La terapia insulinica è ancora il gold standard?

E. Guastamacchia

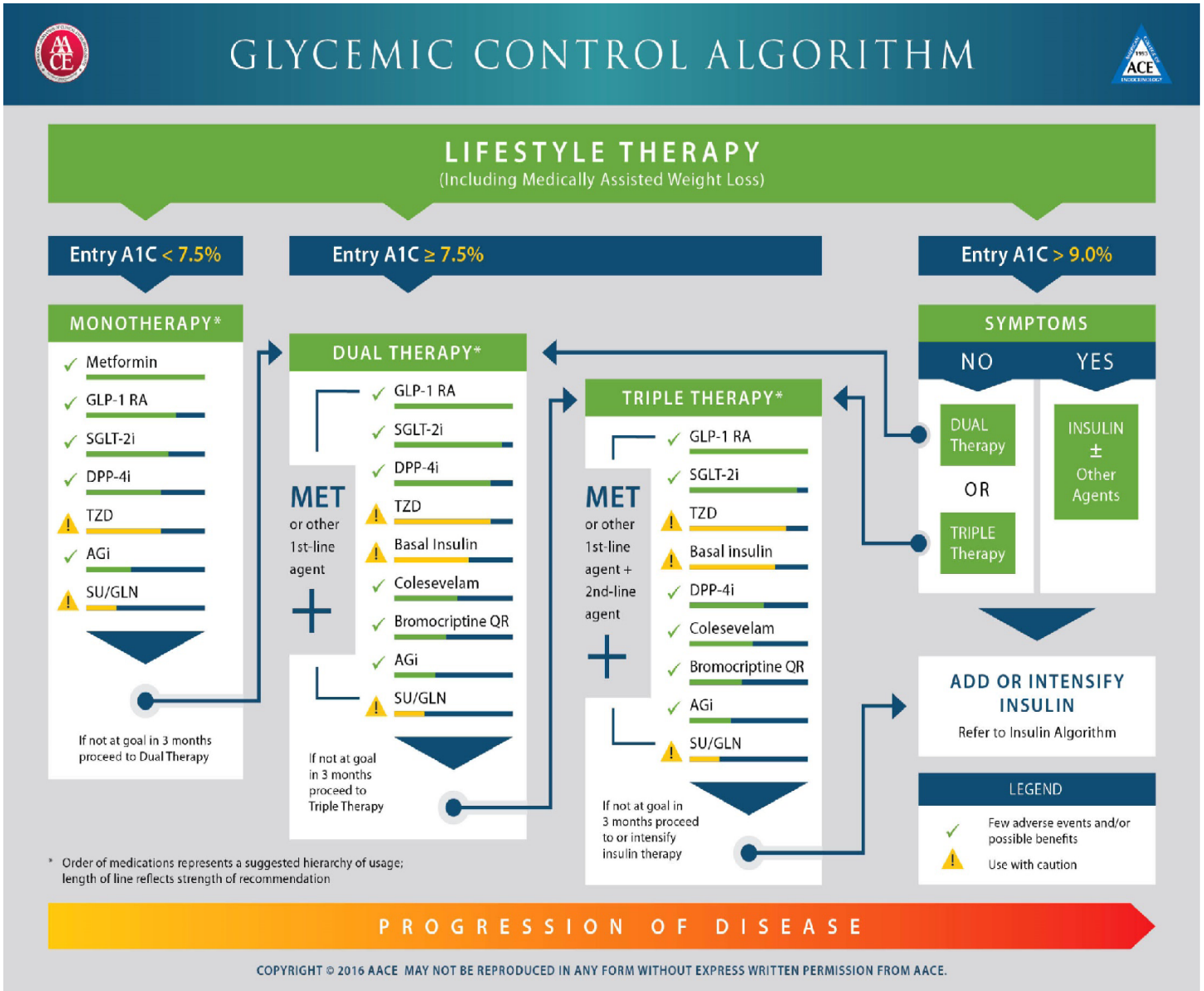
Università degli Studi di Bari
"Aldo Moro"

Conflitti di interesse

- Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Lilly

DM2: raccomandazioni AME-AACE
Quale terapia antidiabetica?



