# Inzulín?
# Apage satanas!!!!!

Milan Kvapil

# Proč ne inzulín?

- **Inzulín je proaterogenní**

# Effect of insulin in the induction and regression of experimental cholesterol atherosclerosis in the rabbit

G. MARQUIÉ

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**Summary**

**A study was undertaken to determine the effects of long-term insulin therapy on the development and regression of lipid perturbations and experimental cholesterol atherosclerosis in rabbits:**

**(1) Insulin administration for 15 days significantly reduced plasma lipid levels and free fatty acids in rabbits fed a high-cholesterol diet; it also inhibited the effects of a single dose of cholesterol. Paradoxically, continued insulin treatment led to the reinforcement of lipaemia through the stimulation of mobilization.**

**Insulin administration during the development of atherosclerosis significantly aggravated the fatty infiltration of the aortic tissue and the lesions of the vessels, and also increased the frequency of coronary lesions.**

**(2) In rabbits fed a cholesterol enriched diet during two months and then a normal diet, insulin treatment accelerated the rate of reduction of hypercholesterolaemia, but aggravated the lipid infiltration of the artery walls, and also prevented regression of coronary atherosclerosis.**

or without high fasting plasma insulin levels (Peters and Hales, 1965). It has been suggested by Stout and Wallance-Owen (1969) that hyperinsulinism may be the common factor linking atherosclerosis with diabetes, obesity and hyperlipidaemia. An acute *in vitro* effect of insulin on the lipid metabolism of the arterial wall has been described (Mahler, 1966; Stout, 1968, 1969, 1971). Under these circumstances, it seemed reasonable to postulate that insulin may have a causal role in atherogenesis.

In view of this problem, experiments were undertaken to explore the effects of exogenous insulin on aorta and coronary atherogenesis in cholesterol-fed rabbits and in rabbits after cessation of the cholesterol diet.

## Materials and methods

The rabbits were male of the Fawn Bourgogne strain and New Zealand White strain and weighed approximately 2·5 kg at the start of the experiment. Upon entering the animal house, the rabbits were placed in individual cages and allowed not less than

Postgraduate Medical Journal (February 1978) 54, 80-85.

# Evidence That Acute Insulin Administration Enhances LDL Cholesterol Susceptibility to Oxidation in Healthy Humans

Alfredo Quiñones-Galvan, Anna Maria Sironi, Simona Baldi, Fabio Galetta, Ulisse Garbin, Anna Fratta-Pasini, Luciano Cominacini, Ele Ferrannini

*Abstract*—Increased free radical production and hyperinsulinemia are thought to play a role in experimental and human atherosclerosis, but the relation between the 2 abnormalities has not been studied. In 23 healthy volunteers, we measured the susceptibility of circulating low-density lipoprotein (LDL) cholesterol particles to in vitro copper sulfate oxidation (measured as the lag phase) and cell-mediated oxidative modification (measured as malondialdehyde generation in LDL during incubation with human umbilical vein endothelial cells), as well as the vitamin E content of LDL cholesterol at baseline and after 2 hours of physiological hyperinsulinemia (euglycemic insulin clamp). The lag time of LDL oxidation decreased from control values of 108±3 and 107±3 minutes (at baseline and after 2 hours of saline infusion) to 101±3 minutes after 2 hours of clamping ($P<0.0001$). At corresponding times, cell-mediated malondialdehyde generation in LDL rose from 4.96±0.11 and 4.98±0.10 to 5.28±0.10 nmol/L ($P=0.0006$), whereas the LDL vitamin E content decreased from 6.78±0.06 and 6.77±0.06 to 6.64±0.06 μg/mg ($P<0.04$). The insulin-induced shortening of the lag phase was directly related to the decrement of vitamin E in LDL; furthermore, in subjects with higher baseline serum triglyceride levels, insulin induced a greater shortening of the lag phase than in subjects with low baseline triglycerides. We conclude that in healthy humans acute physiological hyperinsulinemia enhances the oxidative susceptibility of LDL cholesterol particles. This effect may have pathogenic significance for atherogenesis in insulin resistant states. (*Arterioscler Thromb Vasc Biol.* **1999;19:2928-2932.**)

Arterioscler Thromb Vasc Biol. 1999;19:2928-2932.)

# Insulin Causes Endothelial Dysfunction in Humans

## Sites and Mechanisms

Guido Arcaro, MD; Anna Cretti, MD; Sara Balzano, MD; Alessandro Lechi, MD; Michele Muggeo, MD; Enzo Bonora, MD, PhD; Riccardo C. Bonadonna, MD

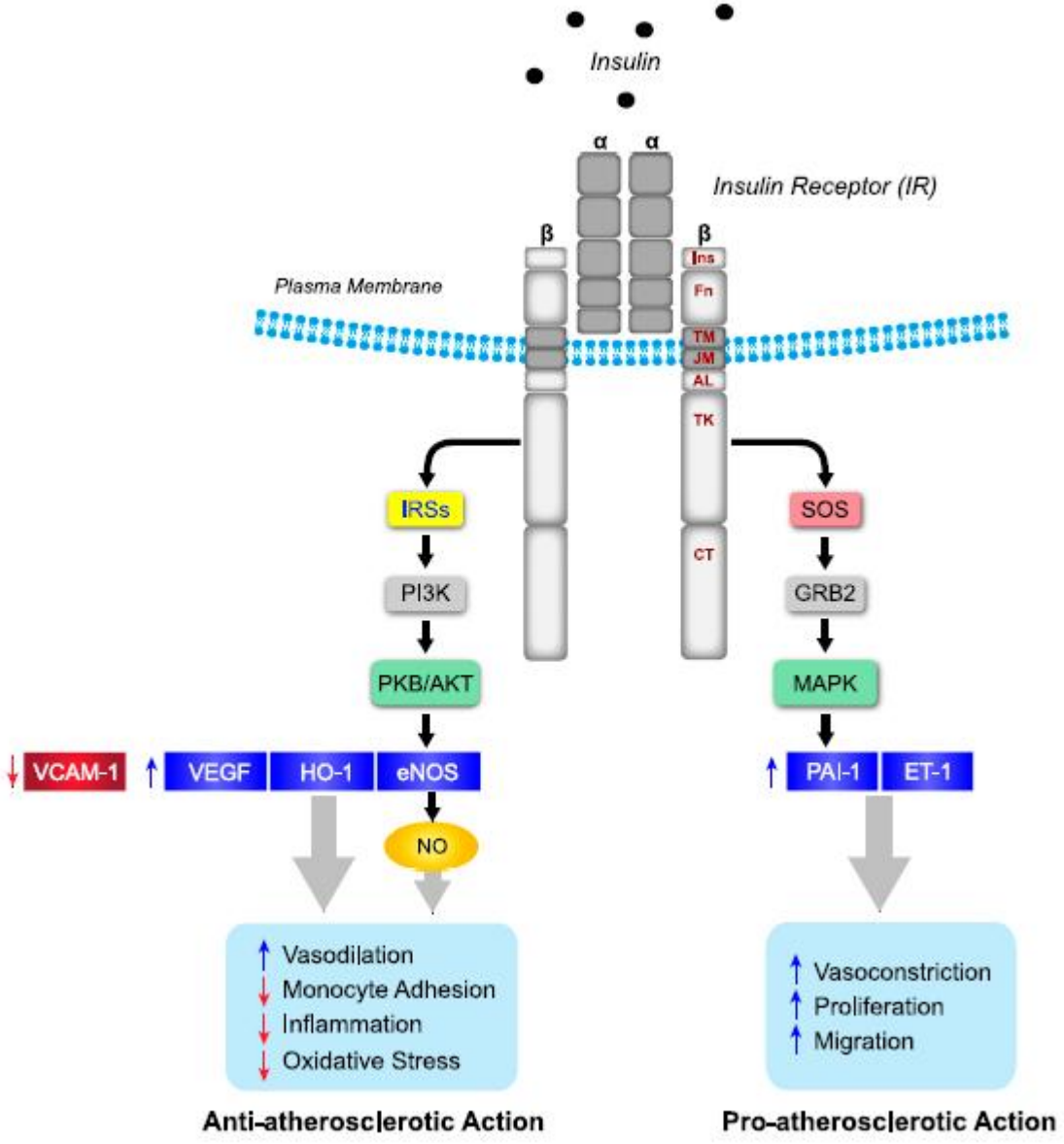
*Background*—Insulin resistance is often accompanied by hyperinsulinemia and may predispose to atherosclerosis. Endothelium plays a central role in atherogenesis. The in vivo effects of hyperinsulinemia on endothelial function of large conduit arteries are unknown.

