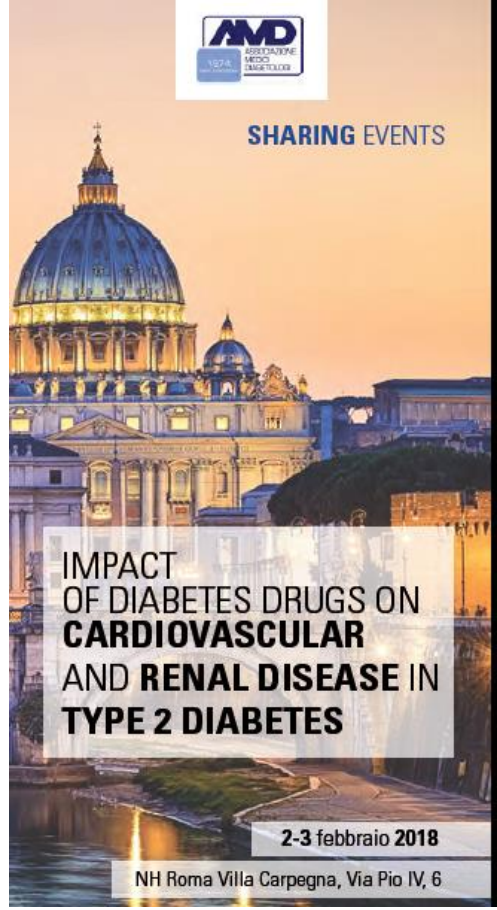
Effetto dei Nuovi Farmaci sul Cuore: Insuline



Paolo Di Bartolo

UO Diabetologia Ravenna, Rete Clinica di Diabetologia, AUSL della Romagna

paolo.dibartolo@auslromagna.it

Paolo Di Bartolo Disclosure

Board Member/Advisory Board

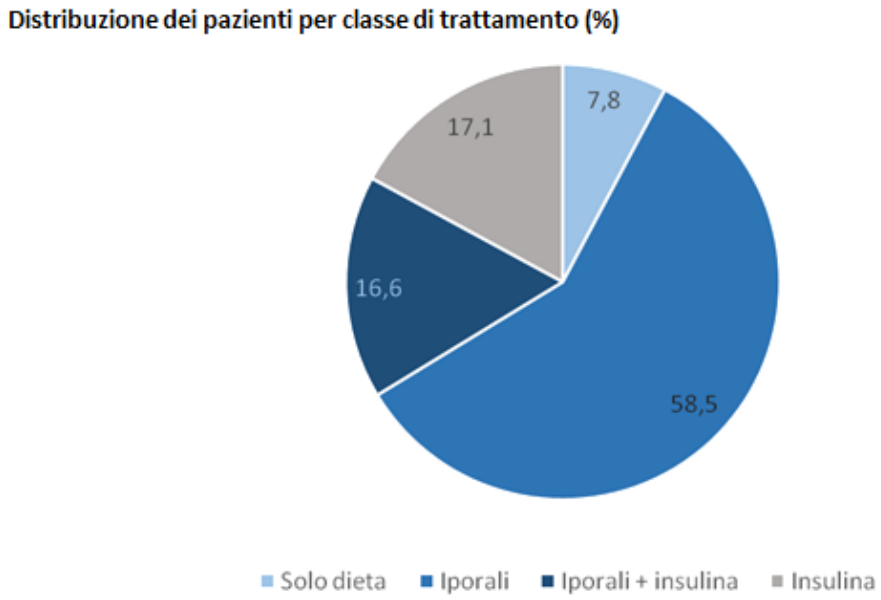
Abbott Diagnostic Italy, Boehringer Ingelheim Italy, Eli Lilly International, Novartis Italy, Novo Nordisk Italy