Cardiovascular effects of basal insulins

Edoardo Mannucci[1]
Stefano Giannini[2]
Ilaria Dicembrini[1]

Drug, Healthcare and Patient Safety 2015:7 113–120

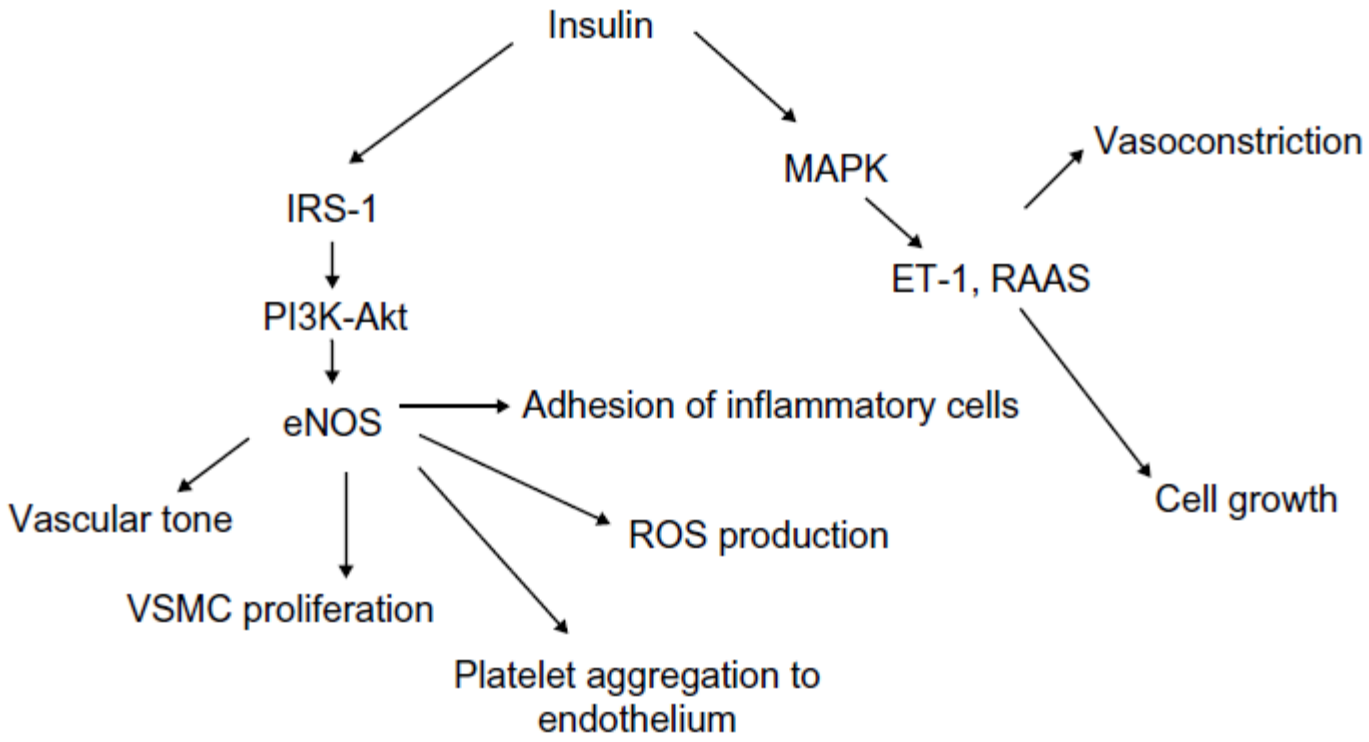
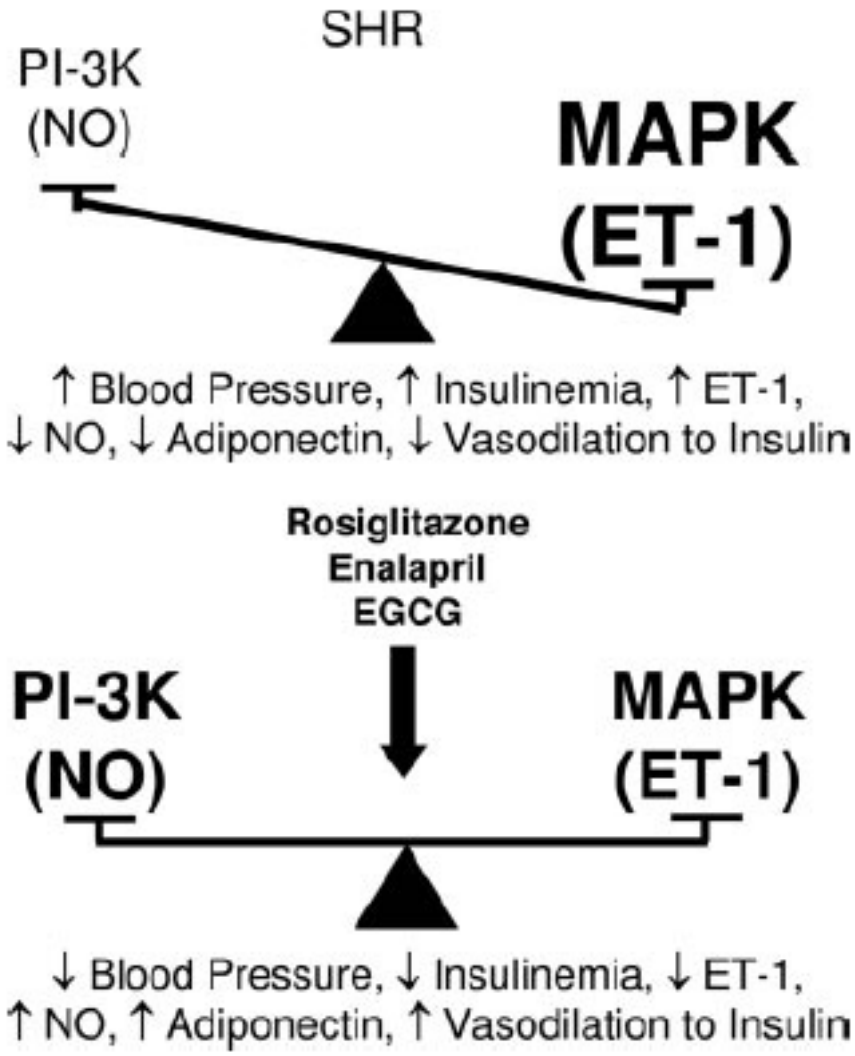