*Methods and Results*—Twenty-five healthy subjects were enrolled for study. In study A (n=9), subjects underwent both a time-control saline study and a euglycemic low-dose insulin (insulin ≈110 pmol/L) clamp for 6 hours. Study B (n=5) was identical to study A except that the euglycemic clamp was performed at high physiological insulin concentrations (≈440 pmol/L). In study C (n=7), subjects underwent two 4-hour euglycemic insulin (≈110 pmol/L) clamps with and without the concomitant infusion of an antioxidant (vitamin C). In study D (n=4), two saline time-control studies were performed with and without the concomitant infusion of vitamin C. In all studies, both at baseline and throughout the experimental period, endothelium-dependent (flow-mediated) and endothelium-independent (nitroglycerin-induced) vasodilation was assessed in femoral and brachial arteries by echo Doppler. Both low (study A) and high physiological (study B) hyperinsulinemia abolished endothelium-dependent vasodilation, whereas endothelium-independent vasodilation was unaffected. Vitamin C fully restored insulin-impaired endothelial function without affecting endothelium-independent vasodilation (study C). Vitamin C had no effects on endothelium-dependent or endothelium-independent vasodilation during saline control studies (study D).

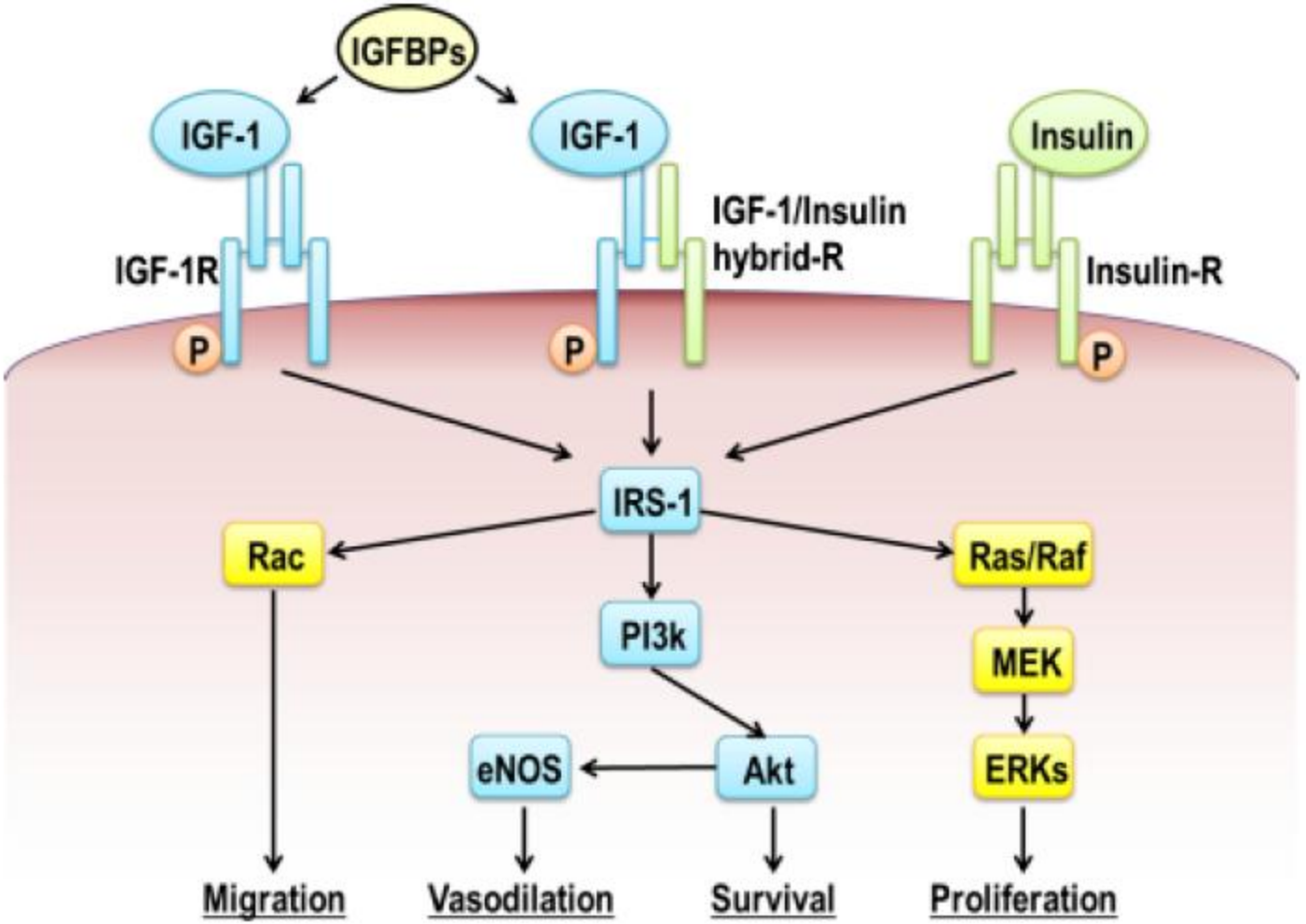
*Conclusions*—Modest hyperinsulinemia, mimicking fasting hyperinsulinemia of insulin-resistant states, abrogates endothelium-dependent vasodilation in large conduit arteries, probably by increasing oxidant stress. These data may provide a novel pathophysiological basis to the epidemiological link between hyperinsulinemia/insulin-resistance and atherosclerosis in humans. (*Circulation*. 2002;105:576-582.)

Circulation. 2002;105:576-582.)