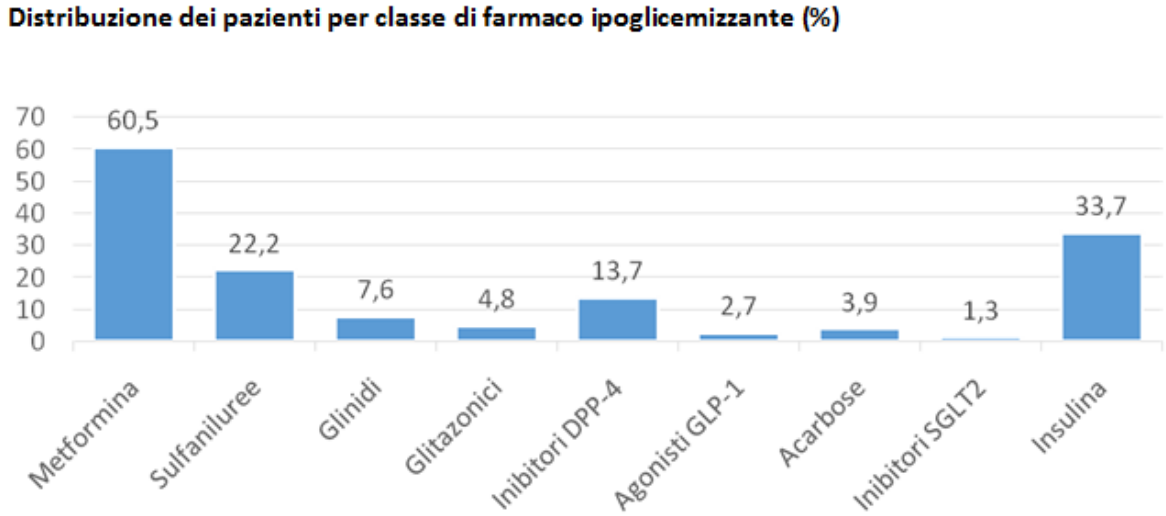
Speaker's Bureau

Abbott Diagnostic Italy, Astra Zeneca BMS Italy, Eli Lilly Italy, Novartis Italy, Novo Nordisk Italy, Sanofi Aventis Italy, Sigma-Tau Italy, Ypsomed Italy.

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Dimensione (FDC)

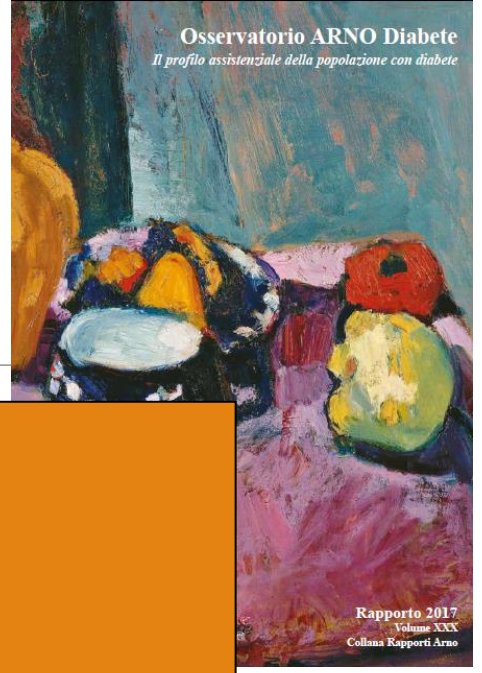




Il 33.7 % dei pazienti seguiti nei Servizi di Diabetologia nel 2015 risultavano trattati con Insulina

