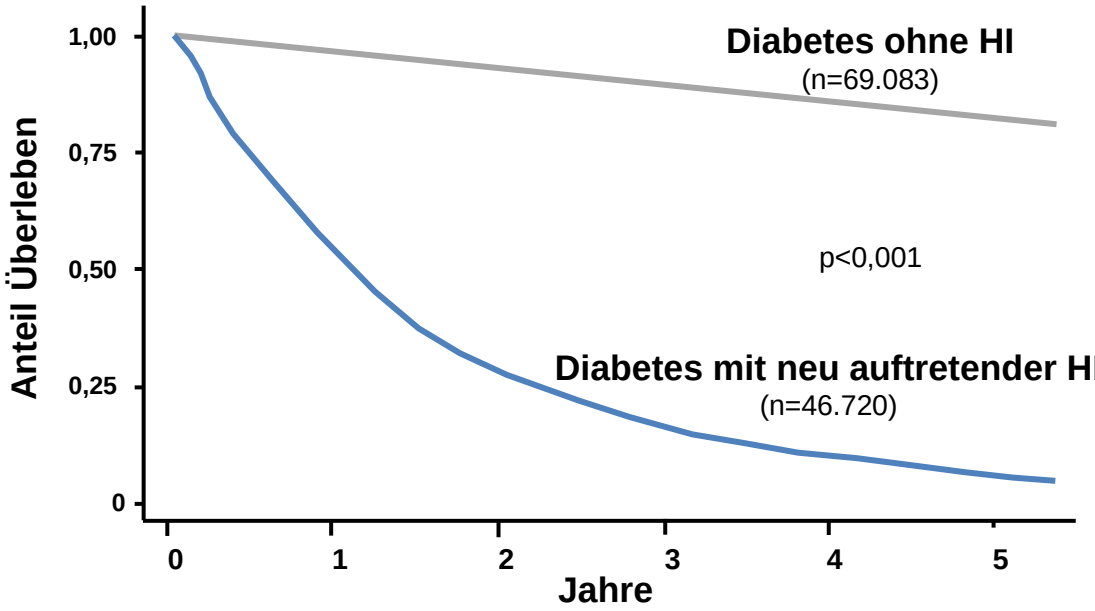
Maßgeschneidertes Risikomanagement und individualisierte Therapiekonzepte bei PatientInnen mit Diabetes – die Rolle des NTproBNP

Martin Hülsmann

Herbstquartett

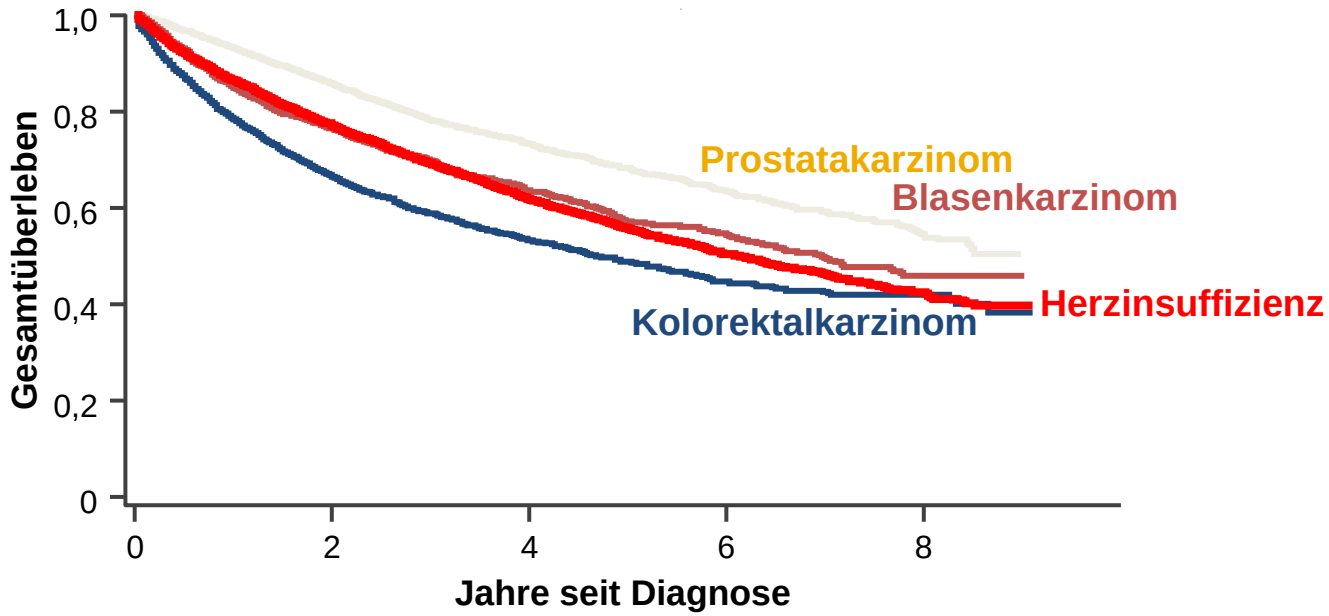
Diagnose Herzinsuffizienz (HI) erhöht die Mortalitätsrate dramatisch

Das Auftreten von HI bei Patienten mit Diabetes ist mit einem erhöhten Mortalitätsrisiko verbunden



Follow-up von Erwachsenen im Alter von ≥65 Jahren in einer Dienstleistungs-Pflegeeinrichtung ohne vorausgehende HI über 5 Jahre (n= 115.803)

Gesamtüberleben von HI im Vergleich zu häufigen Krebsarten



bei Männern in einer schottischen Kohortenstudie in der Primärversorgung

*HI nach MI wurde in dieser HI-Definition nicht eingeschlossen.
CV: kardiovaskulär; HI: Herzinsuffizienz; MACE: schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (*major adverse cardiovascular event*); MI: Myokardinfarkt; pAVK: periphere arterielle Verschlusskrankheit; T2DM: Diabetes mellitus Typ 2

Modifiziert nach: Bertoni AG, et al. Diabetes Care. 2004; 27: 699-703. Modifiziert nach: Mamas MA, et al. Eur J Heart Fail 2017; 19:1095-104.

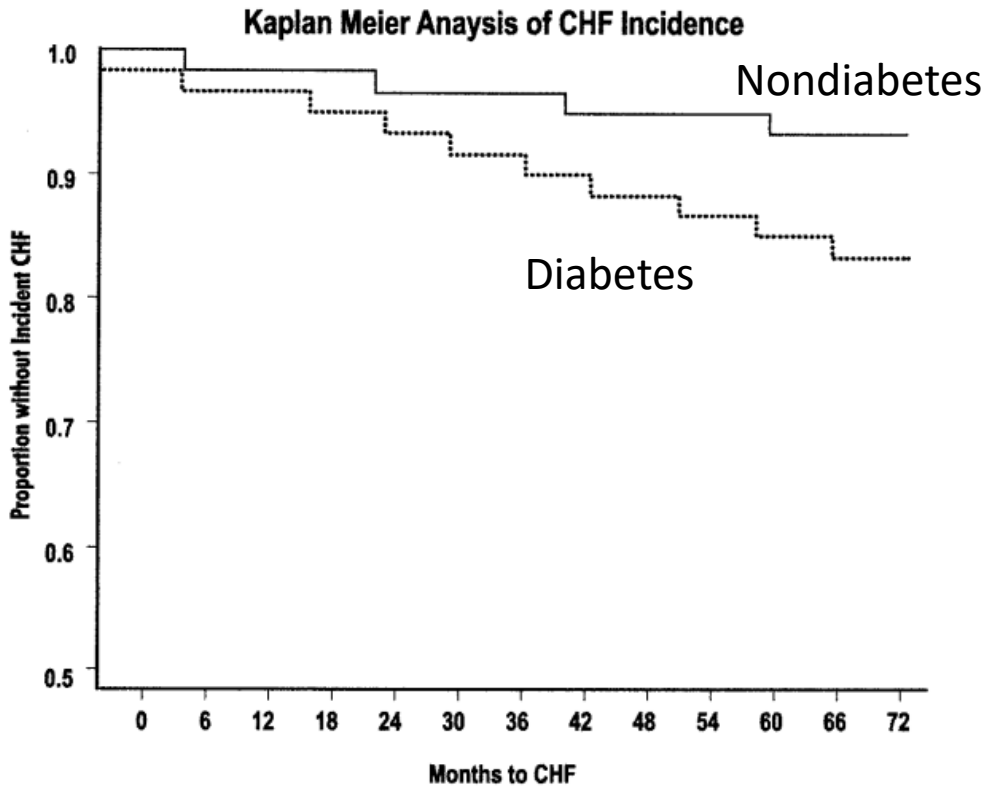
Epidemiology/Health Services/Psychosocial Research
ORIGINAL ARTICLE

The Incidence of Congestive Heart Failure in Type 2 Diabetes

An update

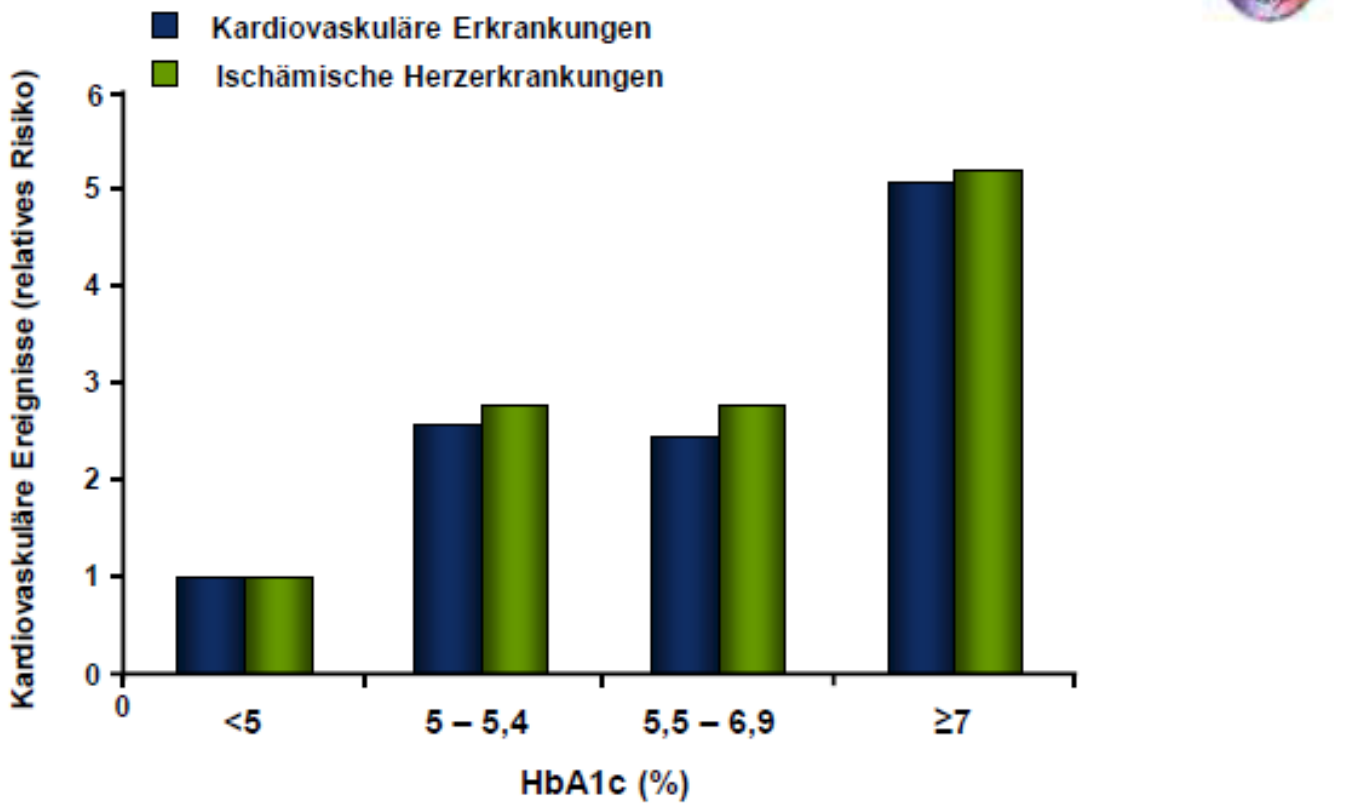
Gregory A. Nichols, PHD[1]
Christina M. Gullion, PHD[1]
Carol E. Koro, PHD[2]
Sara A. Ephross, PHD[2]
Jonathan B. Brown, PHD, MPP[1]

Unselected cohort, but prior
Diagnosis of heart failure excluded



Ist der Blutzucker ein guter Risikomarker für das CV Risiko beim Typ-2-Diabetes?

Die kardiovaskuläre Ereignisrate korreliert mit dem HbA1c



Khaw KT et al. BMJ 2001;322:15ff.

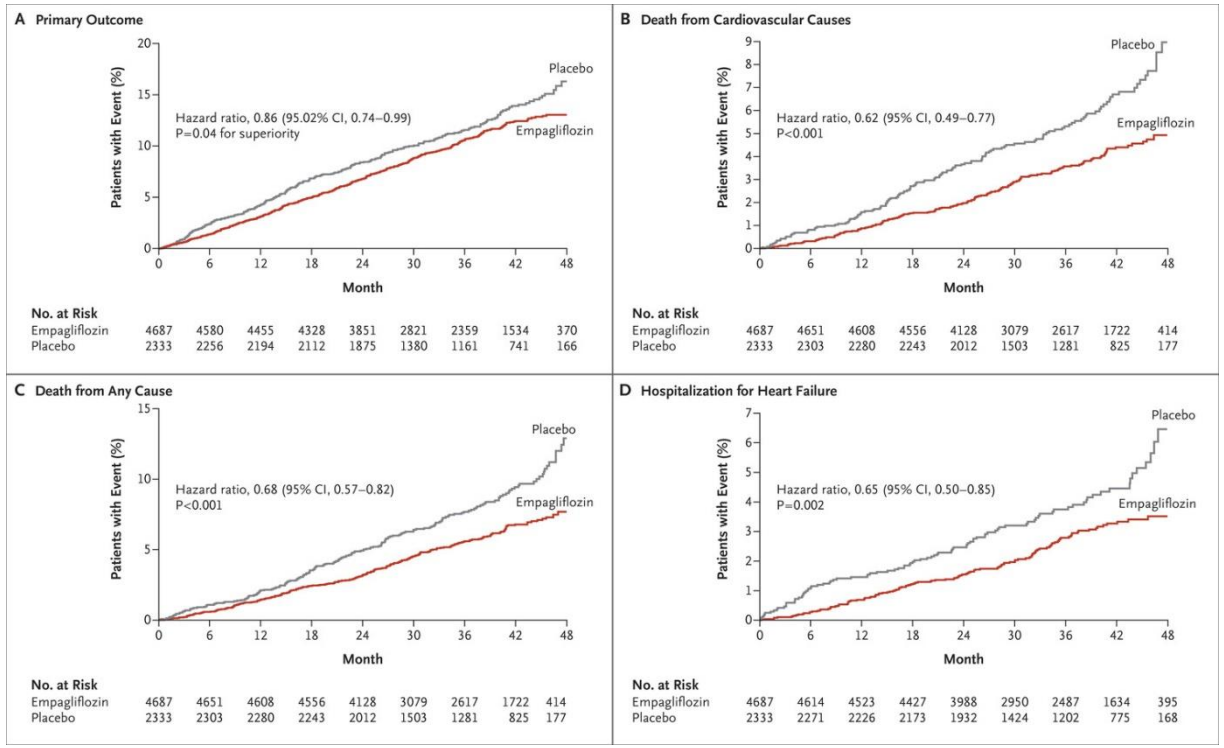
Number needed to harm bei Patienten > 65 Jahre mit Rosiglitazontherapie

- Chronische Herzinsuffizienz 34
- Akuter Myokardinfarkt 26
- Tod 22

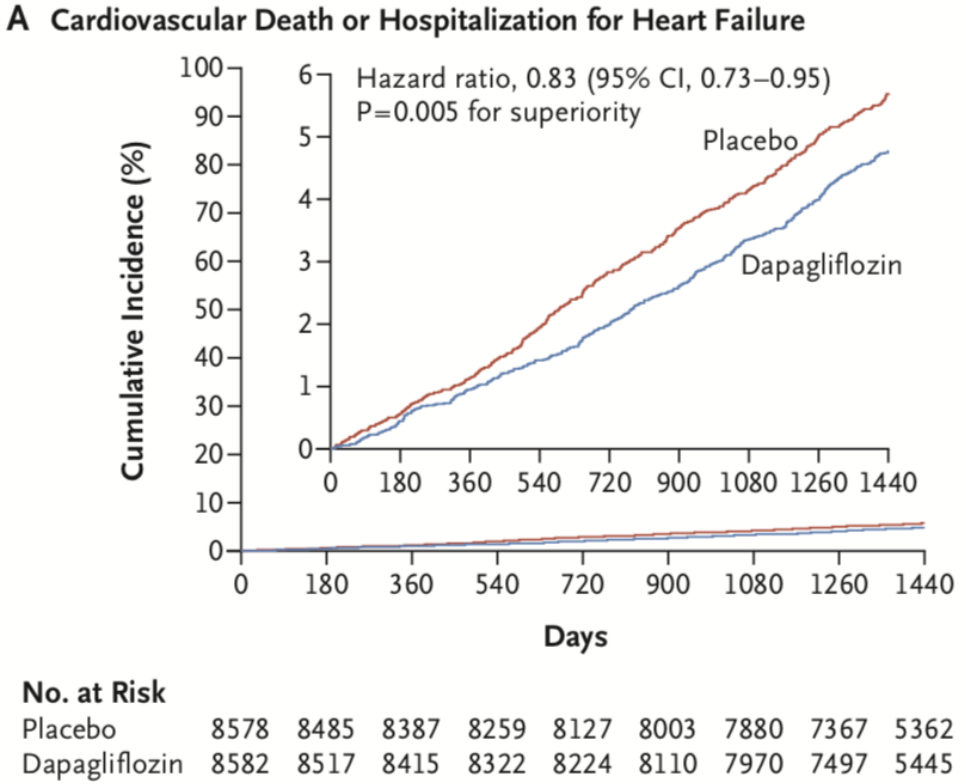
!