# Exogenní hyperinzulínémie může změnit poměr pro/anti aterosklerotického ovlivnění metabolických drah inzulínem a potencovat akcelaraci AS

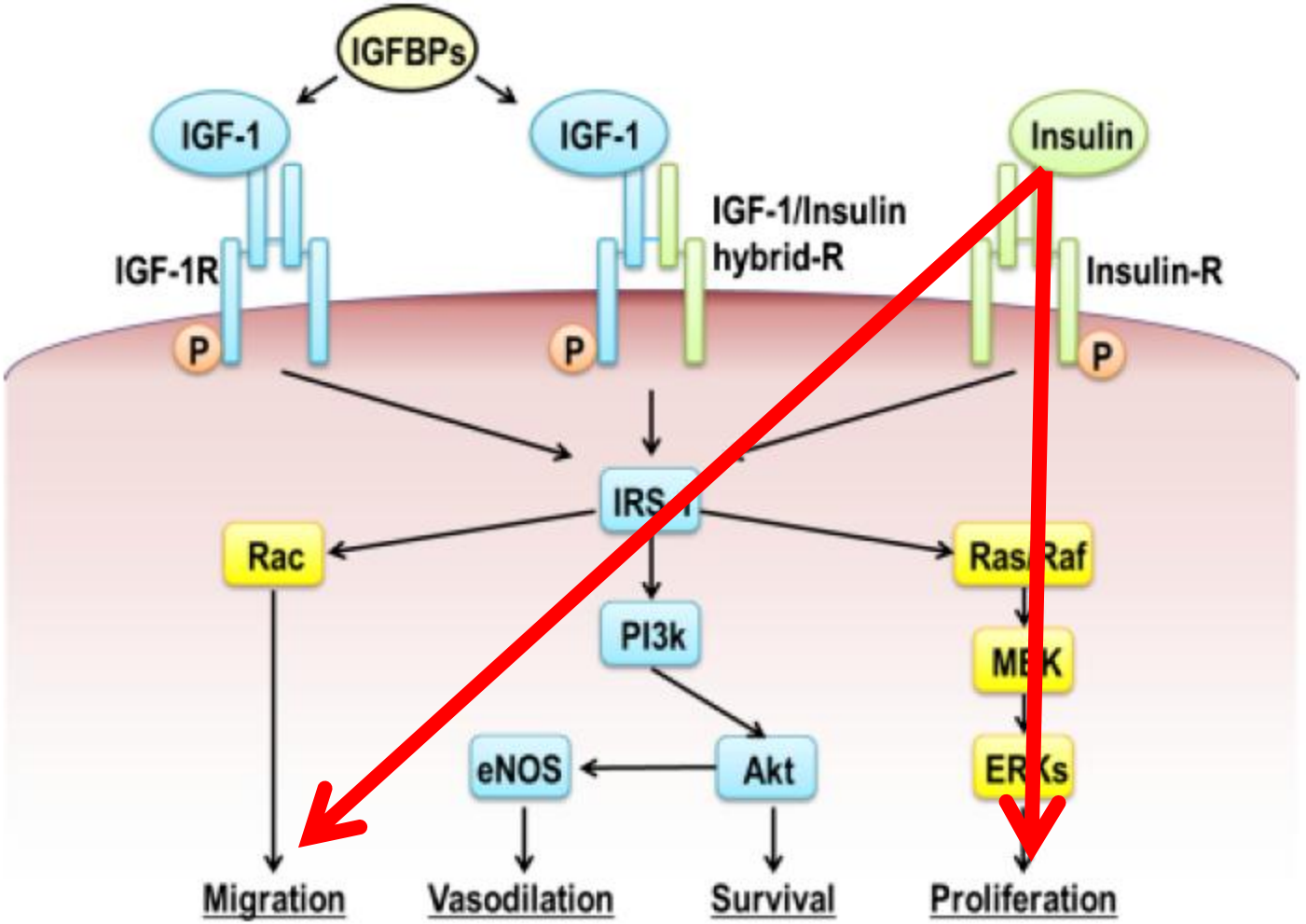



Diabetes 2016;65:1462–1471



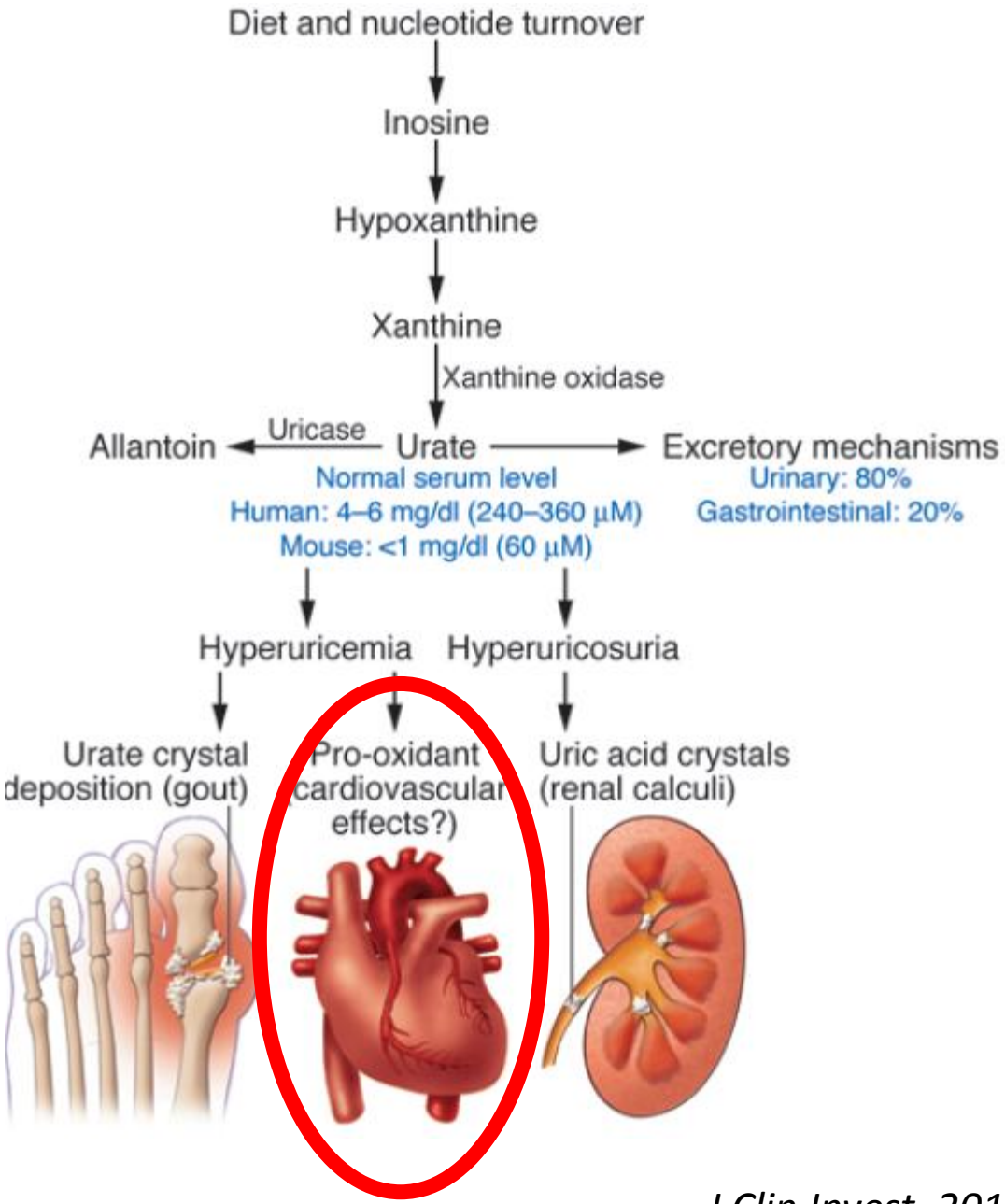

*J Gerontol A Biol Sci Med Sci. 2012 June;67A(6):626–639*

# Inzulín může skrze IRS-1 ovlivnit patogenezu aterosklerózy



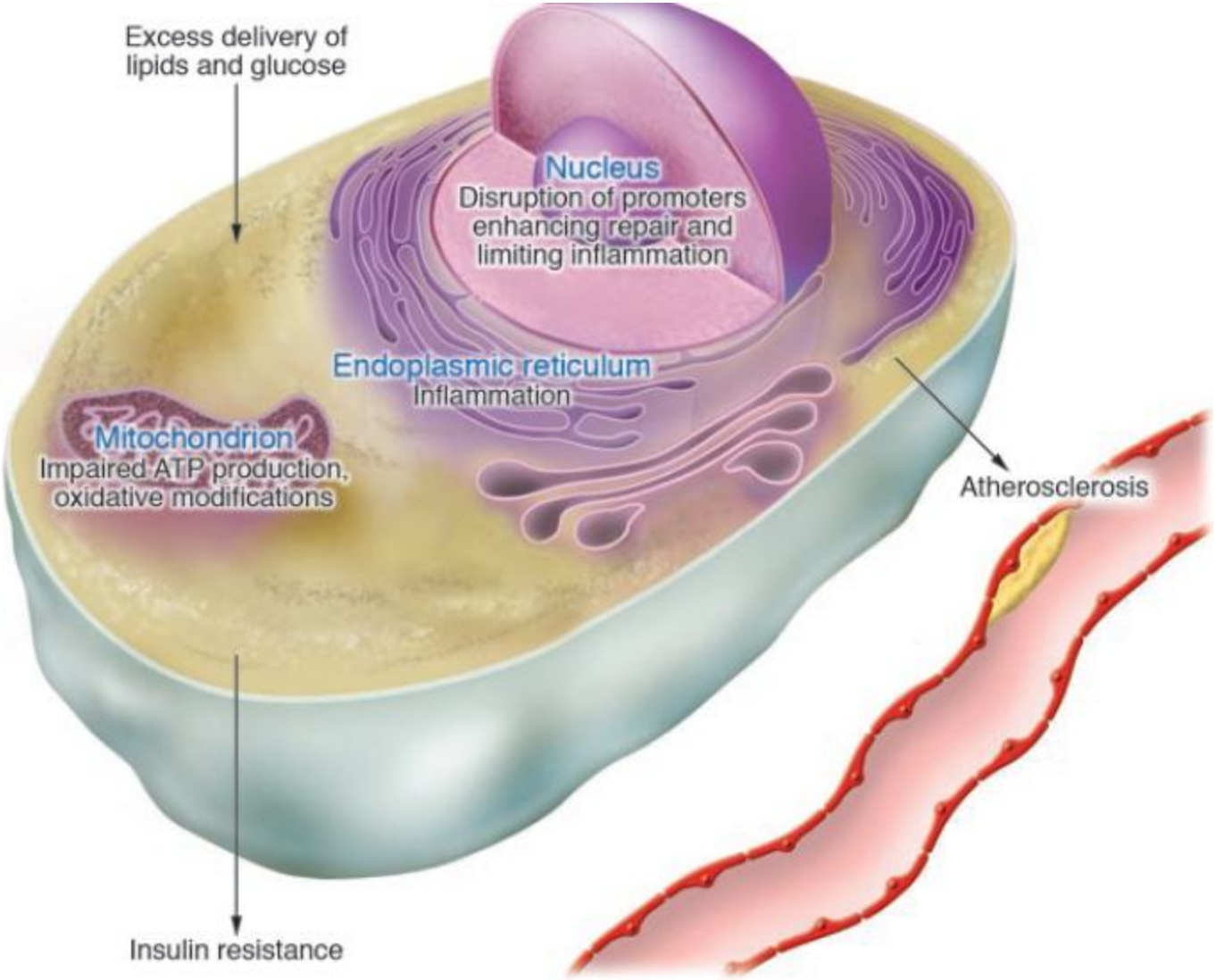

*J Gerontol A Biol Sci Med Sci. 2012 June;67A(6):626–639*

# Hyperinzulinémie zvyšuje urikémii ovlivněním vylučování urátu ledvinami




*J Clin Invest. 2010;120(6):1791–1799.*

# Exogenní hyperinzulinémie může indukovat resp. prohloubit inzulínovou rezistenci




J. Clin. Invest. 116:1813–1822 (2006).

Stroke

ARTICLES

# Relationship Between Insulin and Carotid Atherosclerosis in the General Population

## The Bruneck Study

E. Bonora, J. Willeit, S. Kiechl, F. Oberhollenzer, G. Egger, R. Bonadonna, M. Muggeo

**Hyperinzulinémie je nezávislý rizikový faktor aterosklerozy**

## Abstract

*Background and Purpose* Although several studies have investigated the association between insulin and coronary heart disease, the relationship between this hormone and carotid atherosclerosis is not well established.

*Methods* As a part of a population-based survey on atherosclerosis and its risk factors, serum insulin was measured at fasting (n=888) and at 2 hours after an oral glucose load (n=811; known diabetic subjects were excluded). The study population comprised an age- and sex-stratified random sample of men and women aged 40 to 79 years. Atherosclerosis in the common and internal carotid arteries was assessed twice (in 1990 and 1995) by ...lex sonography. Progression during the 5-year follow-up was defined by an increase in ...sclerosis score of more than the doubled measurement error (>27%) or by the ... new plaques. Subjects were stratified in quintiles according to baseline serum ins... 2 hours after glucose loading.

*Results* Logis... analysis revealed a significant association of carotid atherosclerosis with ...d high insulin (U-shaped relation). This finding was found before and after adjustmen... covariates (sex, age, body mass index, glucose tolerance, triglycerides, apolipopr... and B, fibrinogen, blood pressure status, behavioral variables, and socioeconom...). This relation applied equally to fasting and postglucose insulin and was more pronounced ... prospective analysis than in the cross-sectional analysis.

*Conclusions* We conclude that both "hypoinsulinemia" and hyperinsulinemia are independent risk indicators of carotid atherosclerosis.