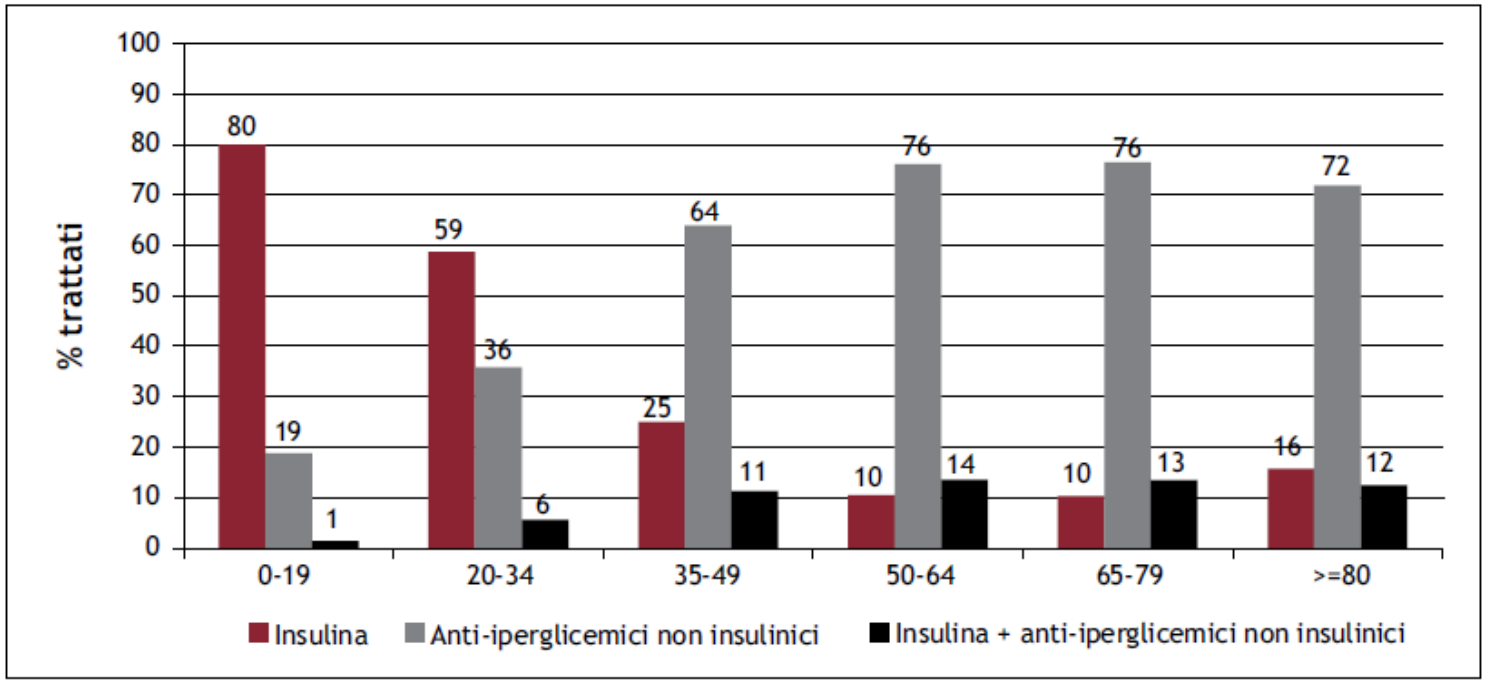
Soon to be published

Dimensione (Arno 2017)



Iperglicemi
Insuline un
Insuline ad
Insuline ad
Insuline ad
Analoghi de
Analoghi ad
Analoghi ad
Analoghi ad
Analoghi ad

Distribuzione per età della tipologia di trattamento del diabete



Il 27

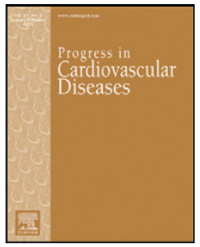
sulina

https://www.cineca.it/sites/default/files/RapportoARNODiabete2017.pdf

Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com



Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes

Mary E. Herman[a, b], *James H. O'Keefe*[c, d, *], *David S.H. Bell*[e], *Stanley S. Schwartz*[f, g]

Insulin therapy increased cardiovascular (CV) risk and mortality among type 2 diabetes (T2D) patients in several recently reported clinical outcomes trials. To assess whether this association is causative or coincidental, PubMed searches were used to query the effects of insulin therapy for T2D on CV health and longevity from large-scale outcomes trials, meta-analyses, and patient registry studies, as well as basic research on insulin's direct and pleiotropic actions. Although several old studies provided conflicting results, the majority of large observational studies show strong dose-dependent associations for injected insulin with increased CV risk and worsened mortality. Insulin clearly causes weight gain, recurrent hypoglycemia, and, other potential adverse effects, including iatrogenic hyperinsulinemia. This over-insulinization with use of injected insulin predisposes to inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure (HF), and arrhythmias. These associations support the findings of large-scale evaluations that strongly suggest that insulin therapy has a poorer short- and long-term safety profile than that found to many other anti-T2D therapies. The potential adverse effects of insulin therapy should be weighed against proven CV benefits noted for select other therapies for T2D as reported in recent large randomized controlled trials.