Endpunkt	Erreicht
Herzinsuffizienz	**7,9 %**
Akuter MCI	**7,9 %**
Tod	**19 %**

Lipscombe et al; JAMA December 2007



Quelle: Zinman B et al.: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-28



Quelle: https://www.nejm.org/doi/full/10.1056/nejmoa1812389

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Craig J Currie, John R Peters, Aodán Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

Lancet 2010; 375: 481–89

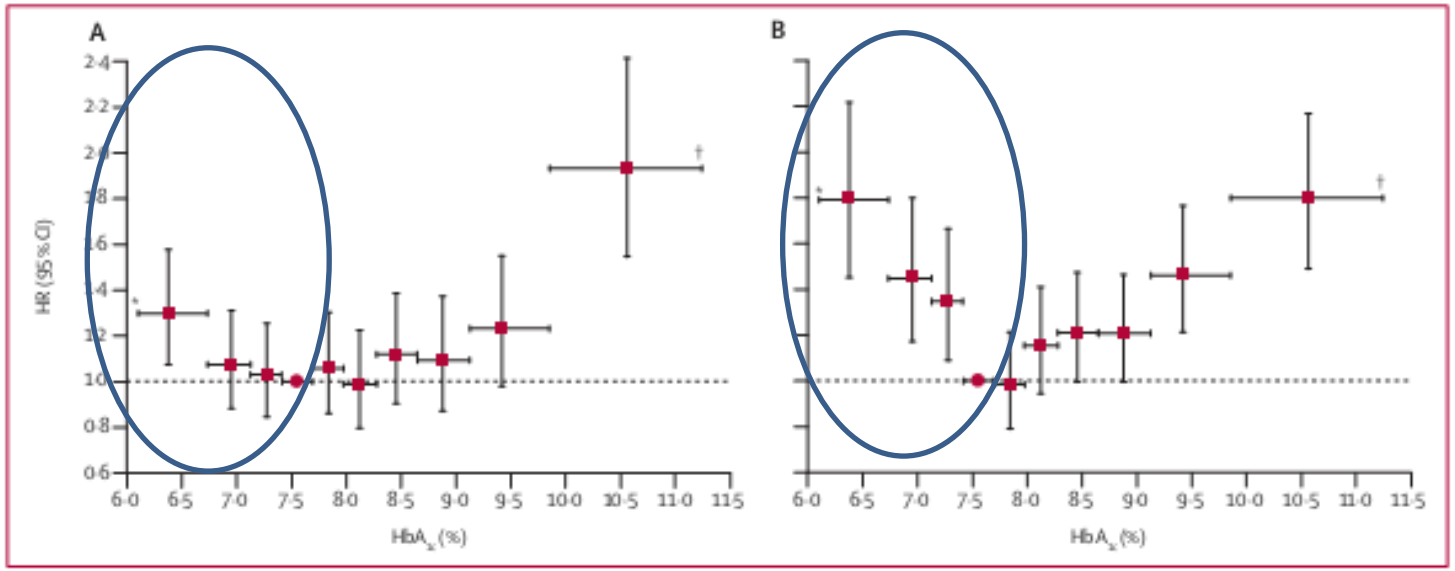


Figure 1: **Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies**
Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Original Article

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group

Table 4. Primary and Secondary Outcomes.*

Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per yr*	*no. of patients (%)*	*% per yr*		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

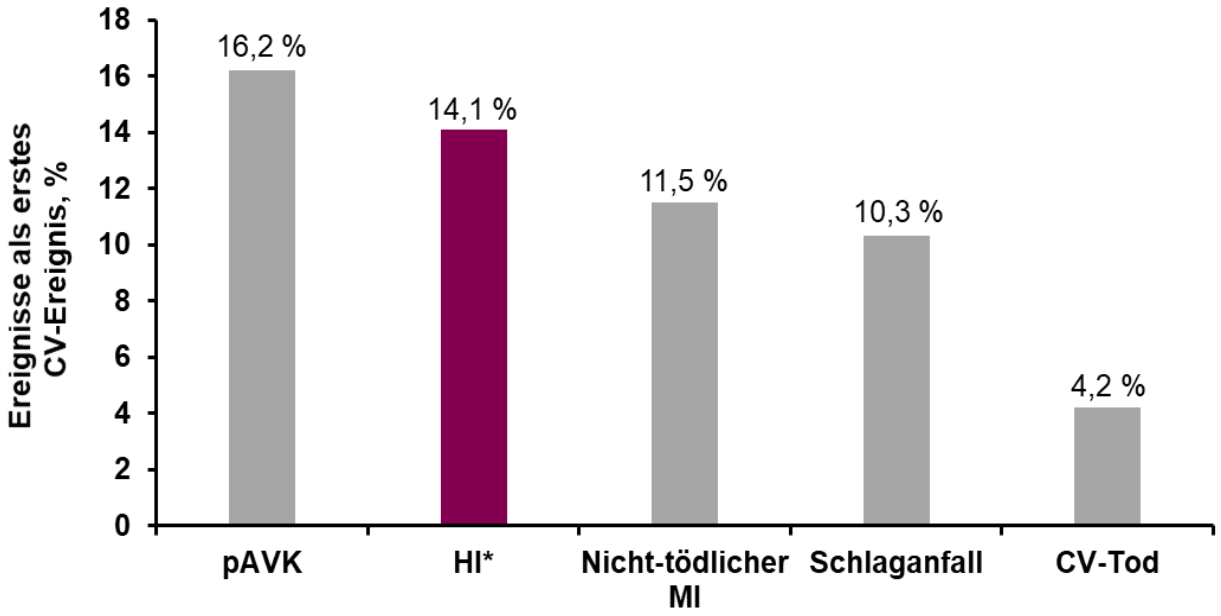
* The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data within categories are not mutually exclusive, and patients who were classified as having more than one possible cause of death are listed in the relevant categories. Hazard ratios are for the intensive-therapy group as compared with the standard-therapy group.
† This condition was a component of the outcome of fatal cardiovascular disease.
‡ Additional details are provided in the Supplementary Appendix.

The NEW ENGLAND JOURNAL of MEDICINE

Volume 358(24): 2545-2559
June 12, 2008

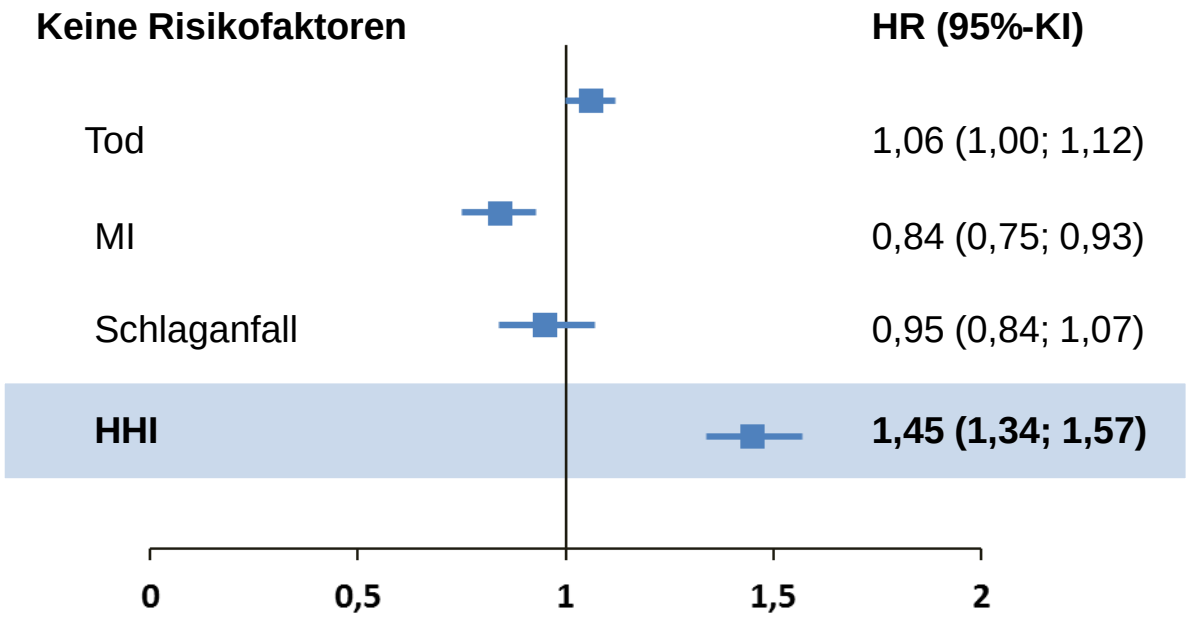
Herzinsuffizienz tritt bei T2D früh und häufig auf, trotz Kontrolle von CV-Risikofaktoren

HI trat als erste Manifestation einer T2D-bedingten CV-Erkrankung häufiger auf als MI oder Schlaganfall



Kohortenstudie bei Patienten mit T2DM und Inzidenz einer CV-Erkrankung (n=1,9 Mio.)

Trotz der Kontrolle bekannter CV-Risikofaktoren weisen T2D-Patienten ein erhöhtes Risiko für Herzinsuffizienz auf



Risiko für ein Ereignis bei T2DM-Patienten (n=271.174) ohne weitere Risikofaktoren außerhalb des Zielbereichs im Vergleich zu Personen ohne Diabetes (n=1.355.870)

*HI nach MI wurde in dieser HI-Definition nicht eingeschlossen.
CV: kardiovaskulär; HI: Herzinsuffizienz; MACE: schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (*major adverse cardiovascular event*); MI: Myokardinfarkt; pAVK: periphere arterielle Verschlusskrankheit; T2DM: Diabetes mellitus Typ 2

Modifiziert nach: Shah AD, et al. Lancet Diabetes Endocrinol. 2015; 3:105-113, Appendix. Modifiziert nach: Rawshani A, et al. N Engl J Med. 2018; 379: 633-644.

Die Blutzuckersenkung beeinflusst nicht die kardiale Ereignisrate

1. Statistical approach – population distribution of plasma glucose	This method is commonly used in clinical practice to define a normal level for a laboratory test. Application of this method requires the 'healthy' population to have a unimodal distribution. The upper limit of normal is typically defined as the mean + 2SD and by definition this approach means that 2.5% of the population is considered abnormal, a situation which is not in keeping with a condition of high prevalence such as diabetes.
2. Clinical approach – risk of adverse outcomes	These studies do not provide a definitive answer to what might be considered a normal plasma glucose but it is clear that risk is lowest at levels which are commonly found in apparently healthy people.

Recommendation 2	Since there are insufficient data to accurately define normal glucose levels, the term 'normoglycaemia' should be used for glucose levels associated with low risk of developing diabetes or cardiovascular disease, that is levels below those used to define intermediate hyperglycaemia.

Quelle: Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia : report of a WHO/IDF consultation
https://apps.who.int/iris/handle/10665/43588

Aretaios von Kappadokien

- ***Eine rätselvolle Krankheit ist der Diabetes, und nicht sehr häufig bei den Menschen. Fleisch und Bein schmilzt im Urin zusammen, Feuchtigkeit und Kälte ist die Veranlassung wie bei der Wassersucht, aber die Flüssigkeit geht auf dem gewohnten Weg durch Nieren und die Blase ab.***
  Die Kranken hören nie auf Harn zu lassen, sondern wie aus geöffneten Schläuchen rinnt es unaufhörlich.
  Über die Entstehung und Entwicklung der Krankheit dauert es einige Zeit, aber sind die Symptome erst vollkommen ausgebildet, so befindet sich auch der Mensch am Ende seiner Tage, denn dann nimmt die Abzehrung rasch überhand, und nach einem elenden und schmerzvollen Leben erfolgt der schnelle Tod.

Substantial Differences in the Diagnostic Criteria Used by Diabetes Experts

Kelly M. West, M.D., Oklahoma City

SUMMARY

A survey of twenty diabetologists revealed that they employ diagnostic criteria differing quite substantially. In some populations, including the general population of the United States, these disparities would result in very major differences in the rates of "diabetes." Under certain common circumstances, some diabetologists would classify as normal more than half of the one- and two-hour values considered to be abnormal by other well-qualified diabetologists. DIABETES *24* :641-44, July, 1975.

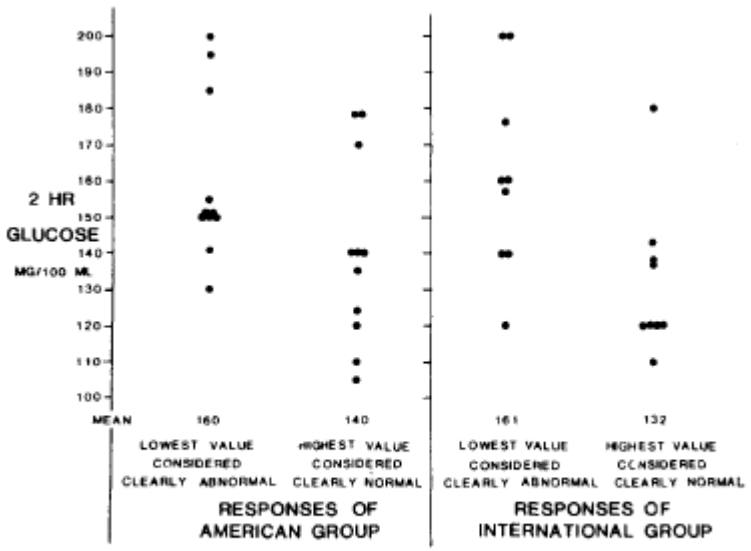


FIG. 1. Diagnostic criteria employed by diabetologists in interpreting two-hour values in a middle-aged subject.