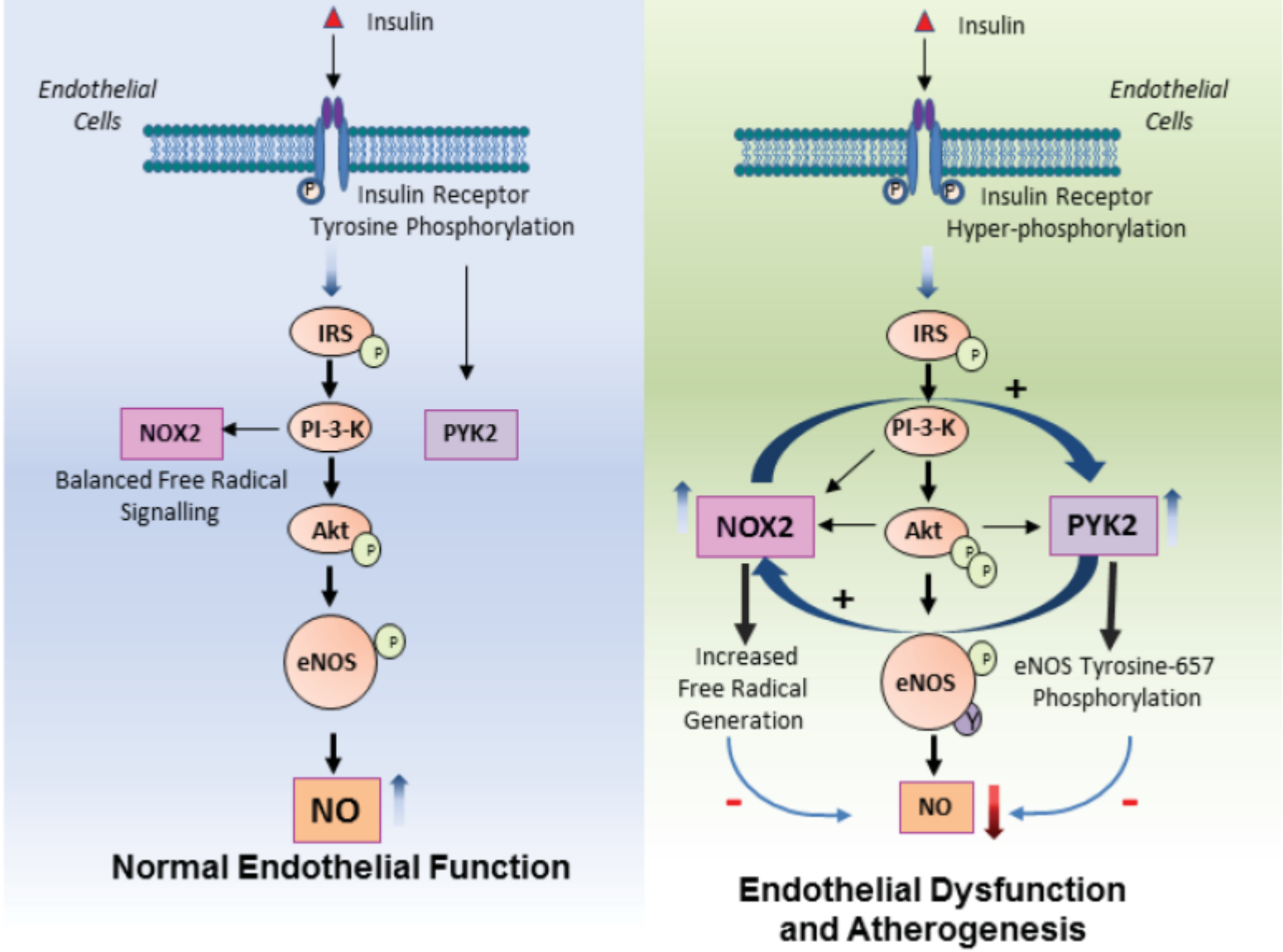
Figure 1 Cardiovascular effects of insulin: molecular mechanisms.
Abbreviations: Akt, Protein kinase B; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase; VSMC, vascular smooth muscle cell; ROS, reactive oxygen species; ET-1, endothelin-1; RAAS, renin-angiotensin-aldosterone system.