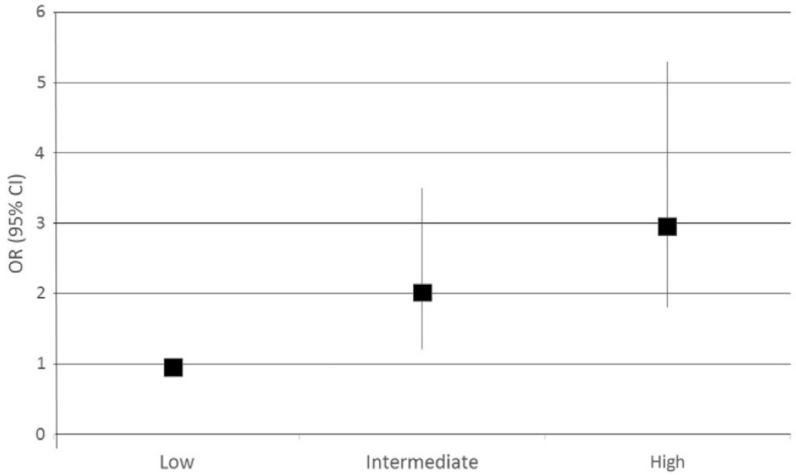


Fig 1 – Association between mean insulin exposure tertiles (low, intermediate, high) and risk of cardiovascular events. Multivariate conditional logistic regression estimates. OR, odds ratio; CI, confidence interval; CVE, cardiovascular event.[42]

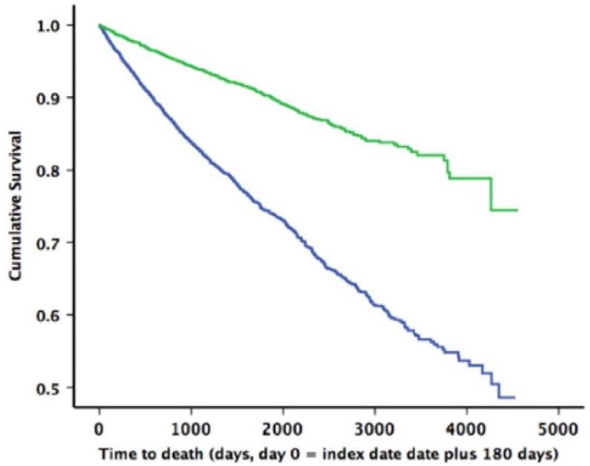


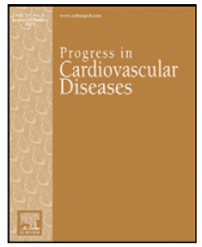
Fig 2 – Kaplan–Meier and adjusted survival curves for comparing insulin monotherapy and insulin plus metformin for all-cause mortality.[45] Blue = insulin monotherapy, green = insulin plus metformin. Time zero refers to index date plus 180 days. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

PROGRESS IN CARDIOVASCULAR DISEASES XX (2017) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com



Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes

Mary E. Herman[a, b], *James H. O'Keefe*[c, d, *], *David S.H. Bell*[e], *Stanley S. Schwartz*[f, g]

Adverse Physiological Effects of Exogenous Insulin

- Hypoglycemia
- Iatrogenic Hyperinsulinemia: Unfavorable Downstream Consequences
- Weight Gain from Insulin Therapy

Table 1 – Insulin Therapy.