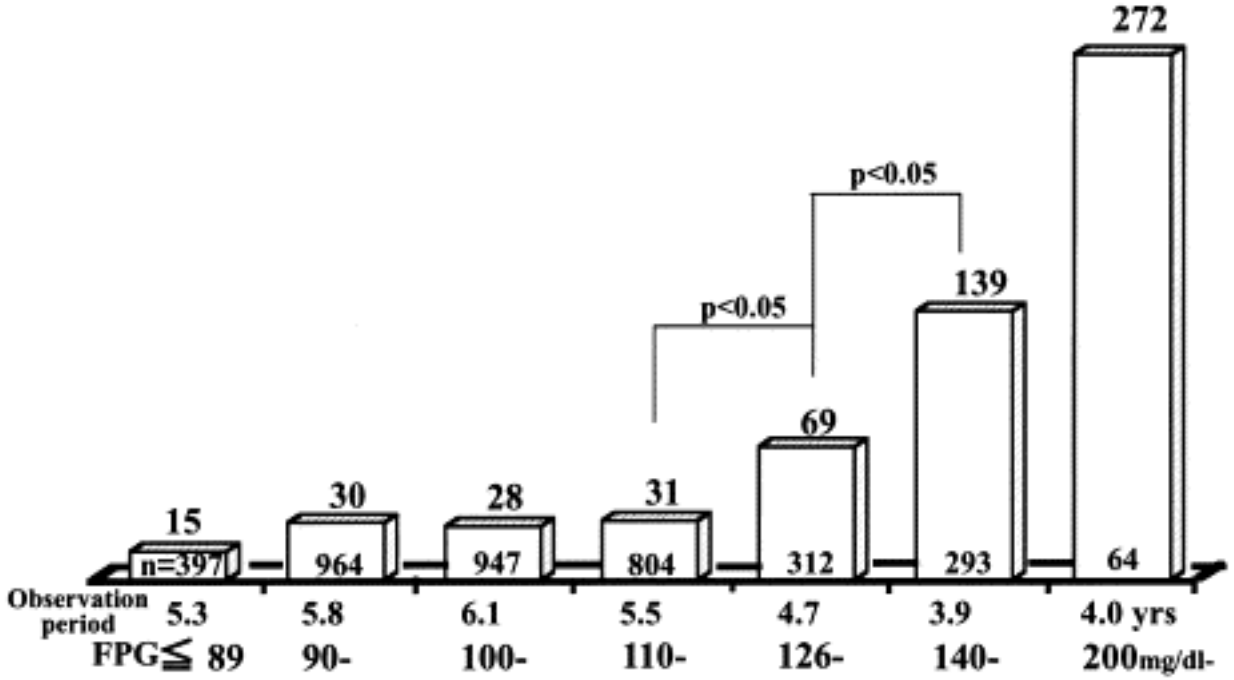


Fig. 2: Incidence (per 10 000 PY) of diabetic retinopathy by fasting plasma glucose levels at the time of initial OGTT examination. The bars represent the numbers of cases in each group. The mean observation periods are shown under the graph.

Chikako Ito, Ryo Maeda, Sakurako Ishida, Hisako Harada, Noriko Inoue, Hideo Sasaki

Importance of OGTT for diagnosing diabetes mellitus based on prevalence and incidence of retinopathy

Diabetes Research and Clinical Practice, Volume 49, Issues 2–3, 2000, 181-186

http://dx.doi.org/10.1016/S0168-8227(00)00156-X

Diabetes

Fasting plasma glucose	≥7.0mmol/l (126mg/dl)
2–h plasma glucose*	**or**
	≥11.1mmol/l (200mg/dl)

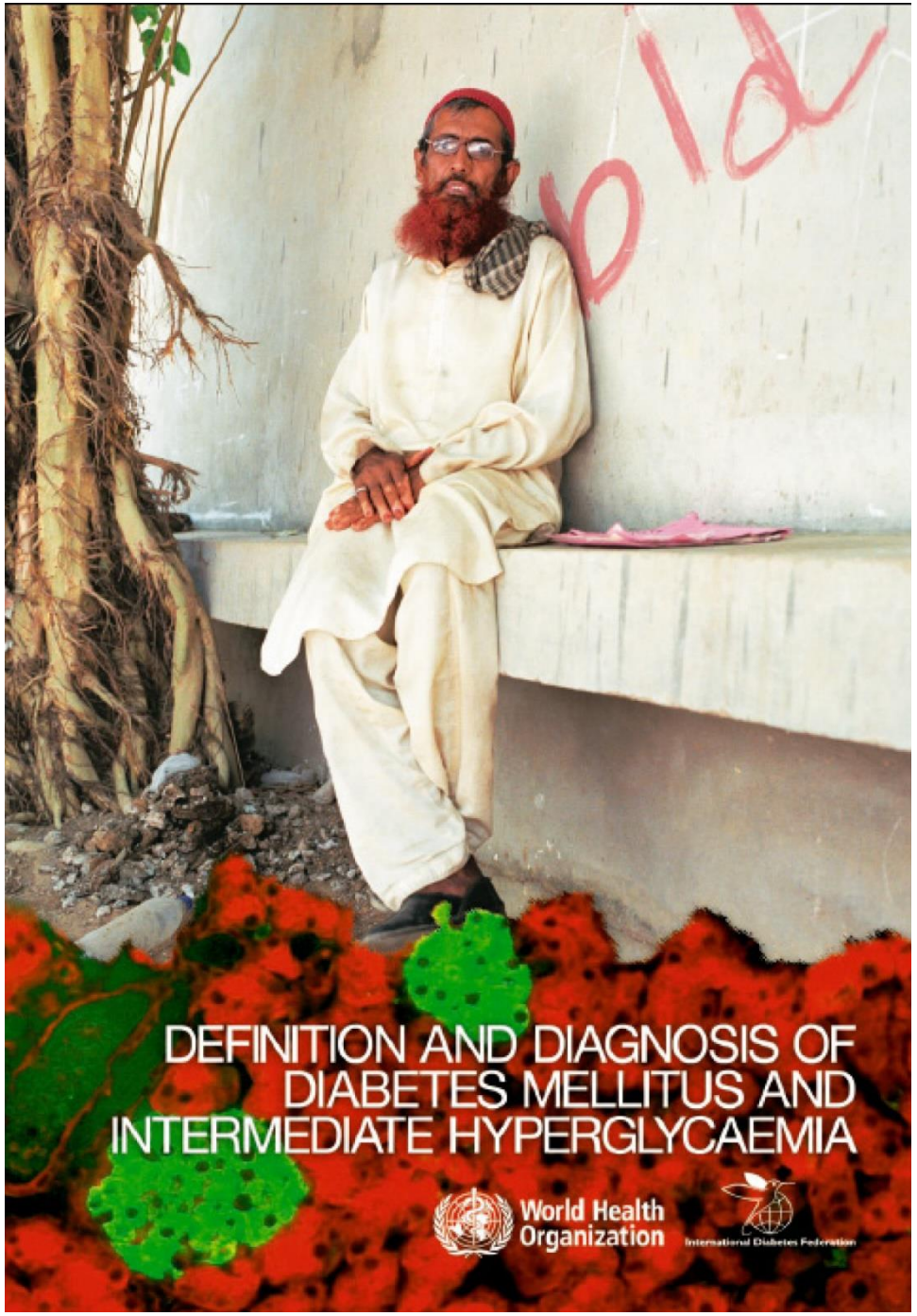
Impaired Glucose Tolerance (IGT)

Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2–h plasma glucose*	**and**
	≥7.8 and <11.1mmol/l
	(140mg/dl and 200mg/dl)

Impaired Fasting Glucose (IFG)

Fasting plasma glucose	6.1 to 6.9mmol/l
2–h plasma glucose*	(110mg/dl to 125mg/dl)
	and (if measured)
	<7.8mmol/l (140mg/dl)

Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage. It is associated with increased risk of macrovascular complications.



Will Rogers Phenomenon

When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.

Beispiel

- DM-Gruppe Überlebenszeit in Jahren
  {3,5,7,12,13} = **8** mean
- Kontrollgruppe {10,15,17, 23, 25} = **16** mean
  Stage migration des kränksten Patienten der Kontrollgruppe
- DM-Gruppe Überlebenszeit in Jahren
  {3,5,7,10,12,13} = **8,3** mean
- Kontrollgruppe {15,17, 23, 25} = **17,5** mean

Was markiert das kardiovaskuläre Risiko bei Diabetes?
Was sagen die Guidelines?

Recommendations for the use of laboratory, electrocardiogram, and imaging testing for cardiovascular risk assessment in asymptomatic patients with diabetes

Recommendations	Class[a]	Level[b]
Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD.[27,38]	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CVD.[38,39]	I	C
Assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier in asymptomatic patients with DM.[60–62]	IIa	B
CAC score with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic patients with DM at moderate risk.[c] [63]	IIb	B
CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with DM for screening of CAD.[47,48,64,65,67–70]	IIb	B
ABI may be considered as a risk modifier in CV risk assessment.[76]	IIb	B
Detection of atherosclerotic plaque of carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with DM at moderate or high risk CV.[c] [75,77]	IIb	B
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended.[62,73,78]	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification.[27,31,35–37]	III	B
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM.	III	C

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventric-

Glucose-lowering treatment

Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events

Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death

Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or very high/high CV risk, to reduce CV events

Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death

Saxagliptin is not recommended in patients with T2DM and a high risk of HF

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Recommendations for cardiovascular risk assessment

Recommendations	Class[a]	Level[b]
Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.	I	C

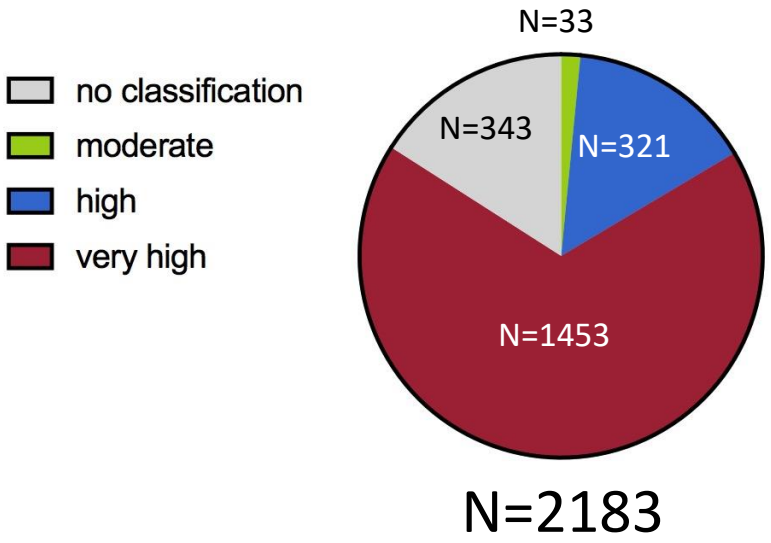
Table 5 Risk categories

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

Recommendation for how to estimate cardiovascular risk

Recommendation	Class[a]	Level[b]	Ref[c]
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age, unless they are automatically categorised as being at *high-risk* or *very high-risk* based on documented CVD, DM (>40 years of age), kidney disease or highly elevated single risk factor (Table 5).	I	C	11, 25

CV = cardiovascular; DM = diabetes mellitus; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.



N=2183

Prausmüller *et al. Cardiovasc Diabetol* (2021) 20:34
https://doi.org/10.1186/s12933-021-01221-w

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Performance of the recommended ESC/EASD cardiovascular risk stratification model in comparison to SCORE and NT-proBNP as a single biomarker for risk prediction in type 2 diabetes mellitus

Suriya Prausmüller[1], Michael Resl[2], Henrike Arfsten[1], Georg Spinka[1], Raphael Wurm[1], Stephanie Neuhold[3], Philipp E. Bartko[1], Georg Goliasch[1], Guido Strunk[4], Noemi Pavo[1*], Martin Clodi[2] and Martin Hülsmann[1]

Prausmüller et al. Cardiovasc Diabetol (2021) 20:34
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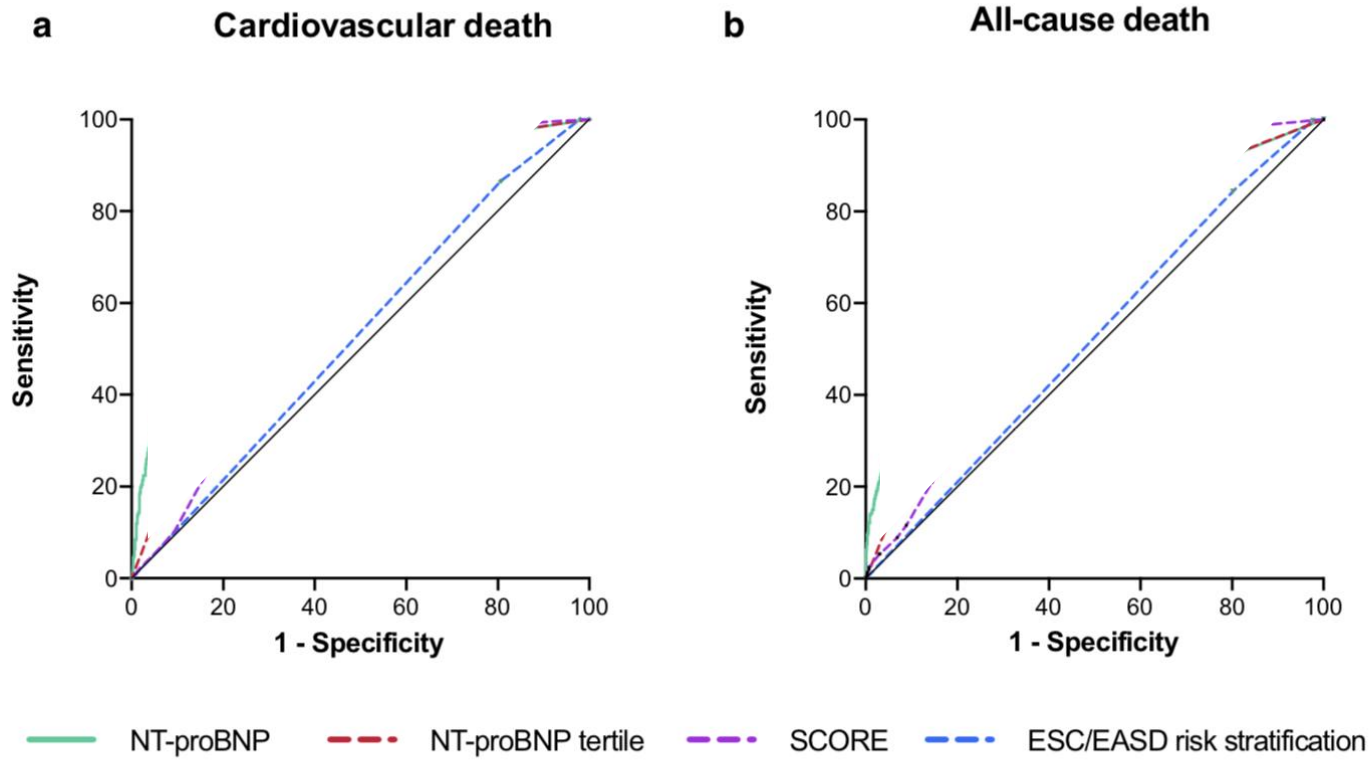

Fig. 3 Receiver operating characteristic curves of the ESC/EASD risk model, NT-proBNP and SCORE for the outcomes (**a**) cardiovascular death and (**b**) all-cause death

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

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PLUS

The addition of circulating biomarkers for CV risk assessment has limited clinical value.(27) Recommendation III B