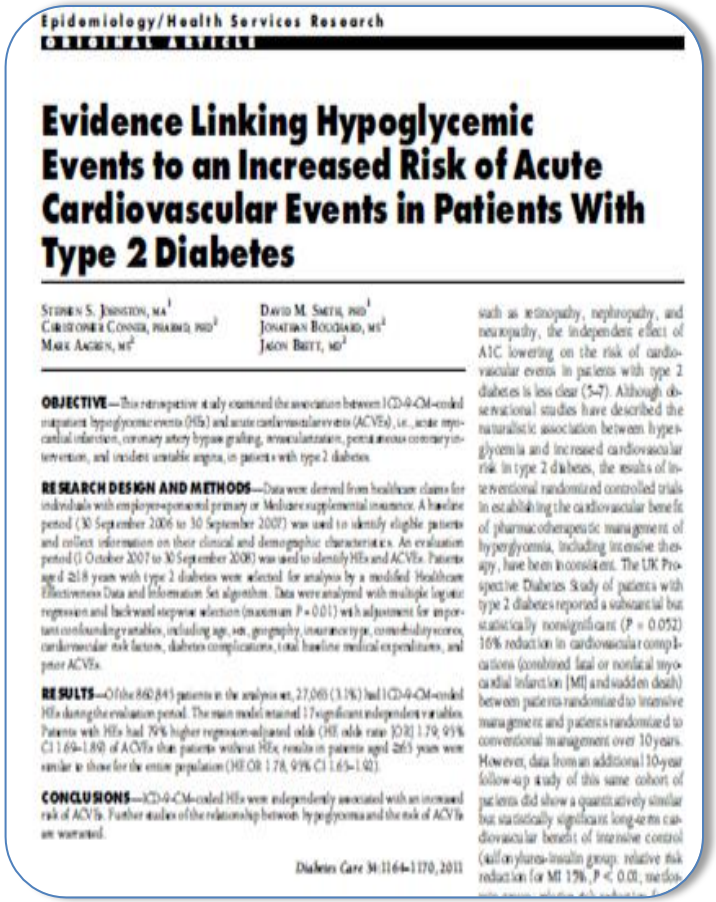
Stroke. 1997;28:1147-1152

# Proč ne inzulín?

- Inzulín je proaterogenní
- Inzulín zvyšuje riziko hypoglykémie

# Souvislost mezi hypoglykémií a vznikem akutních kardiovaskulárních příhod u diabetiků 2. typu

- **Retrospektivní, observační studie (n=860 845)**
- **3.1% pacientů prodělalo hypoglykemickou příhodu během sledovaného období (1 rok)**
- **Pacienti s hypoglykémiemi měli o 79% vyšší pravděpodobnost akutních KV příhod než pacienti bez hypoglykémií**



Epidemiology/Health Services Research

ORIGINAL ARTICLE

**Evidence Linking Hypoglycemic Events to an Increased Risk of Acute Cardiovascular Events in Patients With Type 2 Diabetes**

STEPHEN S. JOHNSTON, MA[1]
CHRISTOPHER COSTNER, PHARMD, PHD[2]
MARK ARGIRIS, MS[2]
DAVID M. SMITH, PHD[1]
JONATHAN BOUCHARD, MS[2]
JASON BRETT, MD[2]

**OBJECTIVE**—This retrospective study examined the association between ICD-9-CM–coded outpatient hypoglycemic events (HEs) and acute cardiovascular events (ACVEs), i.e., acute myocardial infarction, coronary artery bypass grafting, revascularization, percutaneous coronary intervention, and incident unstable angina, in patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—Data were derived from healthcare claims for individuals with employer-sponsored primary or Medicare supplemental insurance. A baseline period (30 September 2006 to 30 September 2007) was used to identify eligible patients and collect information on their clinical and demographic characteristics. An evaluation period (1 October 2007 to 30 September 2008) was used to identify HEs and ACVEs. Patients aged ≥18 years with type 2 diabetes were selected for analysis by a modified Healthcare Effectiveness Data and Information Set algorithm. Data were analyzed with multiple logistic regression and backward stepwise selection (maximum $P = 0.01$) with adjustment for important confounding variables, including age, sex, geography, insurance type, comorbidity scores, cardiovascular risk factors, diabetes complications, total baseline medical expenditures, and prior ACVEs.

**RESULTS**—Of the 860,845 patients in the analysis set, 27,065 (3.1%) had ICD-9-CM–coded HEs during the evaluation period. The main model retained 17 significant independent variables. Patients with HEs had 79% higher regression-adjusted odds (HE odds ratio [OR] 1.79, 95% CI 1.69–1.89) of ACVEs than patients without HEs; results in patients aged ≥65 years were similar to those for the entire population (HE OR 1.78, 95% CI 1.65–1.92).

**CONCLUSIONS**—ICD-9-CM–coded HEs were independently associated with an increased risk of ACVEs. Further studies of the relationship between hypoglycemia and the risk of ACVEs are warranted.

*Diabetes Care* 34:1164–1170, 2011

such as retinopathy, nephropathy, and neuropathy, the independent effect of A1C lowering on the risk of cardiovascular events in patients with type 2 diabetes is less clear (5–7). Although observational studies have described the naturalistic association between hyperglycemia and increased cardiovascular risk in type 2 diabetes, the results of interventional randomized controlled trials in establishing the cardiovascular benefit of pharmacotherapeutic management of hyperglycemia, including intensive therapy, have been inconsistent. The UK Prospective Diabetes Study of patients with type 2 diabetes reported a substantial but statistically nonsignificant ($P = 0.052$) 16% reduction in cardiovascular complications (combined fatal or nonfatal myocardial infarction [MI] and sudden death) between patients randomized to intensive management and patients randomized to conventional management over 10 years. However, data from an additional 10-year follow-up study of this same cohort of patients did show a quantitatively similar but statistically significant long-term cardiovascular benefit of intensive control (sulfonylurea-insulin group: relative risk reduction for MI 15%, $P < 0.01$; metfor-

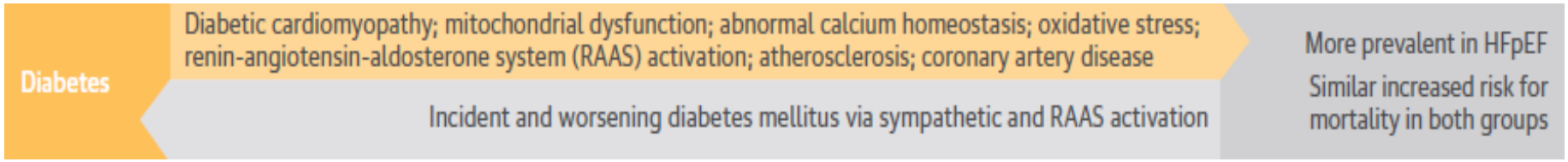
*Diabetes Care* 2011;34:1164–70

# Proč ne inzulín?

- Inzulín je proaterogenní
- Inzulín zvyšuje riziko hypoglykémie
- **Inzulín zvyšuje riziko srdečního selhání**

