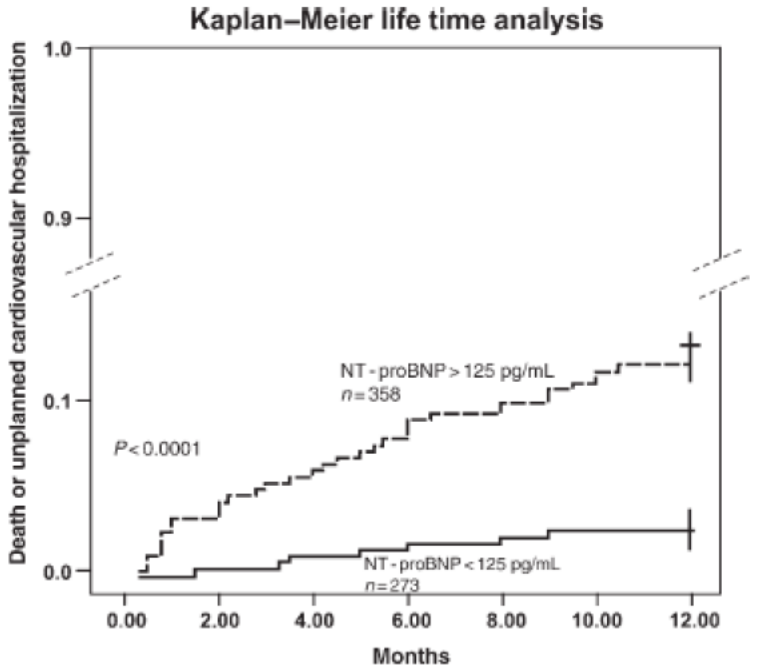

Figure 1 Kaplan–Meier curves of all-cause mortality or unplanned cardiovascular hospitalization in 631 diabetic patients according to plasma-levels of NT-proBNP at baseline. Solid line: patients with NT-proBNP levels below cut-off (<125 pg/mL). Dashed line: patients with NT-proBNP levels above cut-off (>125 pg/mL). Log-rank test for overall difference, $P < 0.0001$.

Table I Baseline clinical and laboratory characteristics

Number of unplanned cardiovascular hospitalization or death %	44 (7.00%)
Age (years)	58.70 ± 13.86
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NT-proBNP (pg/mL)	285.55 ± 489.43
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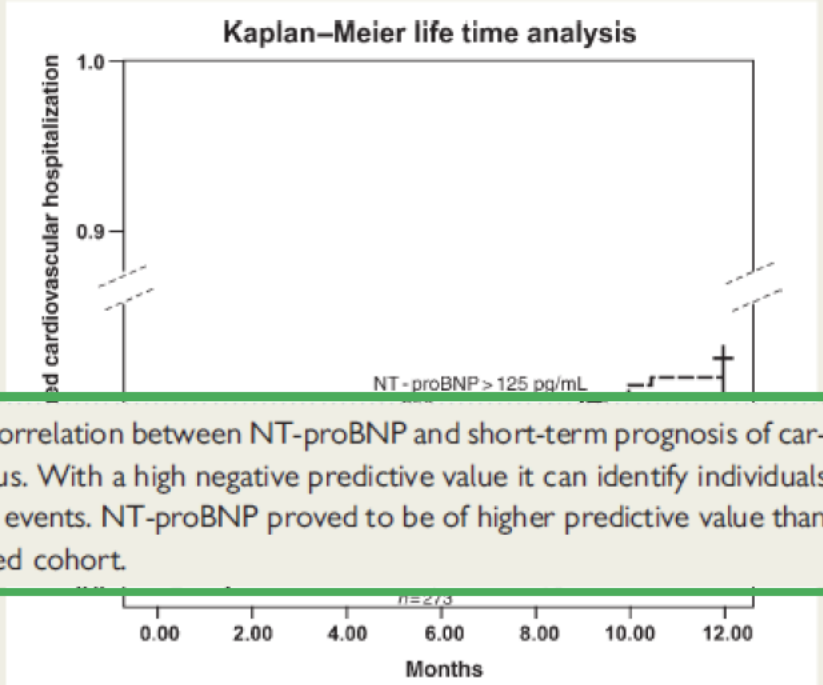
Dyspnoe score (1–10)	1.39 ± 6.60
Duration of diabetes (years)	9.28 ± 10.13
Serum-creatinine (log)	1.67E-3 ± .29
NT-proBNP (log)	4.95 ± 1.03