JACC Vol. 37, No. 7, 2001
June 1, 2001:1781–7

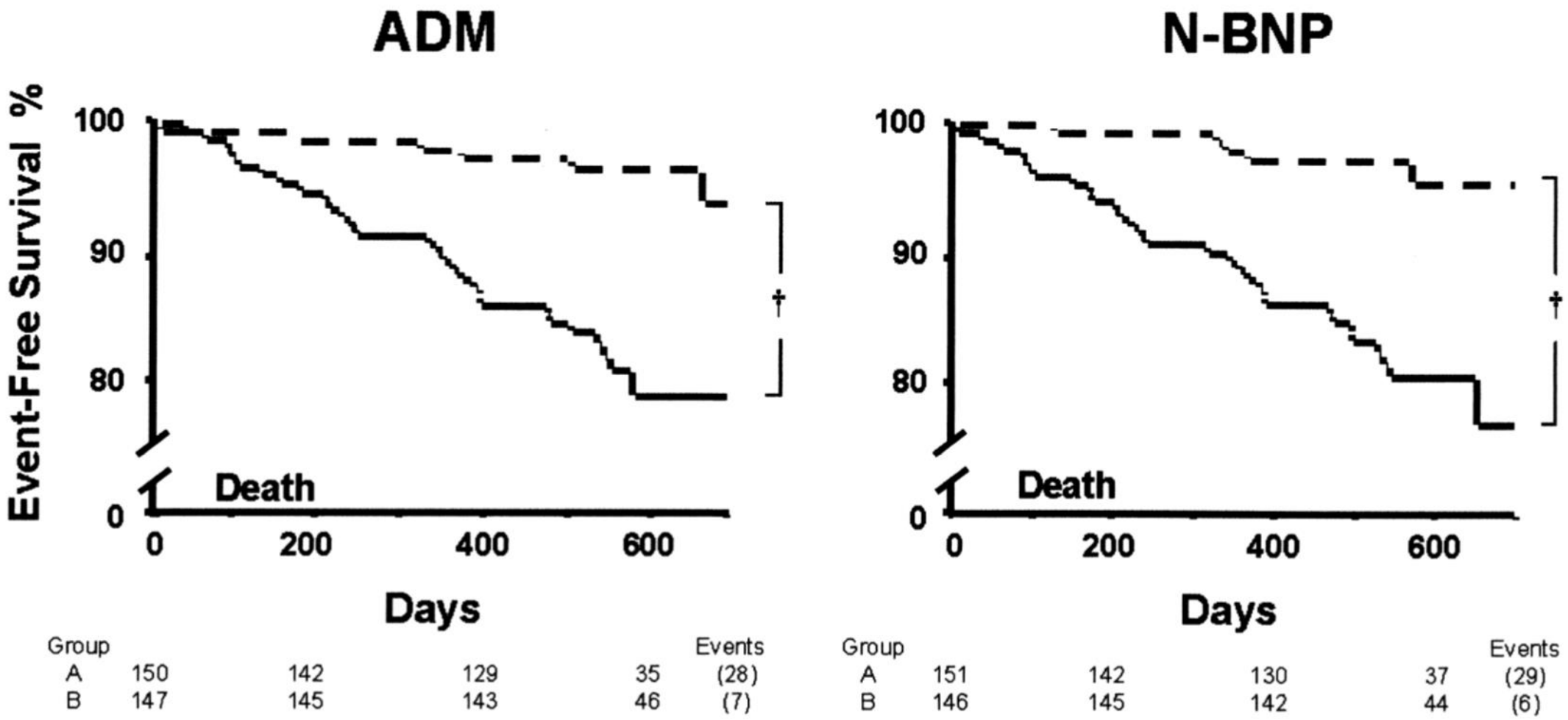

Figure 1. All-cause mortality (death) survival curves for patients with pre-randomization plasma adrenomedullin (ADM, **left**) and N-BNP **(right)** above (group A, **solid line**) and below (group B, **dashed line**) the group median value. †$p < 0.001$.

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

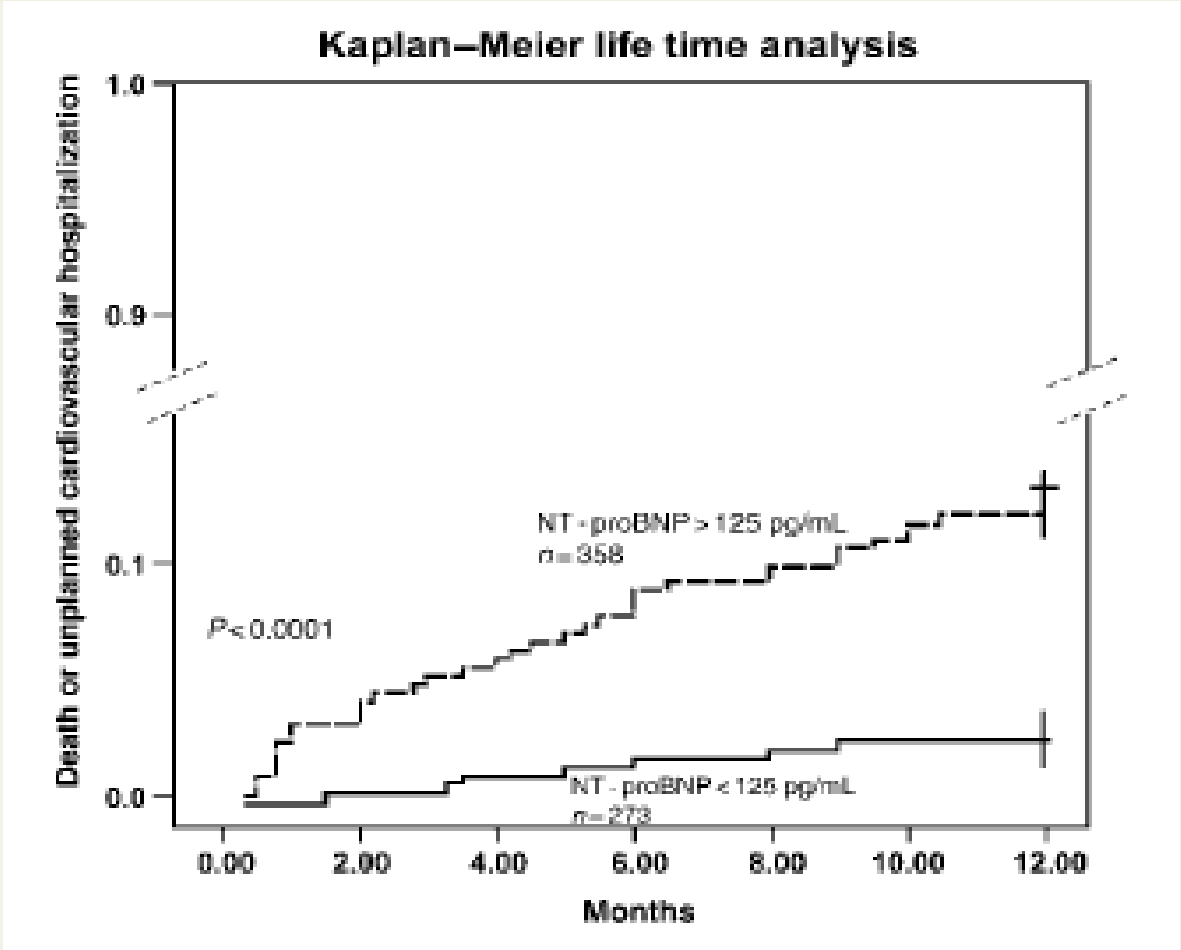

Table 3 Results from stepwise Cox regression for 500 Bootstrap samples. Frequencies of variables within the regression model after stepwise selection

Initially 17 variables	Per cent	Initially 8 variables	Per cent
Logarithm of NT-proBNP	91.8	Logarithm of NT-proBNP	95.2
Duration of diabetes	59.6	MLHFQ	46.4
MLHFQ	48.0	Age	43.2
NYHA-class	46.0	NYHA-class	42.6
History of smoking	32.4	History of any heart disease	21.8
History of any heart disease	31.8	GFR	17.2
Age	31.6	Ischaemic heart disease	10.2
Gender	18.4	Logarithm of serum-creatinine	7.0
Ischaemic heart disease	17.0	NT-proBNP	6.2
Self-assessment Dyspnoe score	15.6	Serum-creatinine	6.0
GFR	15.2		
Hypertension	12.0		
LDL-cholesterol	11.4		
NT-proBNP	11.2		
HbA_{1c}	10.4		
Systolic blood pressure	9.8		
Logarithm of serum-creatinine	5.4		
Serum-creatinine	5.2		
Body mass index	2.6		

Epidemiology and Prevention

Identifying Novel Biomarkers for Cardiovascular Events or Death in People With Dysglycemia

Hertzel C. Gerstein, MD, MSc; Guillaume Paré, MD, MSc; Matthew J. McQueen, MD, PhD; Heinz Haenel, PhD; Shun Fu Lee, PhD; Janice Pogue, PhD; Aldo P. Maggioni, MD; Salim Yusuf, DPhil; Sibylle Hess, PhD; for the Outcome Reduction With Initial Glargine Intervention Trial Investigators

(*Circulation*. 2015;132:2297-2304. DOI: 10.1161/CIRCULATIONAHA.115.015744.)

Markers for all endpoints
NT-proBNP
Angiopoietin 2
Gluthatione S Transferase α

2. List of Biomarkers Assayed (Inter-Run CV at Intermediate Concentrations)[1]

6Ckine (13%)
AXL Receptor Tyr Kinase (10%)
Adiponectin (4%)
Adrenomedullin (7%)
Agouti-Related Protein (7%)
Aldose Reductase (11%)
Alpha-1-Antichymotrypsin (6%)
Alpha-1-Antitrypsin (14%)
Alpha-1-Microglobulin (5%)
Alpha-1-acid glycoprotein 1
Alpha-2-Macroglobulin (6%)
Angiogenin (10%)
Angiopoietin-2 (6%)
Angiopoietin-related protein 3 (8%)
Angiotensin-Converting Enzyme (12%)
Angiotensinogen (6%)
Antithrombin-III (6%)
Apolipoprotein A-I (10%)
Apolipoprotein A-II (8%)
Apolipoprotein A-IV (9%)
Apolipoprotein B (9%)
Apolipoprotein C-I (9%)
Apolipoprotein C-III (20%)
Apolipoprotein D (18%)
Apolipoprotein E (20%)
Apolipoprotein H (12%)
Apolipoprotein(a) (16%)
B Lymphocyte Chemoattractant (10%)
B cell-activating factor (9%)
Beta Amyloid 1-40 (13%)
Beta-2-Microglobulin (13%)
Brain-Derived Neurotrophic Factor (5%)
C-Peptide (4%)
C-Reactive Protein (13%)
CD 40 antigen (8%)
CD163 (11%)
CD40 Ligand (9%)
CD5 Antigen-like
Cathepsin D (9%)
Cellular Fibronectin (17%)
Chemerin (4%)
Chemokine CC-4 (7%)
Chromogranin-A (7%)
Clusterin (10%)
Collagen IV (14%)
Complement C3 (10%)
Complement Factor H - Related Protein 1(9%)
Cortisol (8%)
Creatine Kinase-MB (12%)
Cystatin-C (8%)
E-Selectin (5%)
EN-RAGE (4%)
Endoglin (8%)
Endostatin (10%)
Eotaxin-1 (11%)
Eotaxin-2 (9%)
Eotaxin-3(16%)
Epithelial-Derived Neutrophil-Activating Prot 78 (12%)
Erythropoietin (10%)
Ezrin (10%)
FASLG Receptor (2%)
Factor VII (4%)
Fas Ligand (8%)
Fatty Acid-Binding Protein, adipocyte (6%)
FA-Binding Protein, liver (12%)
Ferritin (6%)
Fetuin-A (17%)
Fibroblast Growth Factor 21 (12%)
Fibroblast growth factor 23 (9%)
Fibulin-1C (9%)
Ficolin-3 (7%)
FSH (16%)
Galectin-3 (8%)
GIP (12%)
Gelsolin (12%)
GLP 1 total (7%)
Glucose-6-P Isomerase (7%)
Glutathione S-Transferase alpha (11%)
Glyc phosphorylase isoenzyme BB (6%)
Granulocyte CSF (6%)
Growth Hormone (9%)
Growth-Regulated alpha protein (5%)
Growth/differentiation factor 15 (10%)
Haptoglobin (8%)
Heat-Shock protein 70 (8%)
Hemopexin (9%)
Hepatocyte Growth Factor (18%)
Hepatocyte Growth Factor receptor (13%)
Hepsin (4%)
Human EGF Receptor 2 (2%)
Immunoglobulin A (11%)
Immunoglobulin E (4%)
Immunoglobulin M (19%)
Insulin (7%)
Insulin-like Growth Factor BP4 (6%)
Insulin-like Growth Factor BP5 (8%)
Insulin-like Growth Factor BP6 (17%)
Insulin-like Growth Factor I (8%)
Insulin-like Growth BP1 (8%)
Insulin-like Growth BP2 (7%)
Insulin-like Growth BP3 (9%)
Intercellular Adhesion Molecule 1 (7%)
Interferon gamma (11%)
IF gamma Induced Protein 10 (8%)
IF -inducible T-cell alpha chemoattractant (16%)
Interleukin-1 beta (10%)
Interleukin-1 receptor antagonist (6%)
Interleukin-10 (8%)
Interleukin-12 Subunit p40 (7%)
Interleukin-16 (5%)
Interleukin-17 (6%)
Interleukin18 (9%)
Interleukin-2 (8%)
Interleukin-2 receptor alpha (2%)
Interleukin-23 (9%)
Interleukin-6 (6%)
IL-6 receptor (6%)
IL-6 receptor subunit beta (9%)
Interleukin-7 (6%)
Interleukin-8 (8%)
Kallikrein 5 (14%)
Kidney Injury Molecule-1 (9%)
Lactoferrin (9%)
Lactoylglutathione lyase (6%)
Latency-Associated Peptide TGF beta 1 (7%)
Lectin-Like Ox LDL Receptor 1 (4%)
Leptin (6%)
Leptin Receptor (11%)
Leucine-rich alpha-2-glycoprotein (4%)
Luteinizing Hormone (6%)
MHC I chain-related protein A (5%)
Macrophage CSF 1 (10%)
Macroph Inflamm Protein-1 alpha (7%)
Macroph Inflam Protein-1 beta (6%)
Macrophage Inflammatory Protein-3 alpha (4%)
Macrophage Migration Inhibitory Factor (6%)
Macrophage inflammatory protein 3 beta (12%)
Macrophage-Derived Chemokine (9%)
Macrophage - Stimulating Protein (6%)
Matrix Metalloproteinase-1 (12%)
Matrix Metalloproteinase-10 (11%)
Matrix Metalloproteinase-3 (9%)
Matrix Metalloproteinase-7 (12%)
Matrix Metalloproteinase-9 (6%)
Matrix Metalloprot-9, total (14%)
Mesothelin (10%)
Methylglyoxal (9%)
Monocyte Chemotactic Protein 1 (5%)
Monocyte Chemotactic Protein 2 (6%)
Monocyte Chemotactic Protein 3 (7%)
Monocyte Chemotactic Protein 4 (7%)
Monokine Induced by Gamma Interferon (10%)
Myeloid Progenitor Inhibitory Factor 1 (4%)
Myeloperoxidase (16%)
Myoglobin (6%)
N-terminal prohormone of BNP (5%)
Neuronal Cell Adhesion Molecule (5%)
Neuropilin-1 (11%)
Neutrophil Activating Peptide 2 (7%)
Neutrophil Gelatinase-Associated Lipocalin (12%)
Omentin (11%)
Osteocalcin (9%)
Osteopontin (9%)
Osteoprotegerin (9%)
P-Selectin (6%)
Pancreatic Polypeptide (13%)
Paraoxanase-1 (16%)
Pentraxin-3 (12%)
Pepsinogen I (6%)
Peptide YY (7%)
Periostin (11%)
Peroxiredoxin-4 (8%)
Phosphoserine Aminotransferase (7%)
Pigment Epithelium Derived Factor (7%)
Plasminogen Activator Inhibitor 1 (8%)
Platelet-Derived Growth Factor BB (6%)
Progesterone (8%)
Progranulin (6%)
Proinsulin, Intact (5%)
Proinsulin, Total (6%)
Prolactin (15%)
Prostasin (6%)
Prostatic Acid Phosphatase (11%)
Protein S100-A4 (7%)
Protein S100-A6 (8%)
Pulmonary and Activation-Regulated Chemokine (10%)
Receptor for AGE Products (5%)
Receptor tyrosine-protein kinase erbB-3 (10%)
Resistin (8%)
Retinol-binding protein 4 (13%)
ST2 (11%)
Secreted Frizzled-Related Protein 4 (12%)
Selenoprotein P (6%)
Serotransferrin (8%)
Serum Amyloid A Protein (11%)
Serum Amyloid P-Component (10%)
Serum Glut Oxaloacetic Transaminase (12%)
Sex Hormone-Binding Globulin (14%)
Sortilin (5%)
Stem Cell Factor (6%)
Stromal cell-derived factor-1 (10%)
Superoxide Dismutase 1, Soluble (7%)
T Lymphocyte-Secreted Protein I-309 (11%)
T-Cell-Specific Protein RANTES (16%)
Tyr. Kinase + Ig & EGF Homology Domains 2 (7%)
Urokinase-type Plasminogen Activator (9%)
Urokinase-type Plasminogen Activator Receptor (8%)
Vascular Cell Adhesion Molecule-1 (8%)
Vascular Endothelial Growth Factor (7%)
Vascular Endothelial Growth Factor C (10%)
Vascular Endothelial Growth Factor D (7%)
Vascular Endothelial Growth Factor Receptor 2 (6%)
Vascular Endothelial Growth Factor Receptor 3 (7%)
Visceral Adipose Tissue - Derived Serpin A12 (7%)
Visfatin (15%)
Vitamin D-Binding Protein (11%)
Vitamin K-Dependent Protein S (9%)
Vitronectin (18%)
von Willebrand Factor (12%)
YKL 40 (8%)
TNF-Related Apoptosis-Inducing Ligand R3 (7%)
Tamm-Horsfall Urinary Glycoprotein (17%)
Tenascin-C (4%)
Testosterone, Total (7%)
Tetranectin (15%)
Thrombin-activable Fibrinolysis Inhibitor (5%)
Thrombomodulin (7%)
Thrombospondin-1 (14%)
Thyroid-Stimulating Hormone (8%)
Thyroxine-Binding Globulin (15%)
Tissue Inhibitor of Metalloproteinases 1 (7%)
Tissue type Plasminogen Activator (5%)
Transthyretin (8%)
Trefoil Factor 3 (7%)
Tumor Necrosis Factor Receptor I (5%)
Tumor Necrosis Factor Alpha (7%)
Tumor Necrosis Factor Receptor 2 (8%)