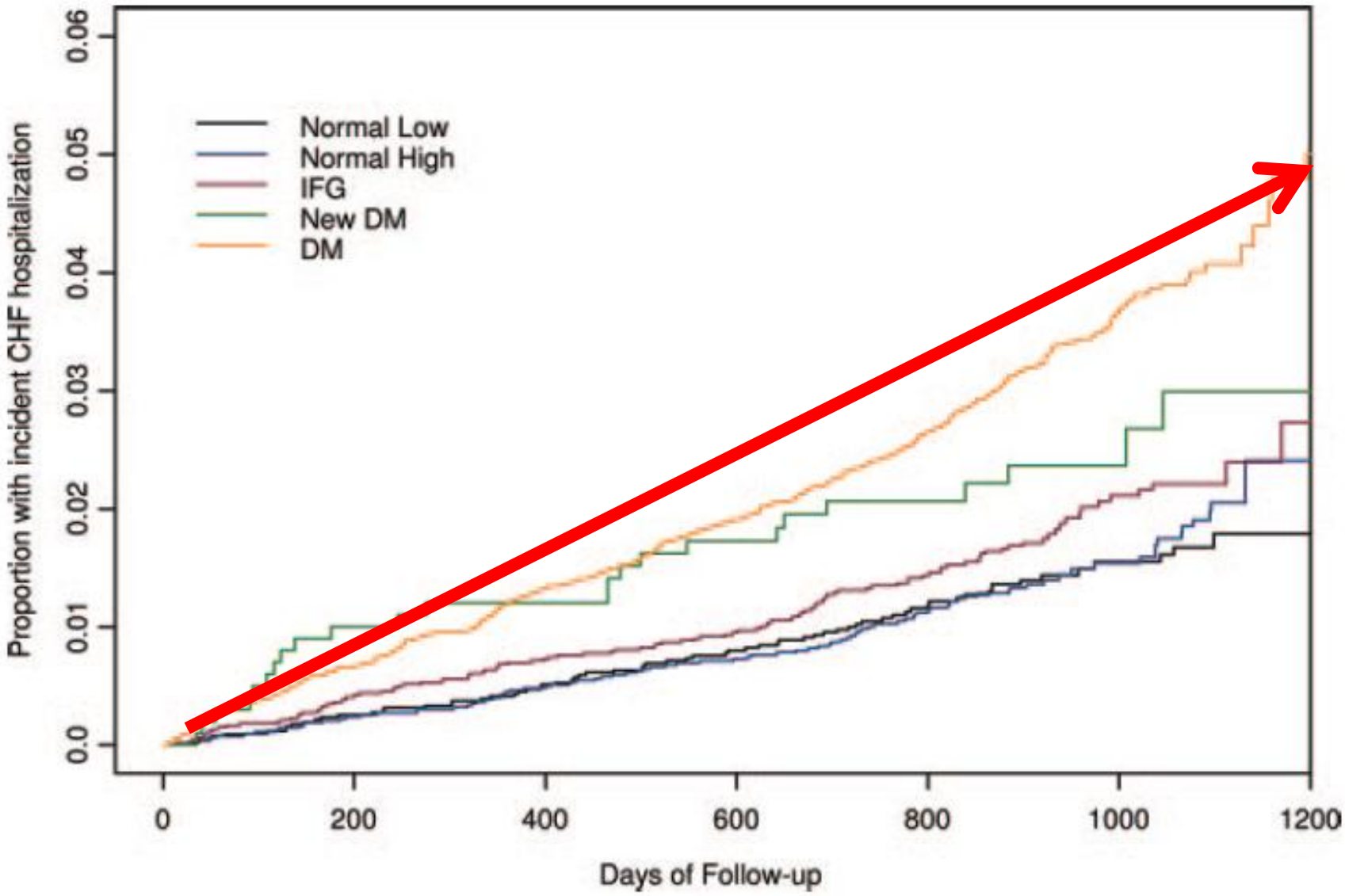
# Diabetes mellitus a srdeční selhání

- **Diabetes mellitus zvyšuje riziko srdečního selhání**




*J Am Coll Cardiol 2014;64:2281–93*
*J Am Coll Cardiol 2012;59:998–1005*
*J Am Coll Cardiol 2007;50:768–77*
*J Am Coll Cardiol 2006;47:76–84*

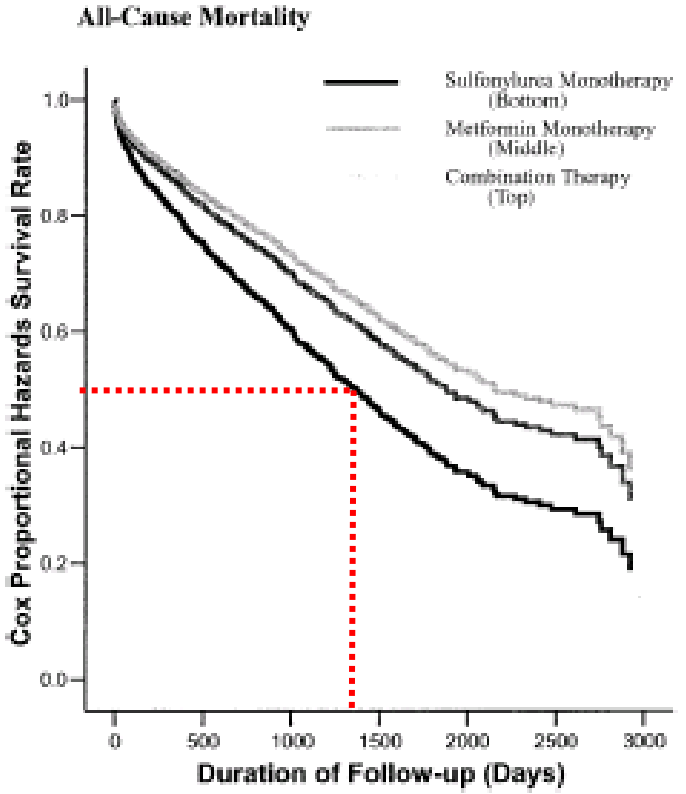
# Glucose Levels Predict Hospitalization for Congestive Heart Failure in Patients at High Cardiovascular Risk




Circulation. 2007;115:1371-1375

# Diabetes mellitus a srdeční selhání

- Diabetes mellitus zvyšuje riziko srdečního selhání
- **Přítomnost srdečního selhání zvyšuje mortalitu pacientů s diabetem**




*Diabetes Care 28:2345–2351, 2005*
*Eur Heart J 2008;29:1377–85*
*Eur Heart J 2004;25:656–62*

# Diabetes mellitus a srdeční selhání

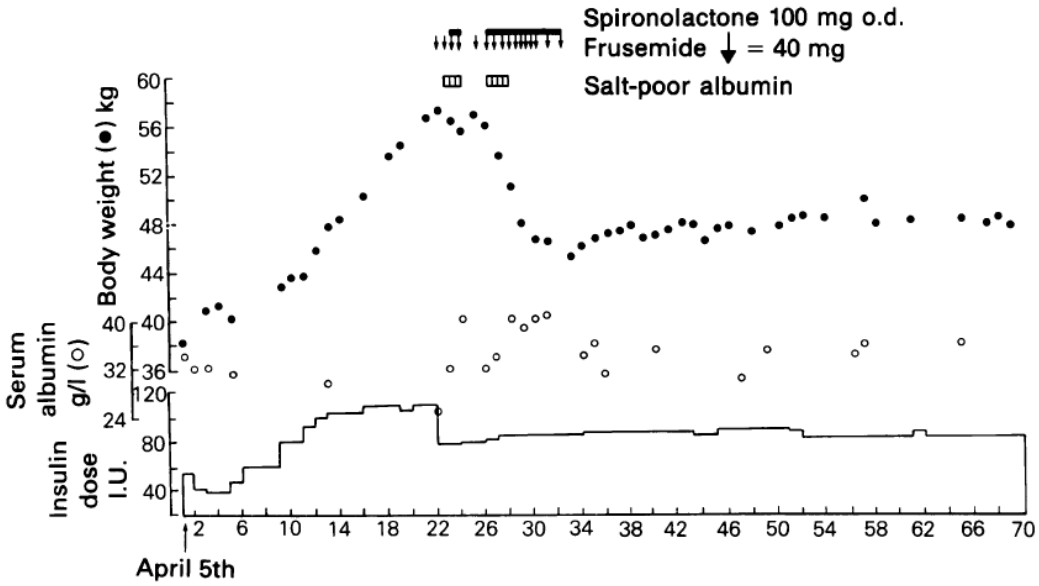
- Diabetes mellitus zvyšuje riziko srdečního selhání
- Přítomnost srdečního selhání zvyšuje mortalitu pacientů s diabetem
- **Inzulín snižuje natriurézu a zvyšuje retenci vody**