Insulin Therapy						
Insulin CV outcomes trials	Duration (Yrs) Time interval	Cohort	Treatment	% of patients receiving insulin	A1c achieved (insulin arm vs comparator)	CV outcome, insulin-treated patients
UKPDS	10 yr Follow-up study Prospective 1977–1991	IGT or early T2DM 8% history CVD (n = 3,867) Mean age = 62 YO	Intensive (sulphonylureas/insulin) vs conventional (life style modification) vs metformin	79% of intensive cohort	7.0% vs 7.9%	↓ **13%** all-cause mortality insulin arm (nonsignificant reduction in MI in metformin arm; 27%)
ORIGIN **ORIGINALE**	6.2 Prospective 2003–2011	Impaired fasting glucose, impaired glucose tolerance or T2DM; 40% with history of CVD (n = 12,537) Mean age = 64 YO	Insulin glargine + add-on drugs for target fasting blood glucose level of ≤95 mg/dL vs standard care	84% in insulin-based arm vs 11% conventional arm	6.2% vs 6.5%	↔ **Neutral** for major CV events
	2 Follow-up					↔ **Neutral** for major CV events
ACCORD ACCORD group	3.5 Prospective 2001–2005	T2D with prior CV event (35%) or high CV risk (n = 10,251) Mean age = 62 YO	Physician choice, with goal for intensive arm to reach A1c <6.0%, standard arm A1c goal of 7.0–7.9%	77% intensive arm vs 55% standard arm	6.4% vs 7.5%	↔ **Neutral** for major CV events; Increased mortality (22%)
	5 Follow-up					↔ **Neutral;** no increased CV death after adjustment for baseline characteristics
ADVANCE The ADVANCE collaborative group	5 Prospective 2001–2008	T2D with prior CV event (32%) or CV risk factors (n = 11,140) Mean age = 66 YO	Intensive (gliclazide-based regimen to target A1c ≤6.5%) vs conventional	40% intensive arm vs 24% standard arm	6.5% vs 7.3%	↔ **Neutral** for major CV events
VADT	6.3 Prospective 2002–2008	T2DM4, 0% with history of CVD (n = 1791) Mean age = 60 YO	Add-on insulin in any patient not A1c <6% in intensive arm and <9% in standard arm	89% vs 74%	6.9% vs 7.9%	↔ **Neutral** for major CV events
DIGAMI-2	2.1 Prospective 2001–2003	T2DM with suspected acute MI (n = 1,145) Mean age = 68 YO	Insulin-based treatment vs insulin during hospitalization + conventional glucose control vs conventional treatment	81% of insulin-based treatment arm on last visit	7.6% vs 7.7% vs 7.8%	↑ **Non-fatal CV events** (OR 1.89). Increased trend in mortality in insulin-based regimens
Euro Heart Survey	1 Prospective 2003–2004	T2DM with CAD (n = 4,676) Mean age = 68 YO	Physician choice	37%	Not reported	↑ **CV events** (HR 1.3) and **mortality** (HR 2.2) vs non-insulin glucose-lowering
NY Limb salvage/survival		Patients with disabling claudication, or critical	Diabetics on insulin monotherapy (n = 146), Diabetics on insuin + oral	72% of diabetic	na	

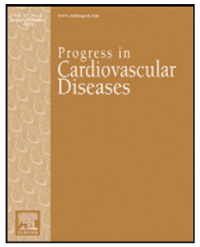
Table 1 (*continued*)

			Insulin Therapy			
	2.2 Prospective 2001–2008	limb ischemia. Choice of antidiabetes treatment was not a controlled variable.	antidiabetes meds (n = 98), Diabetics on oral antidiabetes meds (n = 96), nondiabetics (n = 406)	patients, 33% of all patients		↑ **Mortality** vs non-insulin diabetics (P < 0.001); insulin independently associated with survival (HR 1.5) and limb loss (HR 2.4)
Helsinki Policemen Study	22 Prospective Follow-up 1971–1992	Healthy. Males 34–65 years old free of CVD or diabetes at start of study (n = 970)	No treatment. Investigated association of plasma insulin levels (during an oral glucose tolerance test) with all-cause, CV, and non-CV mortality	0%	na	↑ **CV and all-cause mortality with elevated endogenous postprandial insulin levels in healthy subjects**
Insulin Patient registries	Time interval	Cohort	Treatment	% of patients receiving insulin	A1c achieved (insulin arm vs comparator)	CV outcome
Ahmanson-UCLA Cardiomyopathy Center	2000–2003	T2DM (95%, 5% T1DM) with history of heart failure (n = 554) Mean age = 52 YO	Insulin vs non-insulin-treated beneficiaries	30%	6.9% vs 7.9%	↑ **Risk of mortality** (4-fold)
Kaiser Permanente	2005–2007	T2DM (n = 11,157) Mean age = 65 YO	Insulin vs non-insulin-treated beneficiaries	42%	Not reported	↑ **Risk of mortality** (OR 2.6)
UK's The Health Information Network (THIN)	2002–2006	DM (n = 63,579)	Insulin vs non-insulin-treated beneficiaries	25%	Not reported	↑ **Serious ischemic cardiac outcomes** of 2.9 (2.1,3.9)
UK Clinical Practice Research Datalink	2000–2013 (Mean follow-up of 3.3 yr)	T2DM (n = 6072) Mean age = 60 YO	New users of oral antidiabetes therapy grouped by quartiles of insulin exposure	100%	na	↑ **Mortality** after multivariable adjustment. **aHR** in relation to 1-unit increases in insulin dose were 1.54 [95% confidence interval (CI) 1.32–1.78] for all-cause mortality, 1.37 (95% CI 1.05–1.81) for MACE
Saskatchewan Health	1991–1996	T2DM (n = 12,020) Mean age = 61 YO (insulin + metformin); 67 YO (insulin monotherapy)	Insulin as monotherapy or in combination therapy	100%	Not reported	↑ **Mortality** after multivariable adjustment of low insulin exposure (aHR): 1.75; 95% CI: 1.24–2.47, moderate exposure (aHR: 2.18; 1.82–2.60) and high exposure (aHR: 2.79; 2.36–3.30); P = 0.005 for trend
UK Clinical Practice Research Datalink	2000–2012 (Median follow-up 3·1 yr)	T2DM (n = 6072) Mean age varied with cohort (57–63 YO)	Insulin add-on to metformin	100%		↑ **Mortality and MACE** for insulin monotherapy vs insulin + metformin Multivariable adjusted aHRs for insulin + metformin vs insulin monotherapy of 0.60 (95% CI 0.52–0.68) for all-cause mortality, and 0.75 (0.62–0.91) for MACE

Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com



Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes

Mary E. Herman[a, b], *James H. O'Keefe*[c, d, *], *David S.H. Bell*[e], *Stanley S. Schwartz*[f, g]

Conclusions

Insulin therapy for T2D causes hyperinsulinemia, hypoglycemia and weight gain, and is increasingly associated with adverse CV outcomes. Insulin therapy should be relegated to a lower tier status in treatment algorithms for T2D, and should be used only when absolutely necessary to achieve glycemic control. Numerous T2D drugs have been proven to reduce adverse CV outcomes and mortality, and also reduce weight; these agents should be used in preference to insulin.

Effect of Insulin Therapy on Macrovascular Risk Factors in Type 2 Diabetes

Diabetes Care

Volume 22 Supplement 3
Improving Prognosis in Type 1 Diabetes
Proceedings from an Official Satellite Symposium
of the 16th International Diabetes Federation Congress

Michael S. Boyne, MD
Christopher D. Saudek, MD

Many patients with type 2 diabetes require insulin therapy for improved glycemic control after -cell failure. However, many physicians are reluctant to institute insulin therapy in type 2 diabetes for fear of accelerating atherosclerosis. The epidemiological evidence is reasonably sound that hyperinsulinism correlates with increased cardiovascular disease in nondiabetic people and those with early type 2 diabetes. It is much less clear, however, that insulin concentration plays a negative role when less well controlled diabetes is considered. The data are more consistent, in fact, with the glucose hypothesis, i.e., that hyperglycemia is a risk factor, although the magnitude of the glucose effect is not well defined. Certainly, the dysmetabolism associated with poor glycemic control could increase the risk of macrovascular events through well-known mechanisms. There is direct evidence that insulin therapy can reduce the risk of macrovascular events by improving glycemic control and diabetes-associated dyslipidemias, although the beneficial effects may be significantly compromised by excessive weight gain. Insulin therapy does not appear to induce hypertension independent of changes in body weight. It is concluded that optimal glycemic control confers a known benefit and can only be achieved with insulin therapy in some people with type 2 diabetes. In these circumstances, the use of insulin has a net benefit on cardiovascular risk, mediated primarily through improvement in dyslipidemia and glycemia itself.

Diabetes Care **22 (Suppl. 3):C45–C53, 1999**

RESEARCH ARTICLE

All-Cause and Cause-Specific Mortality among Users of Basal Insulins NPH, Detemir, and G

Arto Y. Stra
Solomon Cl

Backgrou

Insulin therap
impact of diffe
traditional NP
have shown b
into lower mo

Methods

23 751 indivi
2006–2009 w
causes of de
characteristics. Follow-up time was up to 4 years (median 1.7 years).

Conclusion

In real clinical practice, mortality was substantially higher among users of NPH insulin as compared to insulins detemir or glargine. Considering the large number of patients who require insulin therapy, this difference in risk may have major clinical and public health implications. Due to limitations of the observational study design, further investigation using an interventional study design is warranted.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

Cardiovascular or
Chronic kidney Disease and Aged ≥50

OR

Risk Factors for Cardiovascular Disease and Aged ≥60

In conclusion, we found that in patients with type 2 diabetes at high risk for cardiovascular events, degludec was noninferior to glargine in terms of the incidence of cardiovascular events.