Prausmüller et al. Cardiovasc Diabetol (2021) 20:34
https://doi.org/10.1186/s12933-021-01221-w

ORIGINAL INVESTIGATION Open Access

Performance of the recommended ESC/EASD cardiovascular risk stratification model in comparison to SCORE and NT-proBNP as a single biomarker for risk prediction in type 2 diabetes mellitus

Suriya Prausmüller[1], Michael Resl[2], Henrike Arfsten[1], Georg Spinka[1], Raphael Wurm[1], Stephanie Neuhold[3], Philipp E. Bartko[1], Georg Goliasch[1], Guido Strunk[4], Noemi Pavo[1*], Martin Clodi[2] and Martin Hü

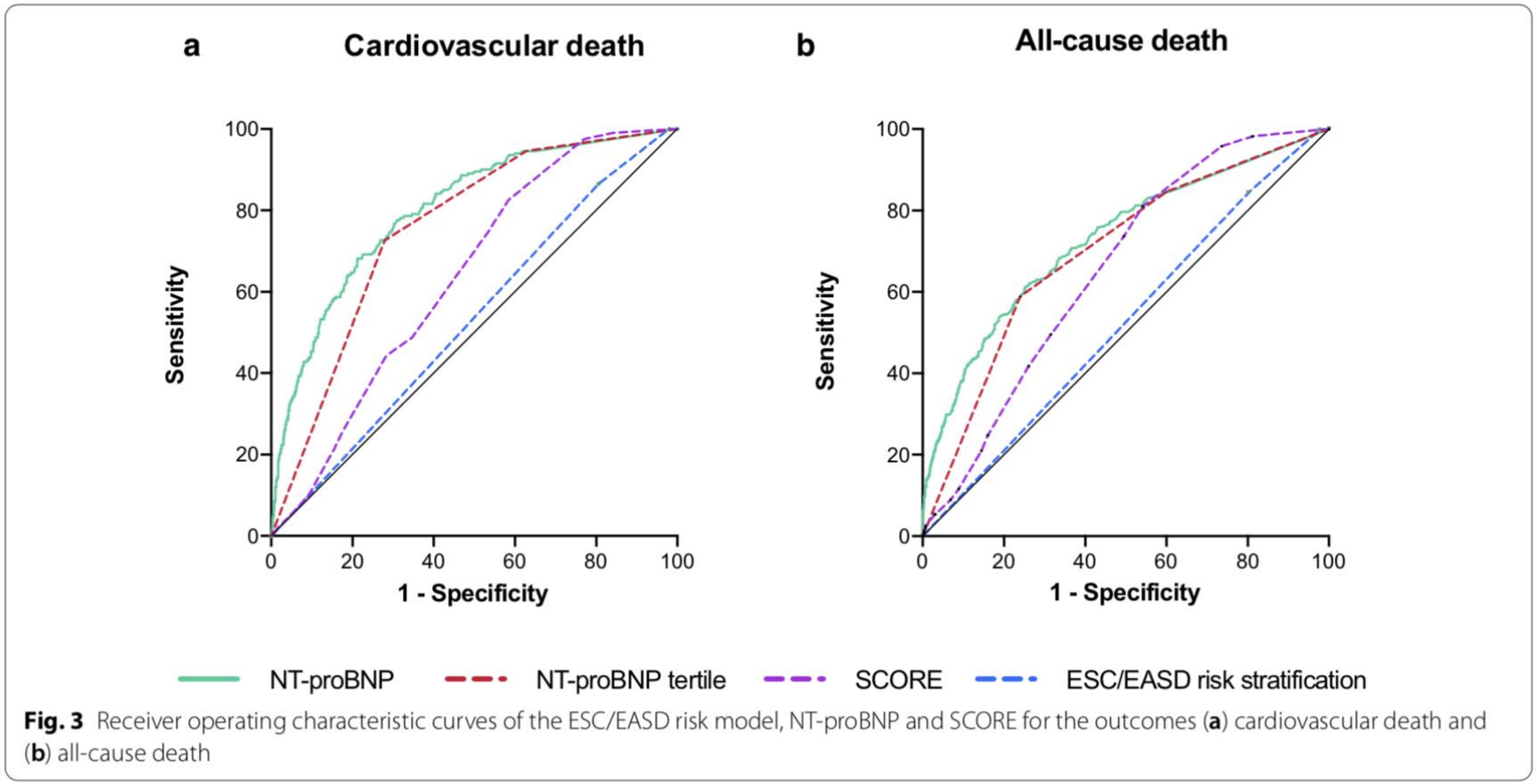

Fig. 3 Receiver operating characteristic curves of the ESC/EASD risk model, NT-proBNP and SCORE for the outcomes (**a**) cardiovascular death and (**b**) all-cause death

Recommendations for the use of laboratory, electrocardiogram, and imaging testing for cardiovascular risk assessment in asymptomatic patients with diabetes

Recommendations	Class[a]	Level[b]
Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD.[27,38]	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CVD.[38,39]	I	C
Assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier in asymptomatic patients with DM.[60–62]	IIa	B
CAC score with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic patients with DM at moderate risk.[c] [63]	IIb	B
CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with DM for screening of CAD.[47,48,64,65,67–70]	IIb	B
ABI may be considered as a risk modifier in CV risk assessment.[76]	IIb	B
Detection of atherosclerotic plaque of carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with DM at moderate or high risk CV.[c] [75,77]	IIb	B
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended.[62,73,78]	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification.[27,31,35–37]	III	B
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM.	III	C

Original scientific paper

European Journal of Cardiovascular Prevention & Rehabilitation

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DOI: 10.1177/1741826711420015
ejcpr.sagepub.com
SAGE

A comparison of NT-proBNP and albuminuria for predicting cardiac events in patients with diabetes mellitus

Martin Clodi[1,*], Michael Resl[1,*], Stephanie Neuhold[1], Martin Hülsmann[1], Greisa Vila[1], Marie Elhenicky[1], Guido Strunk[2], Heidemarie Abrahamian[3], Rudolf Prager[3], Anton Luger[1] and Richard Pacher[1]

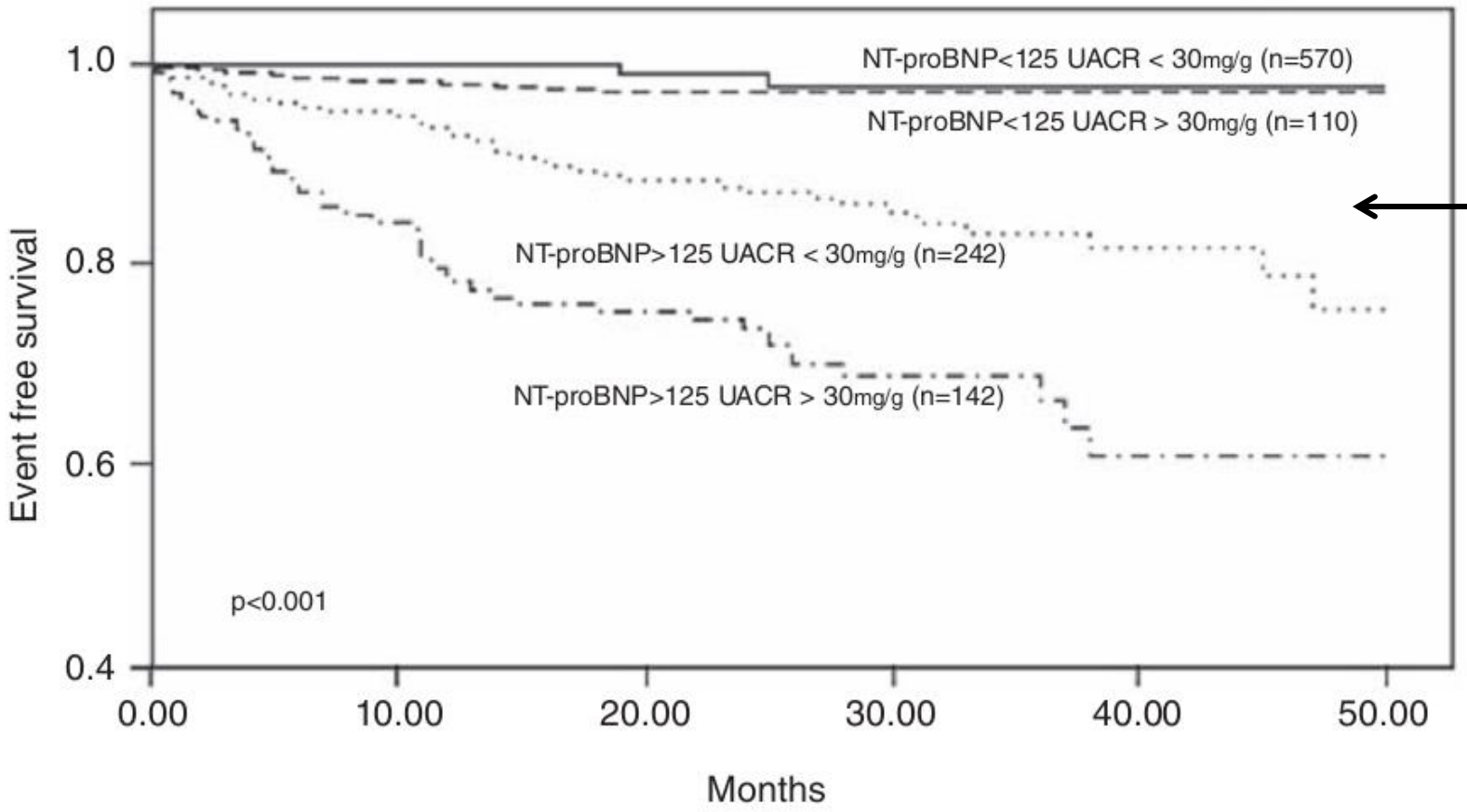


Table 2. Frequency of variables within the stepwise Cox regression for 500 bootstrap samples after stepwise selection

Initially 6 variables	*n* (%)
NT-proBNP	500 (100.0)
Age	380 (76.05)
Proteinuria	245 (49.10)
Gender	164 (32.74)
HbA_{1c}	56 (11.18)
Duration of diabetes	16 (3.19)

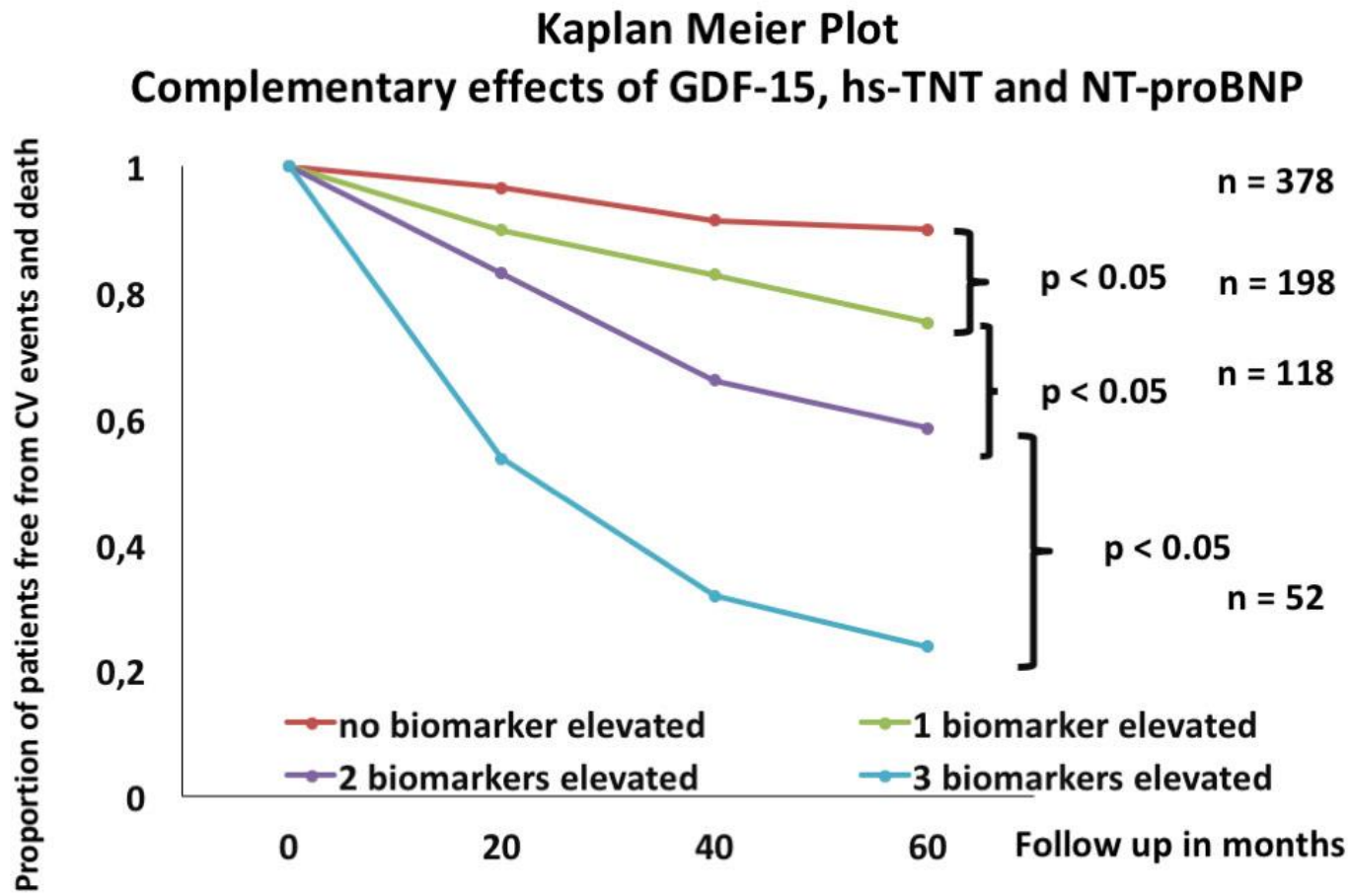
NT-proBNP, N-terminal pro-brain natriuretic peptide.