Baseline clinical and laboratory characteristics of 631 diabetic patients with and without an unplanned cardiovascular hospitalization or death.

Conclusion

We have demonstrated a strong and independent correlation between NT-proBNP and short-term prognosis of cardiovascular events for patients with diabetes mellitus. With a high negative predictive value it can identify individuals who are not at intermediate risk for cardiovascular events. NT-proBNP proved to be of higher predictive value than traditional cardiovascular markers, in this unselected cohort.



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Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 15, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.069

Biomarkers

PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease)

A Prospective Randomized Controlled Trial

Martin Huelsmann, MD,* Stephanie Neuhold, MD,*† Michael Resl, MD,‡ Guido Strunk, PHD,§‖ Helmut Brath, MD,¶ Claudia Francesconi, MD,# Christopher Adlbrecht, MD,* Rudolf Prager, MD,** Anton Luger, MD,‡ Richard Pacher, MD,* Martin Clodi, MD‡

Vienna, Austria; and Dortmund, Germany

Objectives The study sought to assess the primary preventive effect of neurohumoral therapy in high-risk diabetic patients selected by N-terminal pro–B-type natriuretic peptide (NT-proBNP).

Background Few clinical trials have successfully demonstrated the prevention of cardiac events in patients with diabetes. One reason for this might be an inaccurate selection of patients. NT-proBNP has not been assessed in this context.

Methods A total of 300 patients with type 2 diabetes, elevated NT-proBNP (>125 pg/ml) but free of cardiac disease were randomized. The "control" group was cared for at 4 diabetes care units; the "intensified" group was additionally treated at a cardiac outpatient clinic for the up-titration of renin-angiotensin system (RAS) antagonists and beta-blockers. The primary endpoint was hospitalization/death due to cardiac disease after 2 years.

Results At baseline, the mean age of the patients was 67.5 ± 9 years, duration of diabetes was 15 ± 12 years, 37% were male, HbA_{1c} was 7 ± 1.1%, blood pressure was 151 ± 22 mm Hg, heart rate was 72 ± 11 beats/min, median NT-proBNP was 265.5 pg/ml (interquartile range: 180.8 to 401.8 pg/ml). After 12 months there was a significant difference between the number of patients treated with a RAS antagonist/beta-blocker and the dosage reached between groups ($p < 0.0001$). Blood pressure was significantly reduced in both ($p < 0.05$); heart rate was only reduced in the intensified group ($p = 0.004$). A significant reduction of the primary endpoint (hazard ratio: 0.351; 95% confidence interval: 0.127 to 0.975, $p = 0.044$) was visible in the intensified group. The same was true for other endpoints: all-cause hospitalization, unplanned cardiovascular hospitalizations/death ($p < 0.05$ for all).

Conclusions Accelerated up-titration of RAS antagonists and beta-blockers to maximum tolerated dosages is an effective and safe intervention for the primary prevention of cardiac events for diabetic patients pre-selected using NT-proBNP. (Nt-proBNP Guided Primary Prevention of CV Events in Diabetic Patients [PONTIAC]; NCT00562952) (J Am Coll Cardiol 2013;62:1365–72) © 2013 by the American College of Cardiology Foundation