Marso *et al. N Engl J Med* 2017;377:723–32

Diabetologia (2018) 61:48–57
DOI 10.1007/s00125-017-4423-z

ARTICLE

Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2)

Bernard Zinman[1] · Steven P. Marso[2] · Neil R. Poulter[3] · Scott S. Emerson[4] · Thomas R. Pieber[5] · Richard E. Pratley[6,7] · Martin Lange[8] · Kirstine Brown-Frandsen[8] · Alan Moses[8] · Ann Marie Ocampo Francisco[8] · Jesper Barner Lekdorf[8] · Kajsa Kvist[8] · John B. Buse[9] · on behalf of the DEVOTE Study Group

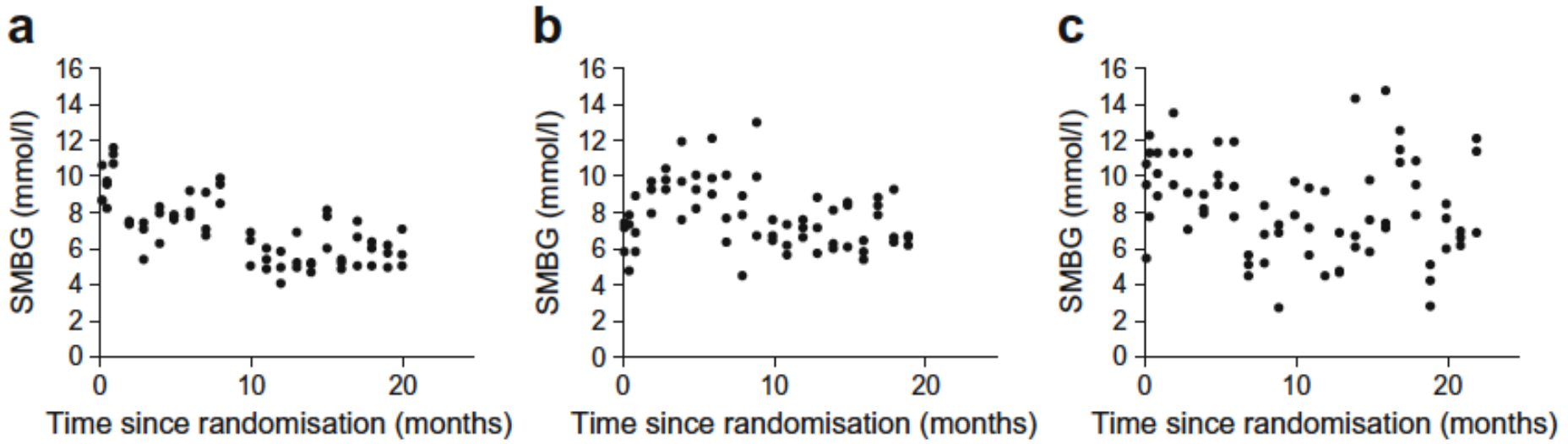
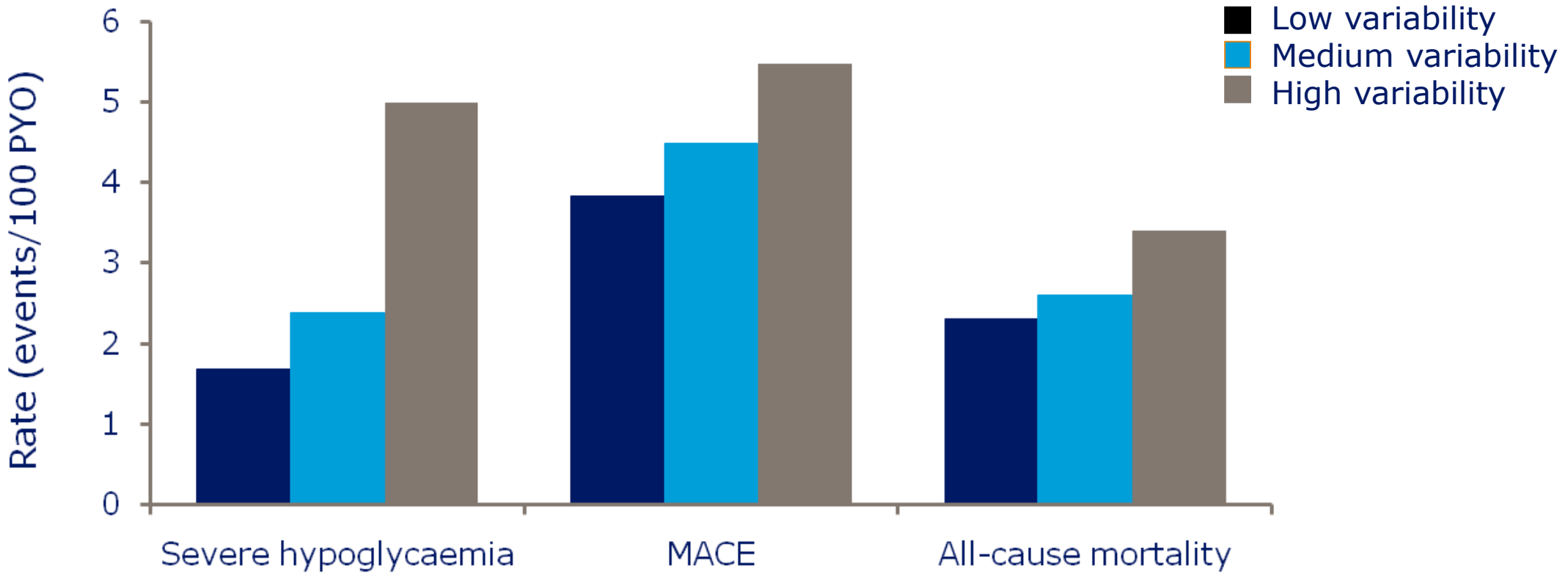