if NT-proBNP low no information by proteinuria

British Heart Journal now published as Heart

Targeted multiple biomarker approach in predicting cardiovascular events in patients with diabetes

M Resl,[1,2] M Clodi,[2] G Vila,[1] A Luger,[1] S Neuhold,[3] R Wurm,[4] C Adlbrecht,[4] G Strunk,[5,6] M Fritzer-Szekeres,[7] R Prager,[8] R Pacher,[4] M Hülsmann[4]



Patients at Risk

No biomarker elevated	378	364	350	346
1 biomarker elevated	198	178	160	149
2 biomarkers elevated	118	98	80	67
3 biomarkers elevated	52	27	16	13

Repeat measurements of glycated haemoglobin A_{1c} and N-terminal pro-B-type natriuretic peptide: divergent behaviour in diabetes mellitus

Stephanie Neuhold*, Michael Resl†, Martin Huelsmann‡, Guido Strunk§,¶, Christopher Adlbrecht‡, Claus Rath‡, Rudolf Prager**, Anton Luger†, Martin Clodi† and Richard Pacher‡

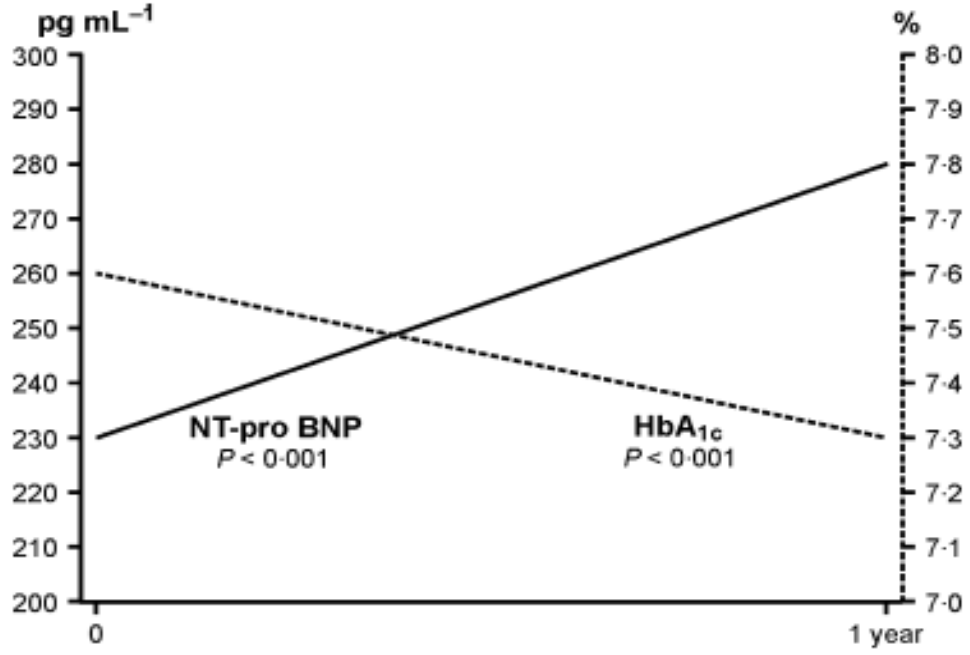


Table 3 Regression coefficients for changes in concentration of NT-proBNP and HbA_{1c} within the multivariate regression models for absolute change in concentration

	Delta NT-proBNP			Delta HbA_{1c}		
Endpoints	HR	CI	*P*	HR	CI	*P*
All-cause mortality	0·9994	0·9987–1·0002	n.s.	0·8818	0·6089–1·2770	n.s.
Cardiac hospitalization	0·9983	0·9977–0·9990	< 0·001	1·2872	0·9992–1·6583	n.s.
CV-hospitalization	0·9987	0·9981–0·9994	0·003	1·1069	0·8872–1·3809	n.s.
All-cause hospitalization	0·9991	0·9986–0·9996	< 0·001	1·0852	0·9514–1·2378	n.s.

Zusammenfassung I

- Es sind nicht die Marker des Diabetes (Blutzucker, HBA_{1c}) und nicht die renalen Marker, welche das kardiovaskuläre Risiko darstellen.

Just simple:

- Kardiale Marker stellen das kardiale Risiko dar.

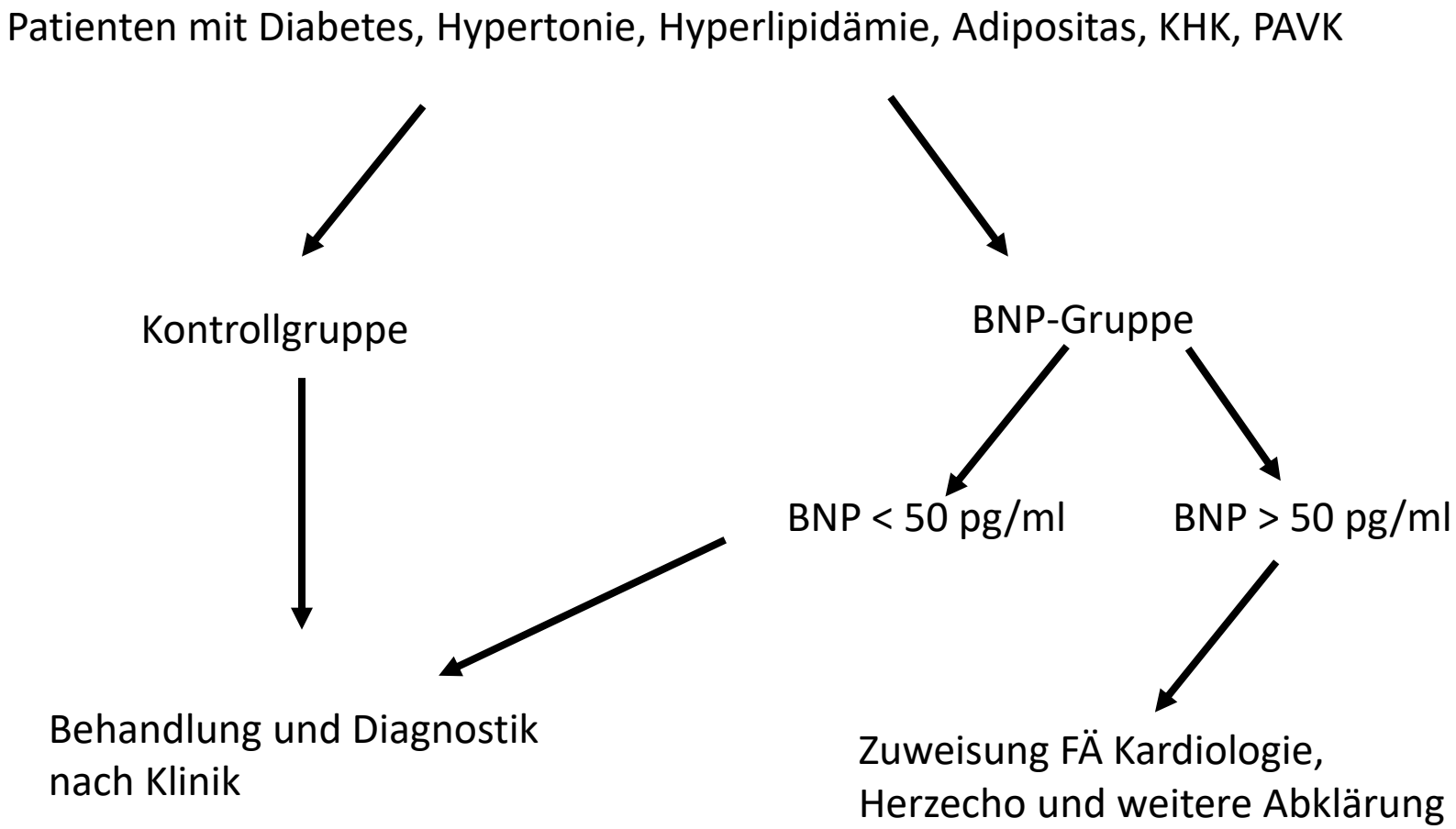
JAMA. 2013;310(1):66-74.

Original Investigation

Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

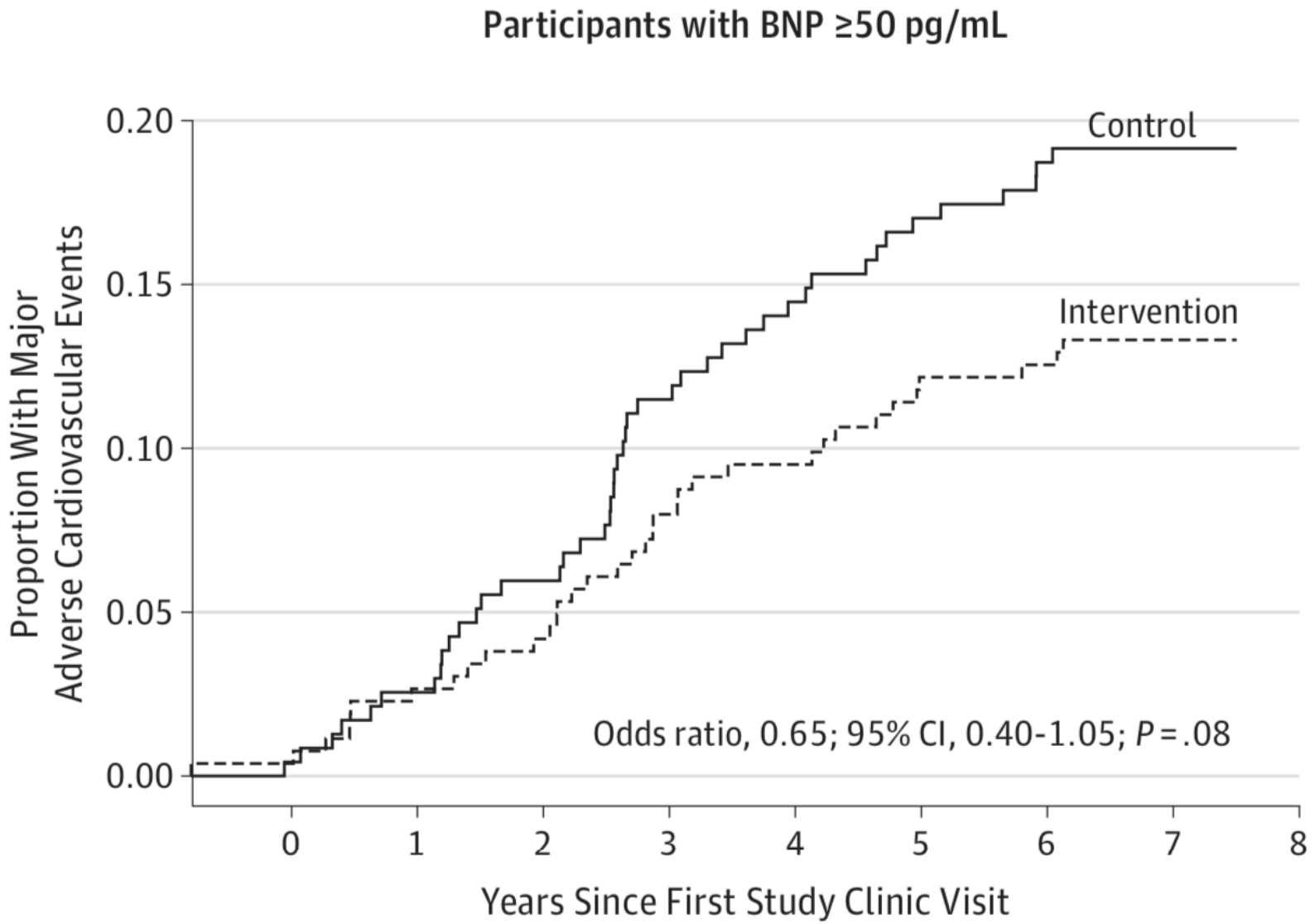
The STOP-HF Randomized Trial

Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O'Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabhagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD


Patienten mit Diabetes, Hypertonie, Hyperlipidämie, Adipositas, KHK, PAVK
Kontrollgruppe
BNP-Gruppe
BNP < 50 pg/ml
BNP > 50 pg/ml
Behandlung und Diagnostik
nach Klinik
Zuweisung FÄ Kardiologie,
Herzecho und weitere Abklärung

	Tests (per 1000 patient-years)				Number (%) of patients tested		
	Control	**Intervention**	**p-value**		**Control**	**Intervention**	**p-value**
All Patients							
Patient-years	2898.26	2917.16		*N*	677	697	
Exercise Stress Test	70 (24.2)	106 (36.3)	.01		58 (8.6%)	86 (12.3%)	.02
Holter	88 (30.4)	78 (26.7)	.41		69 (10.2%)	48 (6.9%)	.03
Electrocardiogram	367 (126.6)	591 (202.6)	<.001		217 (32.1%)	273 (39.2%)	.01
Angiogram	85 (29.3)	111 (38.1)	.07		71 (10.5%)	89 (12.8%)	.19
ABPM	228 (78.7)	464 (159.1)	<.001		140 (20.7%)	205 (29.4%)	<.001
Cardiac Imaging	347 (119.7)	942 (322.9)	<.001		224 (33.1%)	320 (45.9%)	<.001
Chest X-ray	217 (74.9)	159 (54.5)	.002		131 (19.4%)	109 (15.6%)	.07
Carotid Ultrasound	35 (12.1)	27 (9.3)	.30		32 (4.7%)	20 (2.9%)	.07
BNP ≥ 50 pg/mL patients							
Patient-years	1051.17	1150.29		*N*	235	263	
Exercise Stress Test	31 (29.5)	58 (50.4)	.02		24 (10.2%)	45 (17.1%)	.03
Holter	56 (53.3)	62 (53.9)	.95		42 (17.9%)	36 (13.7%)	.20
Electrocardiogram	188 (178.8)	415 (360.8)	<.001		104 (44.3%)	167 (63.5%)	<.001
Angiogram	43 (40.9)	74 (64.3)	.02		38 (16.2%)	56 (21.3%)	.15
ABPM	99 (94.2)	340 (295.6)	<.001		53 (22.6%)	130 (49.4%)	<.001
Cardiac Imaging	165 (157)	745 (647.7)	<.001		101 (43%)	179 (68.1%)	<.001
Chest X-ray	123 (117)	100 (86.9)	.03		64 (27.2%)	68 (25.9%)	.73
Carotid Ultrasound	16 (15.2)	17 (14.8)	.93		15 (6.4%)	12 (4.6%)	.37

ABPM: Ambulatory Blood Pressure Monitor; Cardiac Imaging: transthoracic echocardiography, transesophageal echocardiography and cardiac magnetic resonance imaging