PONTIAC STUDY, JACC 2013

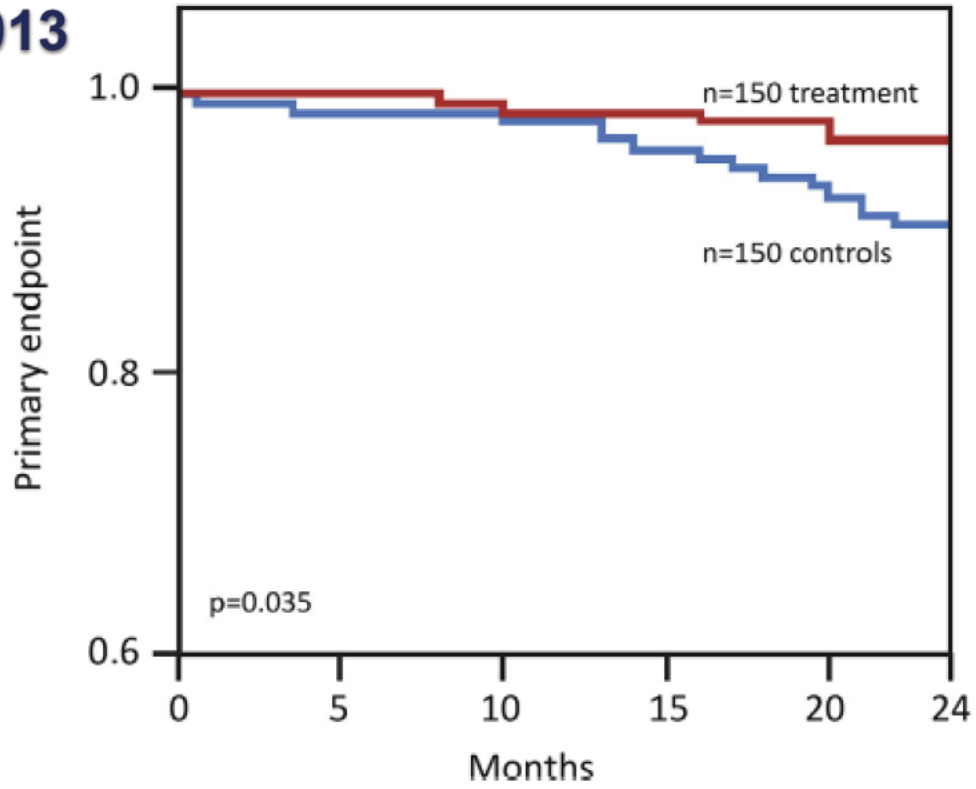

Figure 2 Kaplan-Meier Curves of the Primary Endpoint Hospitalization or Death Due to Cardiac Disease According to Treatment Strategy