***Saudek CD, Boulter PR, Knopp RH, Arky RA.***
***Sodium retention accompanying insulin treatment of diabetes mellitus.***
***Diabetes. 1974 Mar;23(3):240-6***

# Diabetes mellitus a srdeční selhání

- Diabetes mellitus zvyšuje riziko srdečního selhání
- Přítomnost srdečního selhání zvyšuje mortalitu pacientů s diabetem
- Inzulín snižuje natriurézu a zvyšuje retenci vody
- **Iniciace intenzivní terapie inzulínem může být kausální příčinou manifestace srdečního selhání u pacientů s hyperglykémií a glykosúrií indukovanou osmotickou diurézou**

*Nord Med. 1955 Jan 13;53(2):58-9*
*Am J Med. 1985 Jul;79(1):147-8*



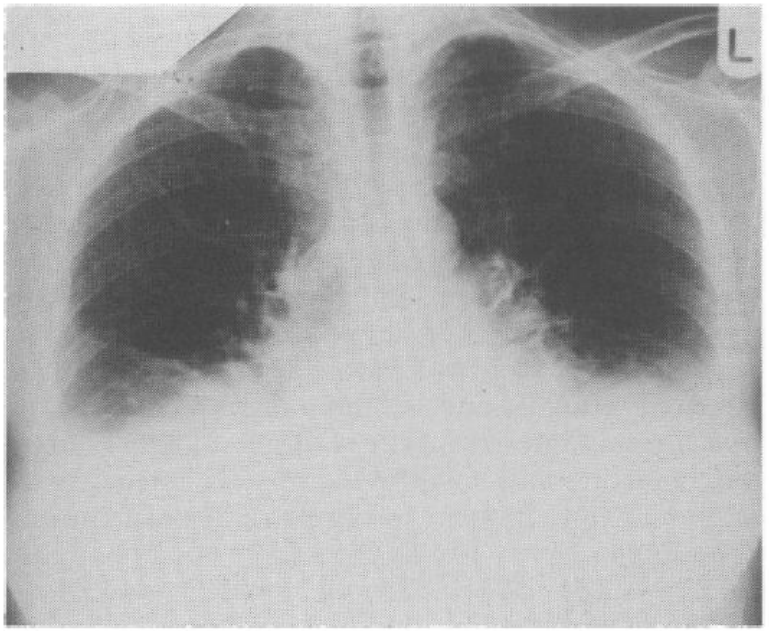



**Figure 2** Chest X-ray at day 22 of admission, showing bilateral pleural effusions and peri-hilar shadowing.

# Insulin oedema

David J. Evans, Kathryn Pritchard-Jones and Beatrice Trotman-Dickenson

*John Radcliffe Hospital, Headington, Oxford, UK.*

**Summary: A 35 year old markedly underweight woman presented with uncontrolled diabetes. Following insulin therapy she developed gross fluid retention with extensive peripheral oedema, bilateral pleural effusions and weight gain of 18.8 kg in 22 days, accompanied by a fall in plasma albumin. She responded well to treatment with diuretics and salt-poor albumin, losing 10.3 kg in 6 days without recurrence of oedema. Severe insulin oedema is an uncommon complication of insulin therapy and may be due to effects of insulin on both vascular permeability and the renal tubule.**

Postgrad Med J. 1986;62(729): 665-8.

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International Diabetes Federation

# Prediction of heart failure in patients with type 2 diabetes mellitus—A systematic review and meta-analysis

Ying Wang, Tomoko Negishi, Kazuaki Negishi, Thomas H. Marwick *

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Type 2 diabetes mellitus
Heart failure
Predictor
Risk factors

ABSTRACT

Background: Heart failure (HF) is a major cause of mortality and disability in type 2 diabetes mellitus (T2DM). This study sought to improve the assessment of HF risk in patients with T2DM—a step that would be critical for effective HF screening.

Methods: A systematic literature search was performed on electronic databases including MEDLINE and EMBASE, using MeSH terms 'heart failure', 'risk factor', 'T2DM', 'cardiac dysfunction', 'stage B heart failure', 'incident heart failure', 'risk assessment', 'risk impact', 'risk score', 'predictor', 'prediction' and related free text terms. The search was limited to human studies in full-length publications in English language journal from 1946 to 2014. Univariable and multivariable relative risk (RR) and hazard ratio (HR) were obtained from each study.

Results: Twenty-one studies (n = 1111,569, including 507,637 subjects with T2DM) were included in this analysis with a follow-up ranging from 1 to 12 years. Associations between incident HF and risk variables described in ≥3 studies were reported. This association was greatest for insulin use (HR 2.48; 1.24–4.99), HbA1c 7.0–8.0% (2.41; 1.62–3.59), 5 years increase in age (1.47; 1.25–1.73), fasting glucose (1.28; 1.10–1.51 per standard deviation) and HbA1c (1.18; 1.14–1.23 each 1% increase). After adjustment for confounders, there were strong associations with coronary artery disease (1.77; 1.31, 2.39), HbA1c ≥ 10% (1.66; 1.45–1.89), insulin use (1.43; 1.14–1.79), HbA1c 9.0–10.0% (1.31; 1.14–1.50), fasting glucose (1.27; 1.10–1.47 per standard deviation) and 5 years increase in age (1.26; 1.13–1.40).

Conclusion: Among patients with T2DM, five common clinical variables are associated with significantly increased risk of incident HF.