Quelle:
https://jamanetwork.com/journals/jama/fullarticle/1707723

Therapeutische Konsequenzen

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

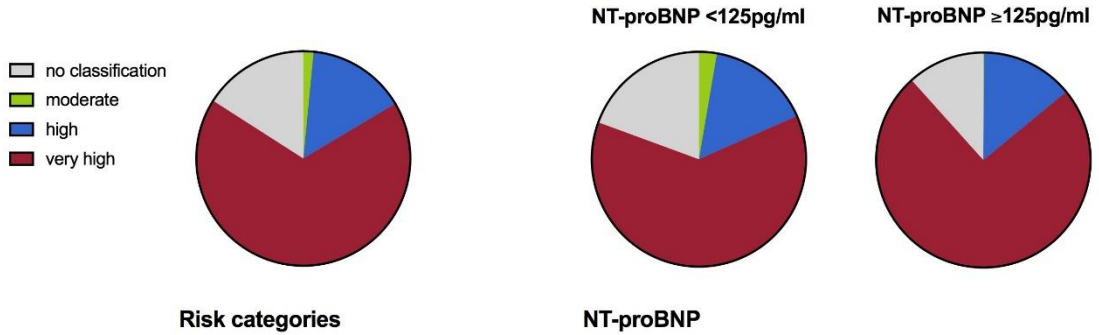


Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventric-

Glucose-lowering treatment

Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events

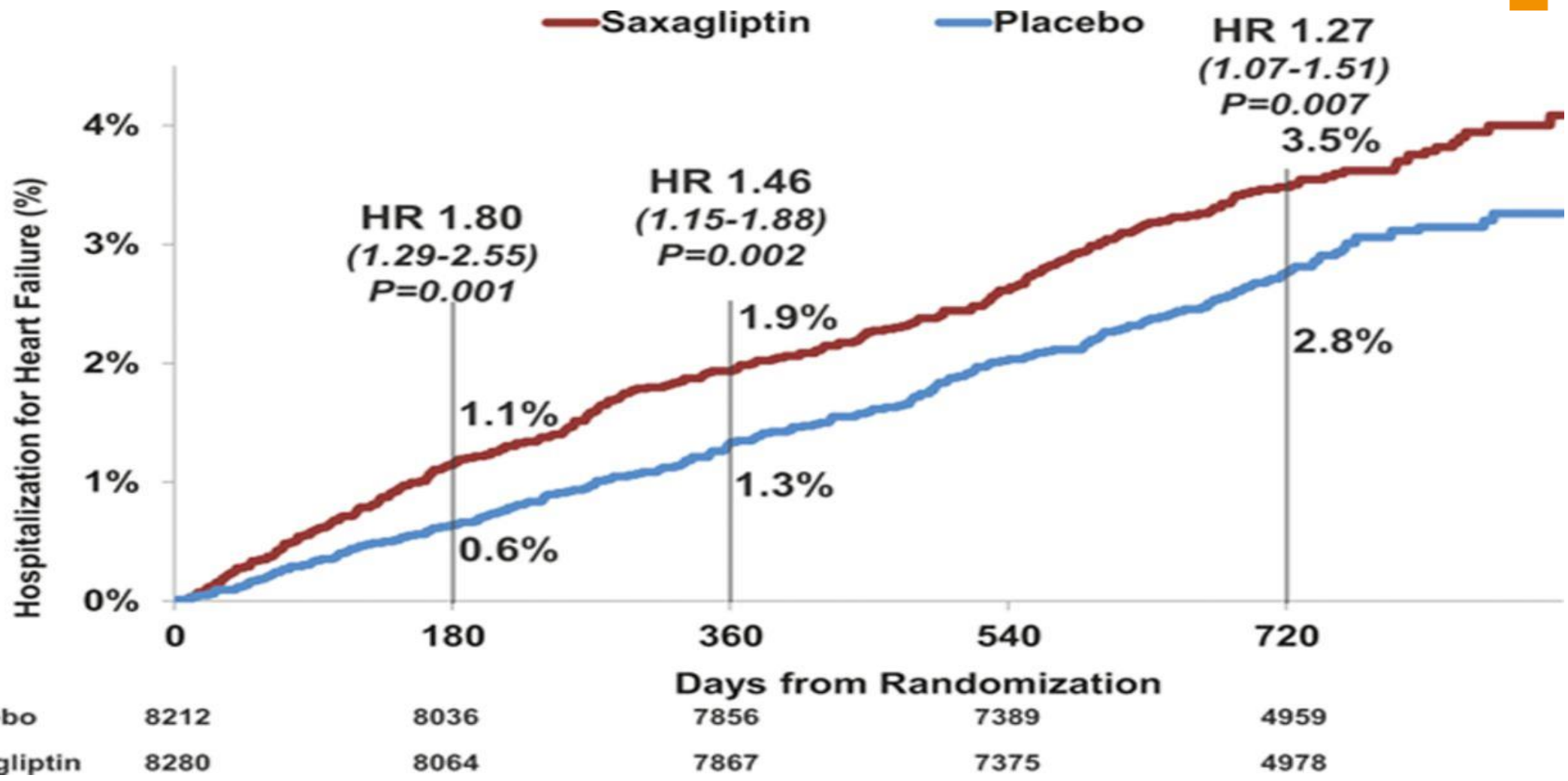
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death

Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or very high/high CV risk, to reduce CV events

Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death

Saxagliptin is not recommended in patients with T2DM and a high risk of HF

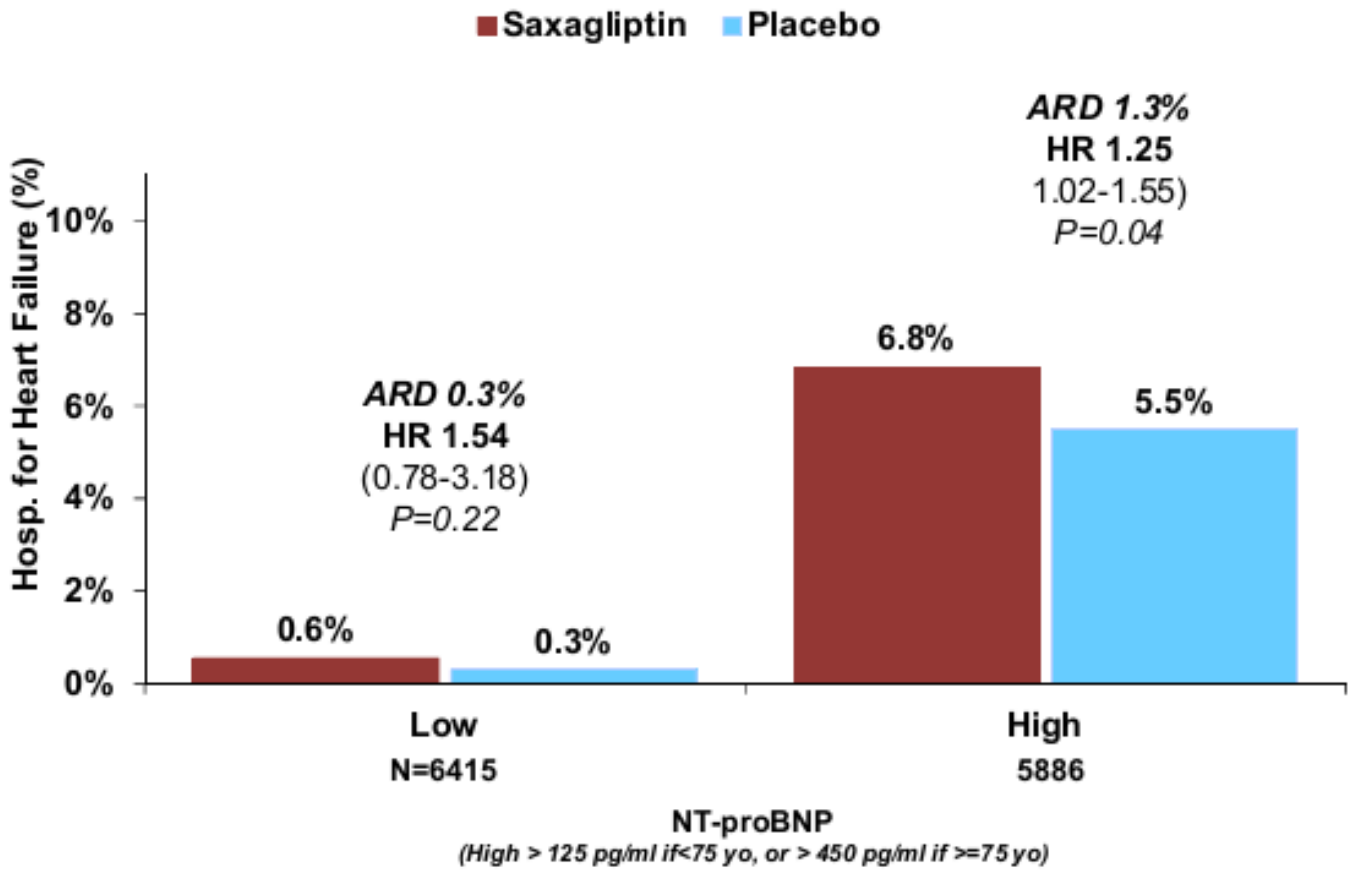
Kaplan-Meier failure estimates of hospitalization for heart failure according to treatment with saxagliptin versus placebo. (Savor-TIMI 53)



Benjamin M. Scirica et al. Circulation. 2014;130:1579-1588

American Heart Association.

SAVOR-TIMI 53
Risk of hospitalization for heart failure according to established cut-point



ARD 1.3%
HR 1.25
1.02-1.55)
P=0.04

American Heart Association.

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The NEW ENGLAND JOURNAL of MEDICINE

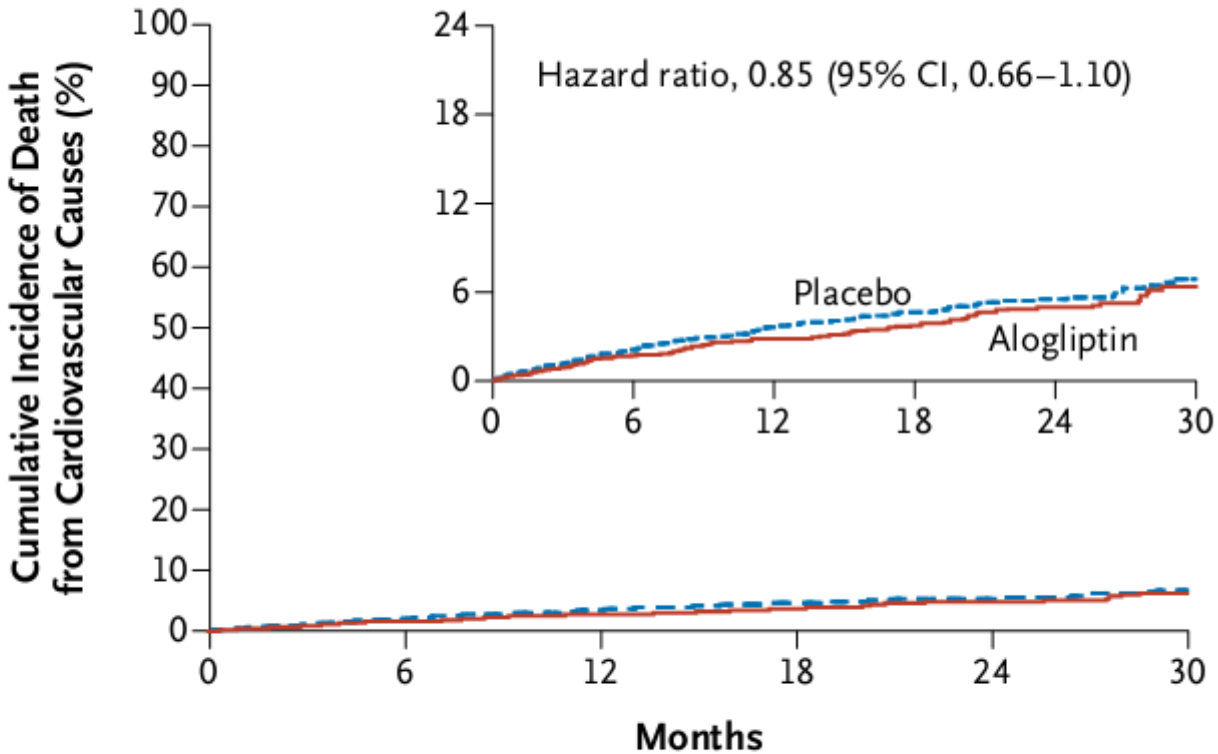
ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

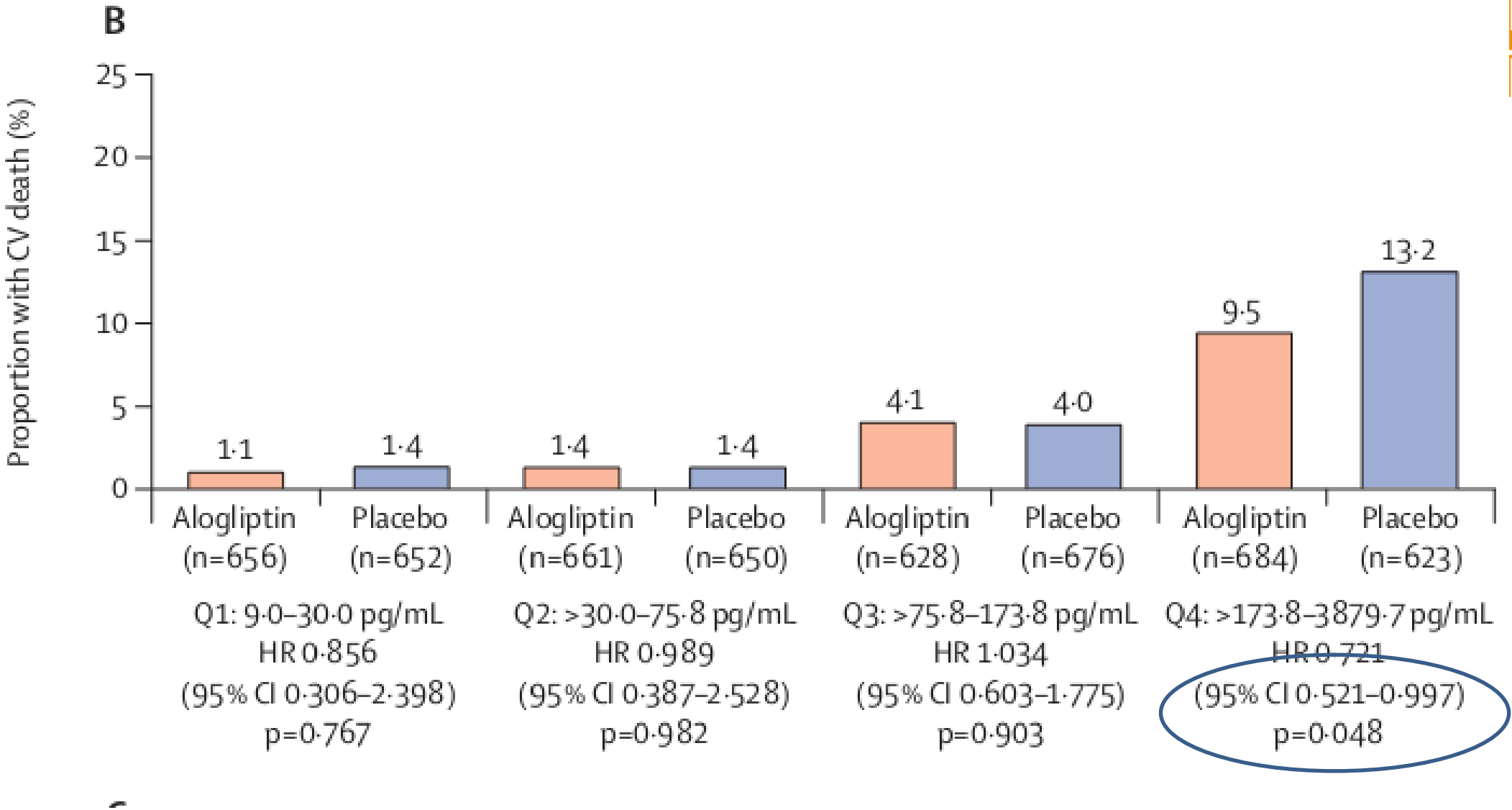
William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

PLUS

B



No. at Risk						
Placebo	2679	2384	1996	1477	889	324
Alogliptin	2701	2402	2023	1504	894	320



Faiez Zannad, Christopher P Cannon, William C Cushman, George L Bakris, Venu Menon, Alfonso T Perez, Penny R ...