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PONTIAC STUDY, JACC 2013

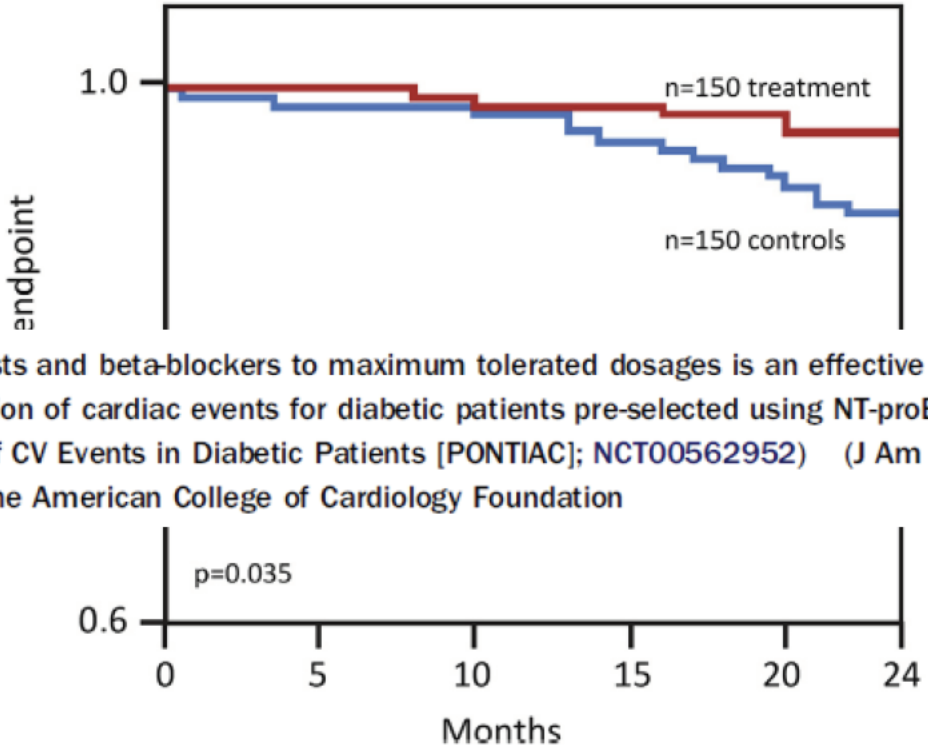

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Figure 2 Kaplan-Meier Curves of the Primary Endpoint Hospitalization or Death Due to Cardiac Disease According to Treatment Strategy

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Clinical assessment of cardiovascular damage in DM

- The presence of **albuminuria** (30-299) mg/day) is associated with increased risk of CVD and chronic kidney disease (CKD) in T1DM and T2DM.
- Measurement of albuminuria may predict kidney dysfunction and warrant renoprotective interventions

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OPEN ACCESS Freely available online PLOS MEDICINE

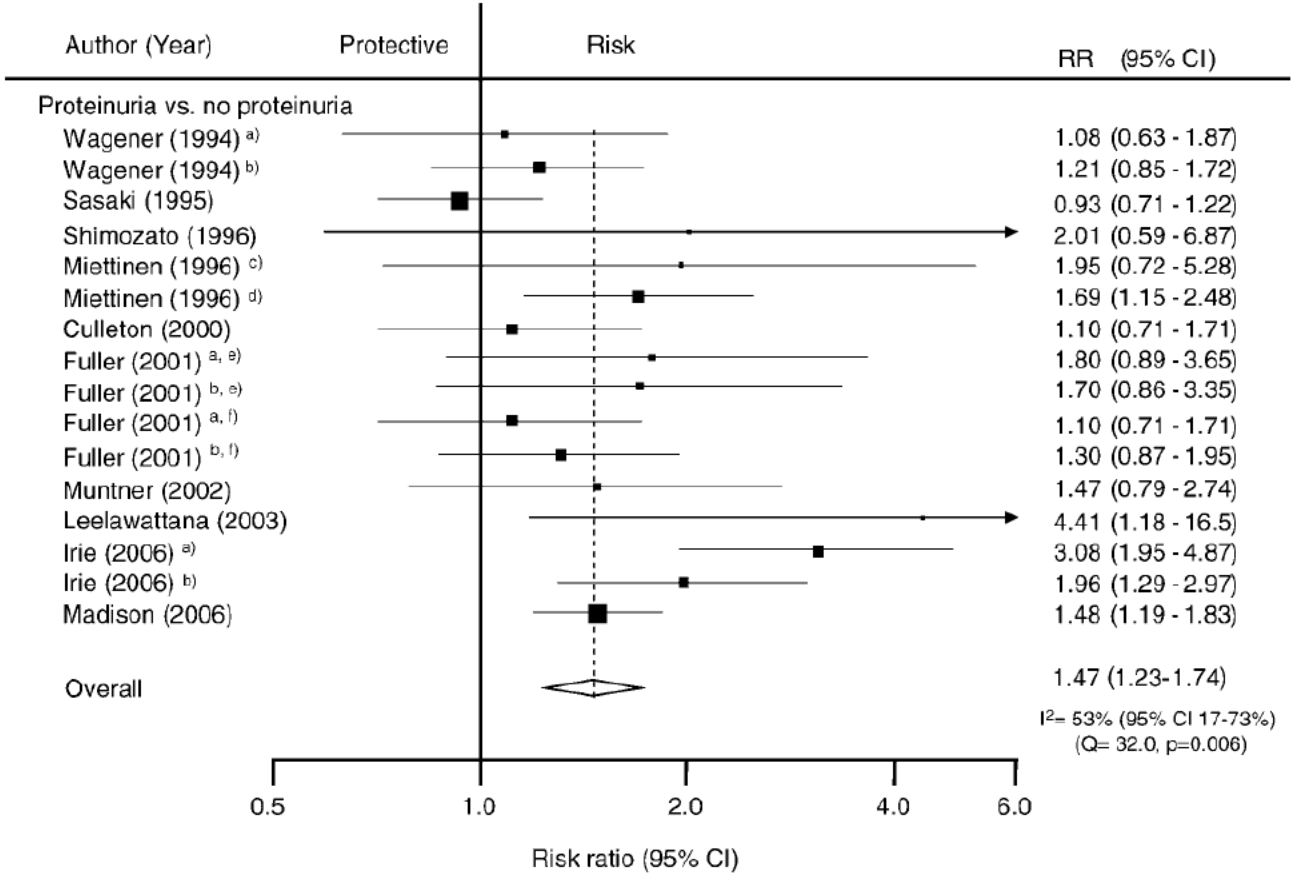
The Relationship between Proteinuria and Coronary Risk: A Systematic Review and Meta-Analysis