**This association was greatest for**

**- insulin use (HR 2.48; 1.24–4.99)**

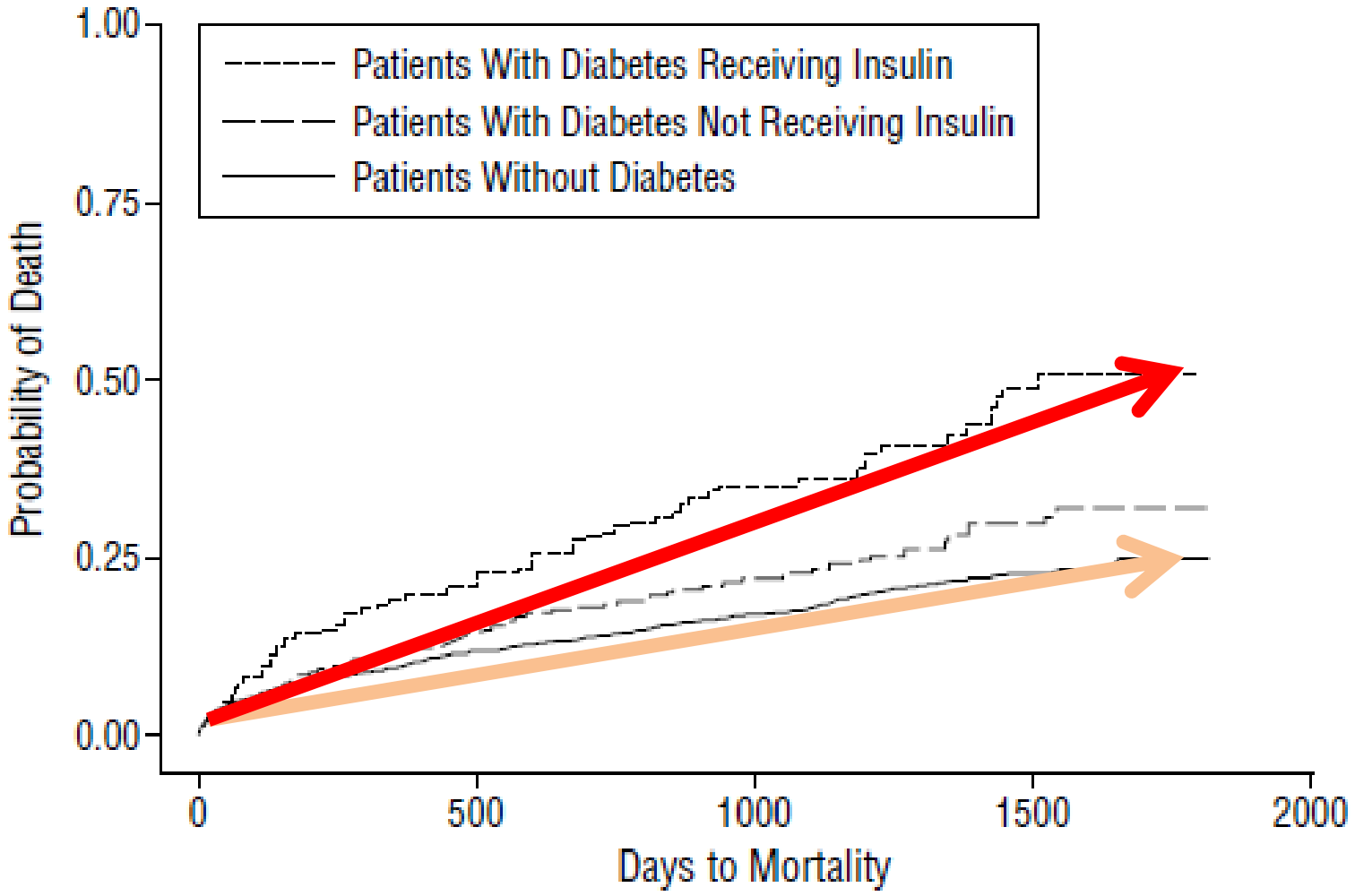
**- HbA1c 7.0–8.0% (2.41; 1.62–3.59),**

**- 5 years increase in age (1.47; 1.25–1.73)**

**Po adjustaci**

**insulin use (1.43; 1.14–1.79)**

Diabetes Res Clin Pract. 2015 Apr;108(1):55-66.



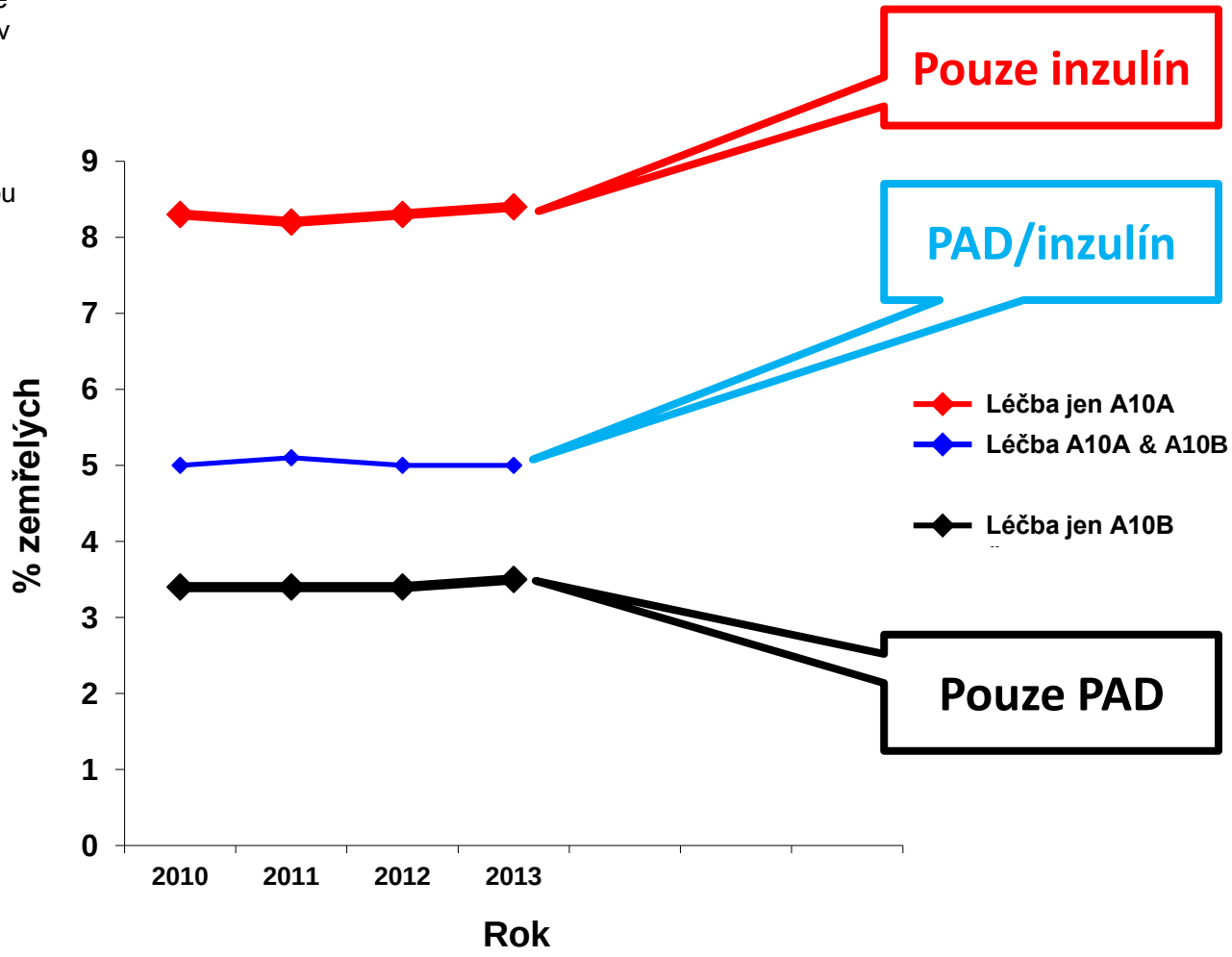

Arch Intern Med. 2004;164:2273-2279

# Proč ne inzulín?

- Inzulín je proaterogenní
- Inzulín zvyšuje riziko hypoglykémie
- Inzulín zvyšuje riziko srdečního selhání
- Pacienti léčení inzulínem mají vyšší mortalitu

# Celková mortalita pacientů se zaznamenanou antidiabetickou terapií v letech 2010–2013 (n=440 669 v r. 2013)

Pacient je do jedné ze čtyř definovaných skupin přiřazen vždy na základě zaznamenané terapie jak v daném roce tak i v roce předcházejícím. Pro přiřazení pacienta do určité skupiny je tedy nutné, aby měl pacient záznam o dané terapii alespoň v jednom z těchto dvou let.




Zdroj: data VZP

# Může být něco temnějšího?