The Lancet, 2015 **Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial**

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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‡

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PLUS

Table 4 Cox Regression Models (Unadjusted)

Endpoints	Hazard Ratio	95% Confidence Interval	p Value
Primary endpoint	0.351	0.127–0.975	0.04
All-cause hospitalizations	0.657	0.465–0.927	0.02
Unplanned cardiovascular hospitalizations or death	0.376	0.157–0.899	0.03
Heart failure hospitalizations	0.140	0.017–1.137	0.07

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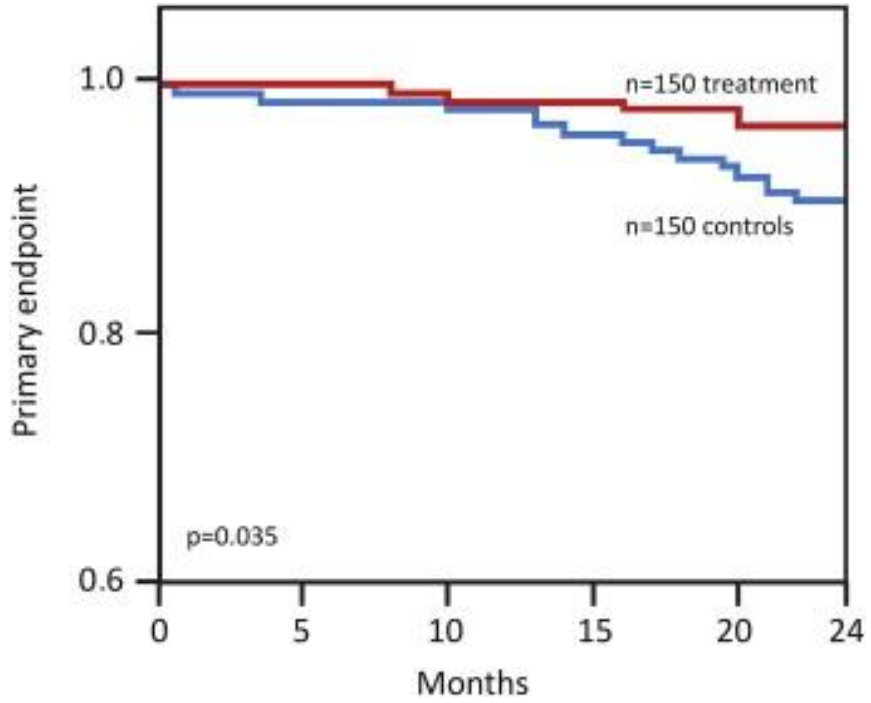
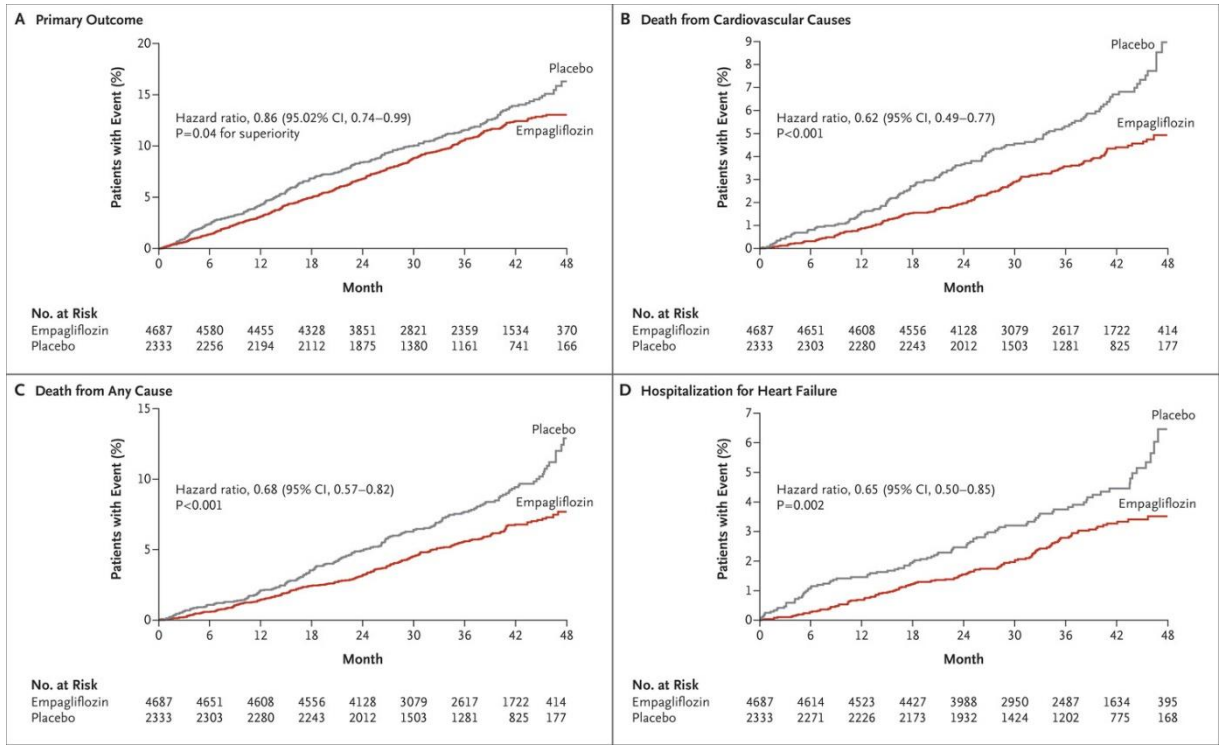


Figure 2. Kaplan-Meier Curves of the Primary Endpoint Hospitalization or Death Due to Cardiac Disease According to Treatment StrategyRed line = intensified group. Blue line = control group. Log-rank test for overall difference, p = 0.035.

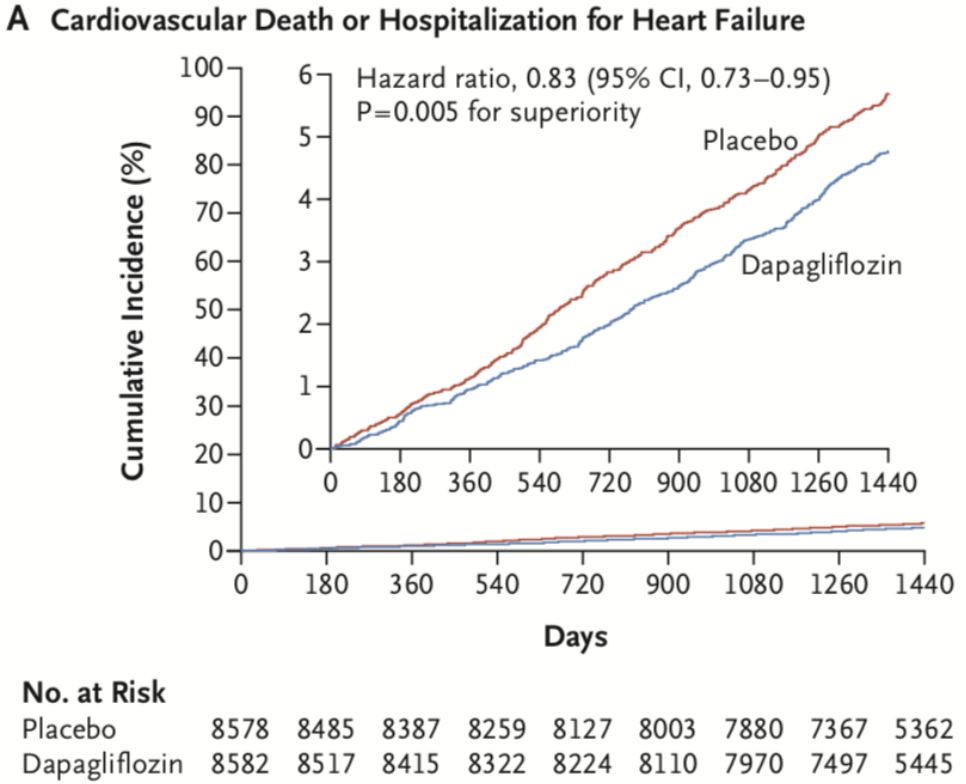
Table 4 Reasons for Hospitalizations

Hospitalization Due to	All	Control	Intensified	p Value
Any reason	135 (45%)	77 (51%)	58 (39%)	0.02
Cardiovascular event	25 (8%)	18 (12%)	7 (5%)	0.02
Cardiac event	19 (6%)	14 (9%)	5 (3%)	0.03
Heart failure	8 (3%)	7 (5%)	1 (1%)	0.003

SGLT2i bei Diabetes

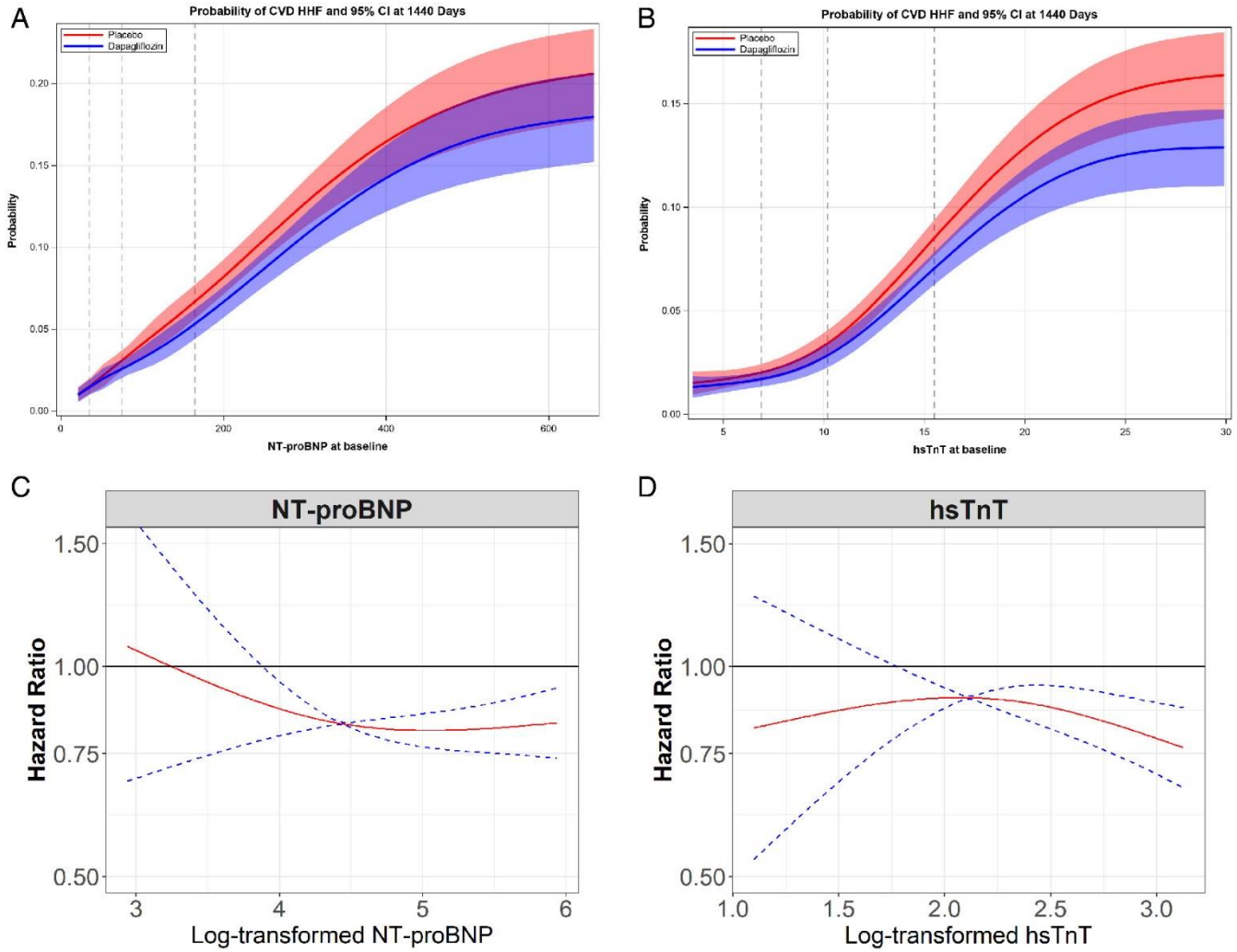


Quelle: Zinman B et al.: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-28



Quelle: https://www.nejm.org/doi/full/10.1056/nejmoa1812389

Relationship between baseline cardiac biomarkers and cardiovascular death or hospitalization for heart failure with and without sodium–glucose co-transporter 2 inhibitor therapy in DECLARE-TIMI 58

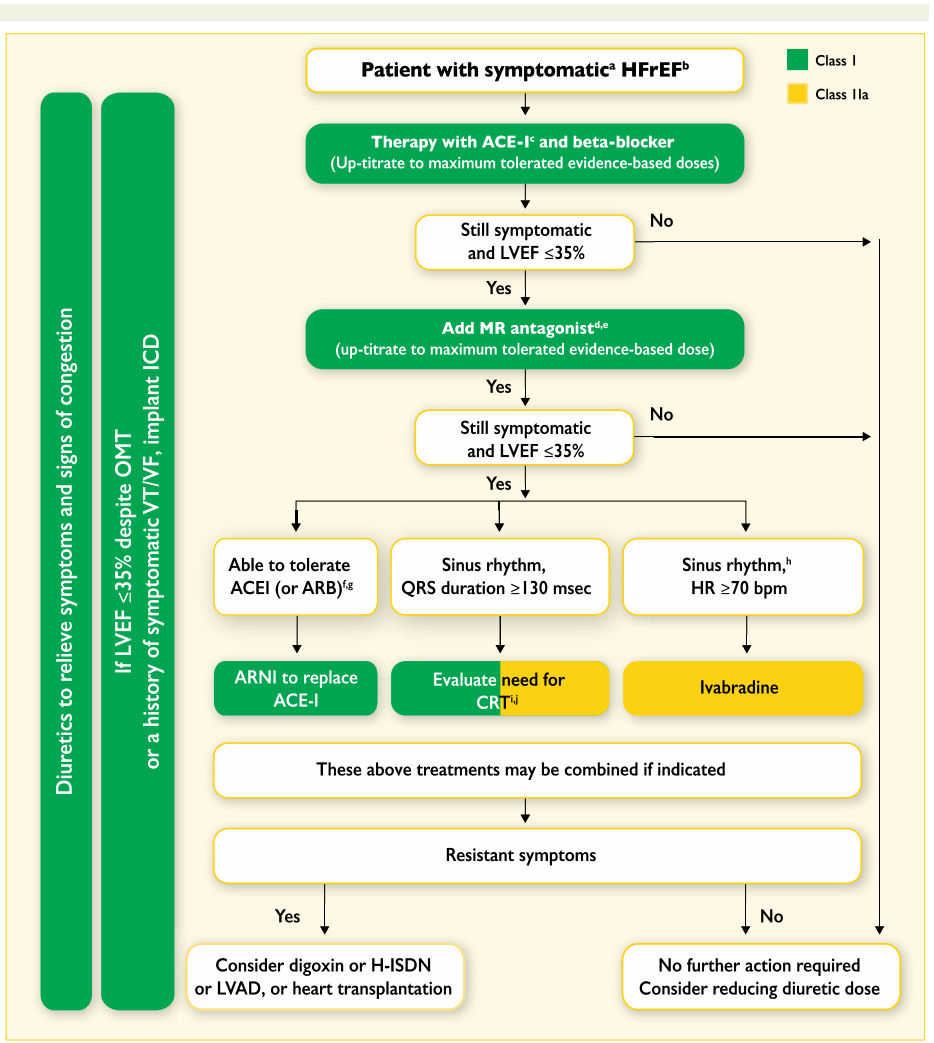


European Journal of Heart Failure, first published: 02 December 2020, DOI: (10.1002/ejhf.2073)

Zusammenfassung

- Kardiale Marker stellen das kardiale Risiko bei Diabetes dar
- NT-proBNP definiert die Wirkung von blutzuckersenkenden Medikamenten
- NT-proBNP definiert die Notwendigkeit einer erweiterten Diagnostik

Therapie



Quelle: https://www.escardio.org/static-file/Escardio/Guidelines/Publications/HF/d8025_Summary_Card-HF-6%20for%20web.pdf

Vielen Dank für Ihre Aufmerksamkeit!