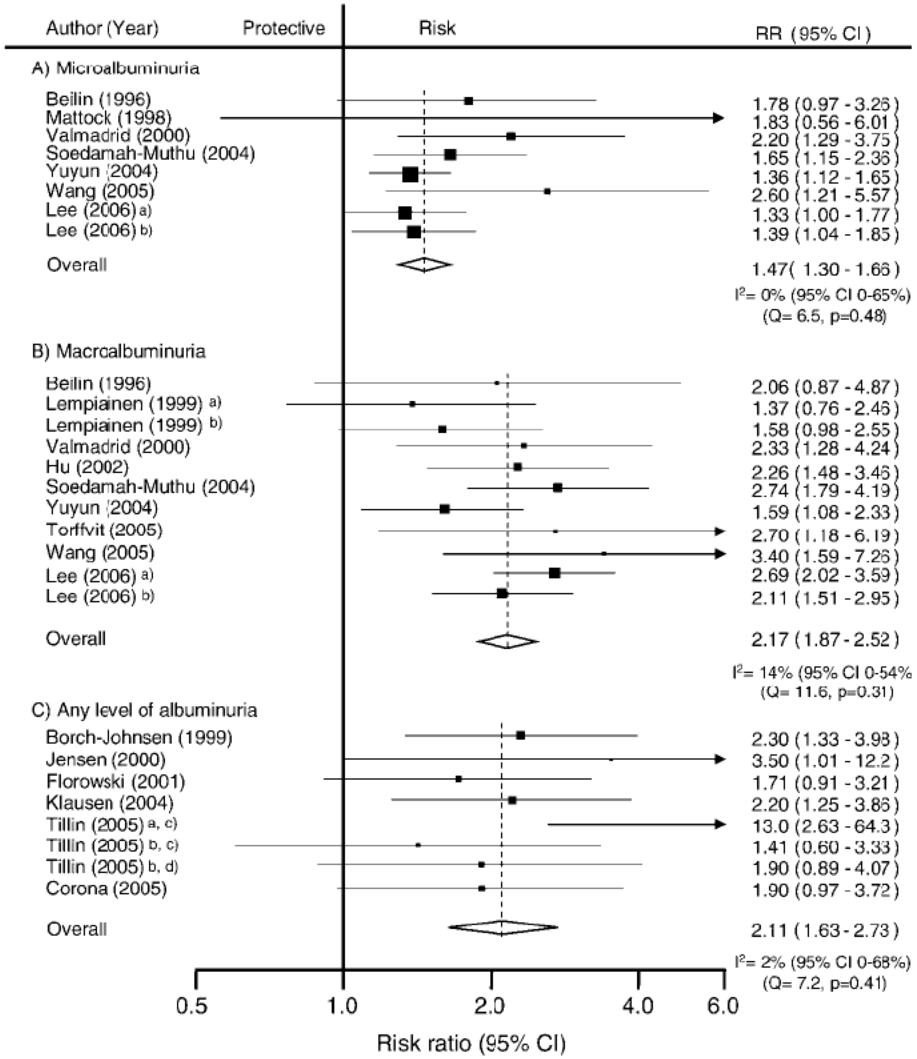
Vlado Perkovic[1,2*], Christine Verdon[2], Toshiharu Ninomiya[1], Federica Barzi[1,2], Alan Cass[1,2], Anushka Patel[1,2], Meg Jardine[1], Martin Gallagher[1,2], Fiona Turnbull[1,2], John Chalmers[1,2], Jonathan Craig[2], Rachel Huxley[1,2]