Fig. 1 Representative SMBG profiles from three separate DEVOTE participants illustrating the low (**a**), medium (**b**) and high (**c**) variability groups. Day-to-day fasting glycaemic variability was based on the standard deviation of the pre-breakfast SMBG measurements

Outcomes by variability tertile



Zinman *et al. Diabetologia* 2017; doi:10.1007/s00125-017-4423-z

	HR (95% CI)	*p* value
Severe hypoglycaemia		
Unadjusted	4.11 (3.15, 5.35)	<0.001

In conclusion, evidence from DEVOTE supports associations between higher day-to-day fasting glycaemic variability and increased risks of severe hypoglycaemia and all-cause mortality.

Zinman *et al. Diabetologia* 2017;10.1007/s00125-017-4423

Diabetologia (2018) 61:58–65
DOI 10.1007/s00125-017-4422-0

ARTICLE

DEVOTE 3: hypoglycaemia, cardiovascular outcomes and mortality

Thomas R. Pieber[1] · Steven P. Marso[2] · Darren K. McGuire[3] · Bernard Zinman[4] · Neil R. Poulter[5] · Scott S. Emerson[6] · Richard E. Pratley[7,8] · Vincent Woo[9] · Simon Heller[10] · Martin Lange[11] · Kirstine Brown-Frandsen[11] · Alan Moses[11] · Jesper Barner Lekdorf[11] · Lucine Lehmann[11] · Kajsa Kvist[11] · John B. Buse[12] · on behalf of the DEVOTE Study Group

In the present analysis, the associations of severe hypoglycaemia with both MACE and all-cause mortality was evaluated in the pooled trial population using time-to-event analyses, with severe hypoglycaemia as a time-dependent variable and randomised treatment as a fixed factor.

Pieber *et al. Diabetologia* 2017; 10.1007/s00125-017-4422-0

Risk of MACE and All Cause Mortality Following a S

Conclusions/interpretation The results from these analyses demonstrate an association between severe hypoglycaemia and all-cause mortality. Furthermore, they indicate that patients who experienced severe hypoglycaemia were particularly at greater risk of death in the short term after the hypoglycaemic episode. These findings indicate that severe hypoglycaemia is associated with higher subsequent mortality; however, they cannot answer the question as to whether severe hypoglycaemia serves as a risk marker for adverse outcomes or whether there is a direct causal effect.

Pieber *et al. Diabetologia* 2017; 10.1007/s00125-017-4422-0

Conclusions

Due to concerns about potential insulin-mediated CV risks an assesment of risk factors should be performed before prescribing insulin therapy.

The insulin formulation associated with the lower risk of severe hypoglycemia and a lower glycemic variability, should be preferred in patients with the highest CV risk.

In these patients, obviously preference should be given to use evidence-based agents shown to reduce CV risk, such as empagliflozin, canagliflozin, liraglutide, semaglutide, and pioglitazone

SGLT-2 inhibitors and GLP-1 agonists have synergistic effects for improving both CV risk and glycemic control, as well as in lowering weight and BP, and thus represent a logical combination, with insulin therapy, for the treatment of T2D