1 The George Institute for International Health, Sydney, New South Wales, Australia, **2** University of Sydney, Sydney, New South Wales, Australia

Table 1. Definitions of Albuminuria and Proteinuria

Measurement Method	Microalbuminuria	Macroalbuminuria	Proteinuria
24 hour urine collection	30–300 mg/day	>300 mg/d	>300 mg/d
Spot urine albumin concentration	3–30 mg/dl	>30 mg/dl	>30 mg/dl
Spot urine dipstick	Specific microalbuminuria dipstick positive	N/A	+ or greater
Spot urine albumin to creatinine ratio	30–300 mg/g or 3.4 g/mmol	>300 mg/g or 34 g/mmol	>200 mg/g or 23 g/mmol


Author (Year)
Protective
Risk
RR (95% CI)
Proteinuria vs. no proteinuria
Wagener (1994) a)
1.08 (0.63 - 1.87)
Wagener (1994) b)
1.21 (0.85 - 1.72)
Sasaki (1995)
0.93 (0.71 - 1.22)
Shimozato (1996)
2.01 (0.59 - 6.87)
Miettinen (1996) c)
1.95 (0.72 - 5.28)
Miettinen (1996) d)
1.69 (1.15 - 2.48)
Culleton (2000)
1.10 (0.71 - 1.71)
Fuller (2001) a, e)
1.80 (0.89 - 3.65)
Fuller (2001) b, e)
1.70 (0.86 - 3.35)
Fuller (2001) a, f)
1.10 (0.71 - 1.71)
Fuller (2001) b, f)
1.30 (0.87 - 1.95)
Muntner (2002)
1.47 (0.79 - 2.74)
Leelawattana (2003)
4.41 (1.18 - 16.5)
Irie (2006) a)
3.08 (1.95 - 4.87)
Irie (2006) b)
1.96 (1.29 - 2.97)
Madison (2006)
1.48 (1.19 - 1.83)
Overall
1.47 (1.23-1.74)
I2= 53% (95% CI 17-73%)
(Q= 32.0, p=0.006)
0.5
1.0
2.0
4.0
6.0
Risk ratio (95% CI)



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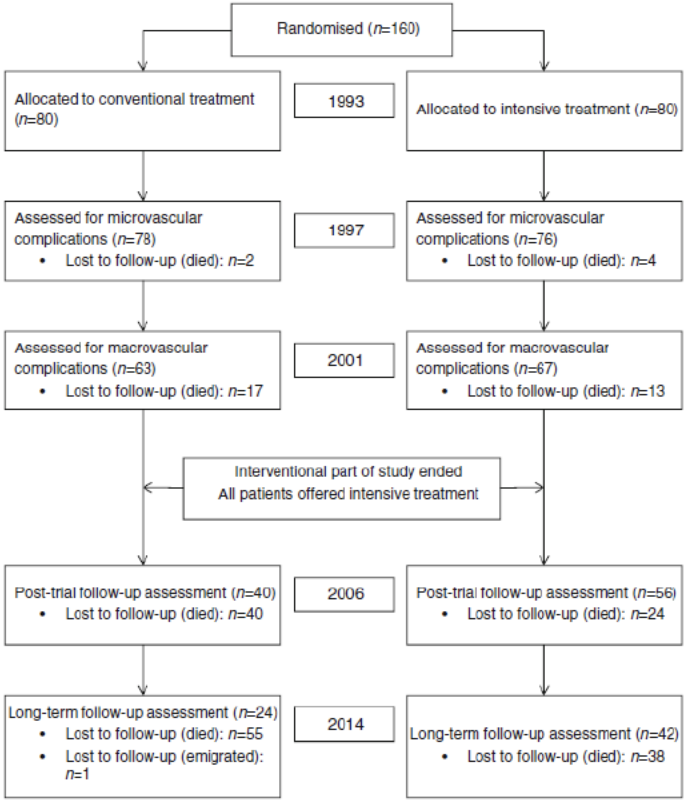
Diabetologia (2016) 59:2298–2307
DOI 10.1007/s00125-016-4065-6

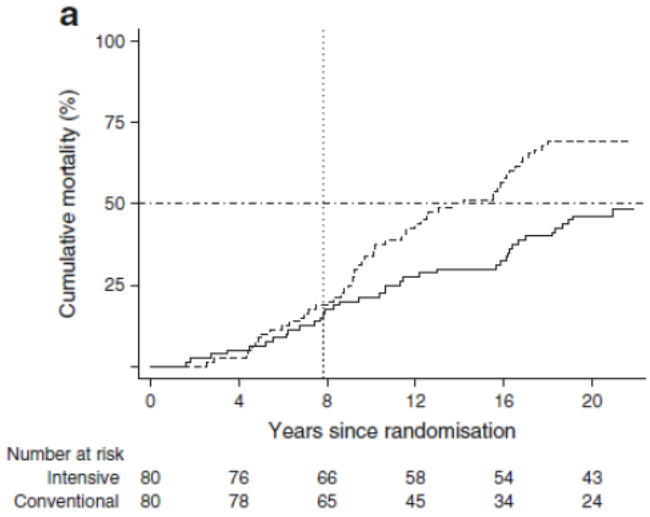
ARTICLE

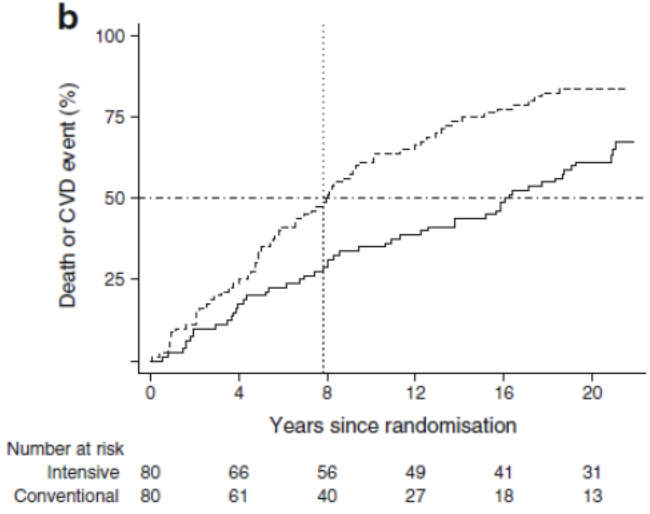
Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

Peter Gæde[1,2] · Jens Oellgaard[1,2,3] · Bendix Carstensen[3] · Peter Rossing[3,4,5] · Henrik Lund-Andersen[3,5,6] · Hans-Henrik Parving[5,7] · Oluf Pedersen[8]

Fig. 1 Consort diagram of patient flow throughout the entire observation period. Procedures for enrolment and randomisation are described in [11]. Numbers lost to follow-up are cumulative







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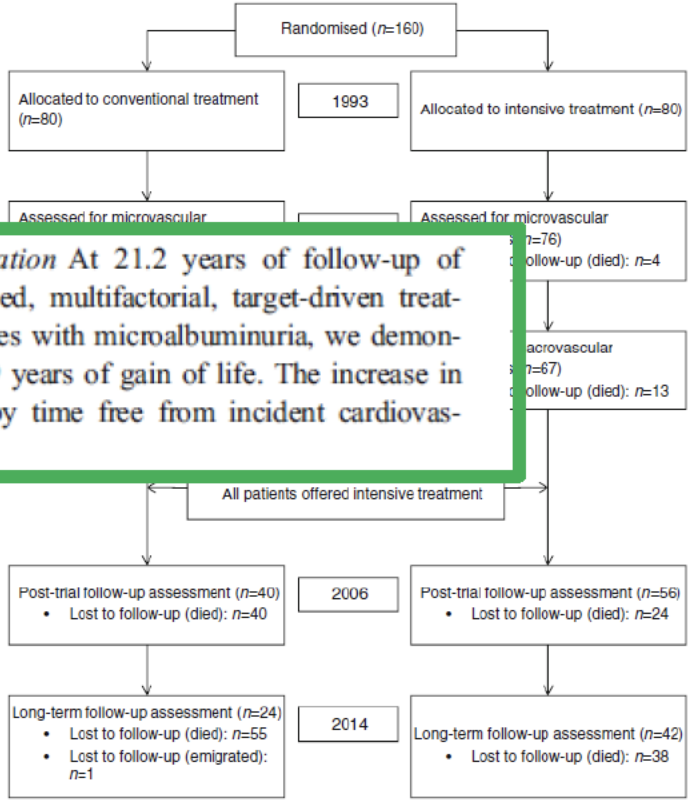
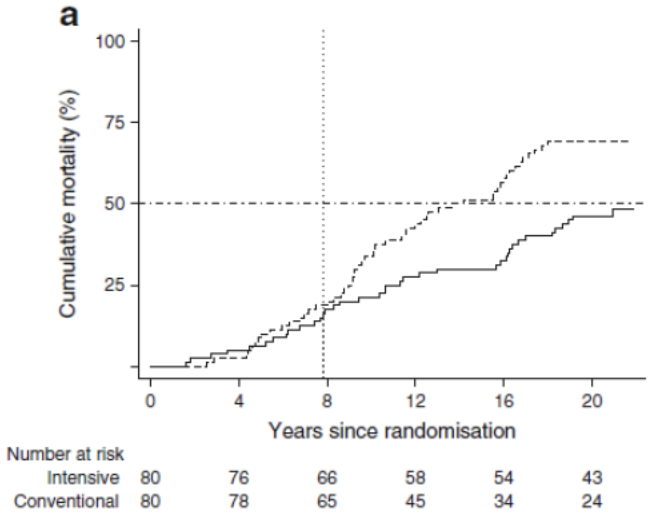
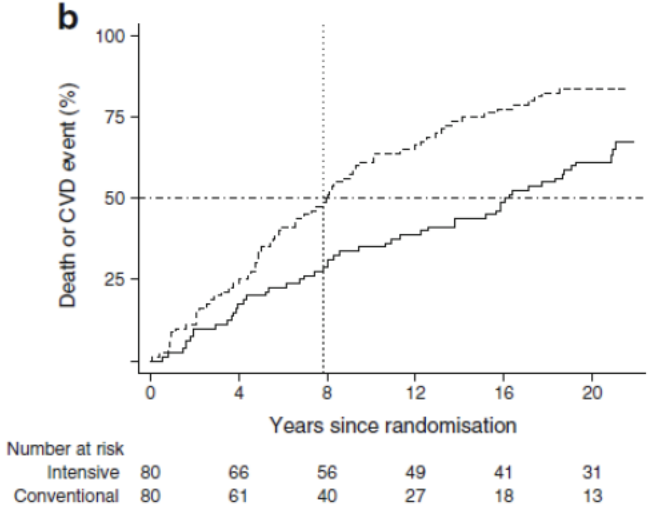


Conclusions/interpretation At 21.2 years of follow-up of 7.8 years of intensified, multifactorial, target-driven treatment of type 2 diabetes with microalbuminuria, we demonstrate a median of 7.9 years of gain of life. The increase in lifespan is matched by time free from incident cardiovascular disease.





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