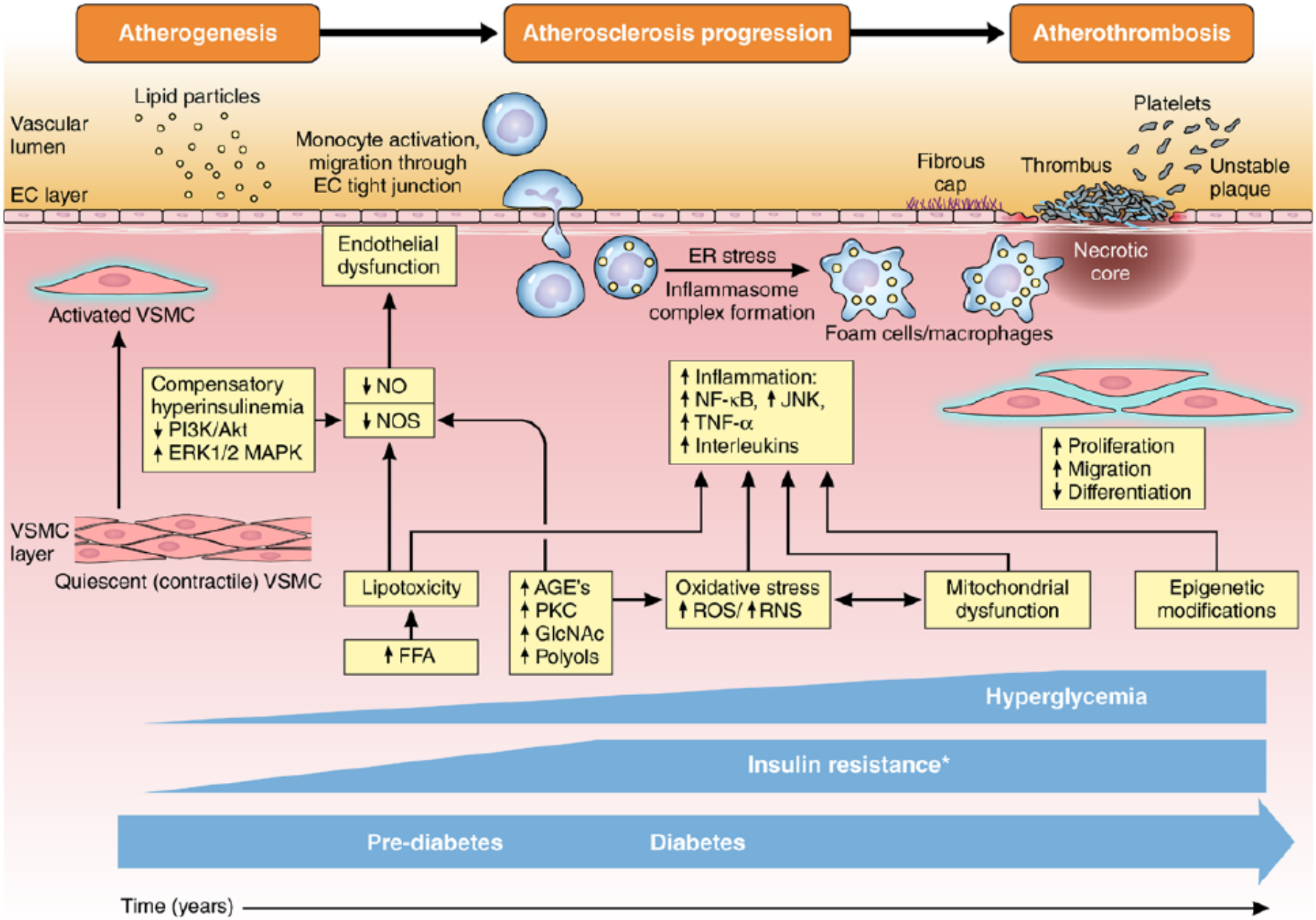


Muniyappa *Endocrine Reviews* 28: 463–491, 2007

FIG. 5. SHRs are an animal model of the metabolic syndrome with hypertension, hyperinsulinemia, insulin resistance, overweight, elevated ET-1 levels, and decreased adiponectin levels. There is decreased vasodilator response to insulin due to decreased PI3K tone and elevated ET-1 levels due to increased MAPK tone. After treatment of SHRs with rosiglitazone, enalapril, or EGCG for 3 wk, blood pressure, insulin levels, and ET-1 levels are lower, whereas adiponectin levels and insulin sensitivity are increased. Increased vasodilator response to insulin is consistent with rebalancing between PI3K and MAPK branches of insulin signaling.

Selective Enhancement of Insulin Sensitivity in the Endothelium In Vivo Reveals a Novel Proatherosclerotic Signalling Loop

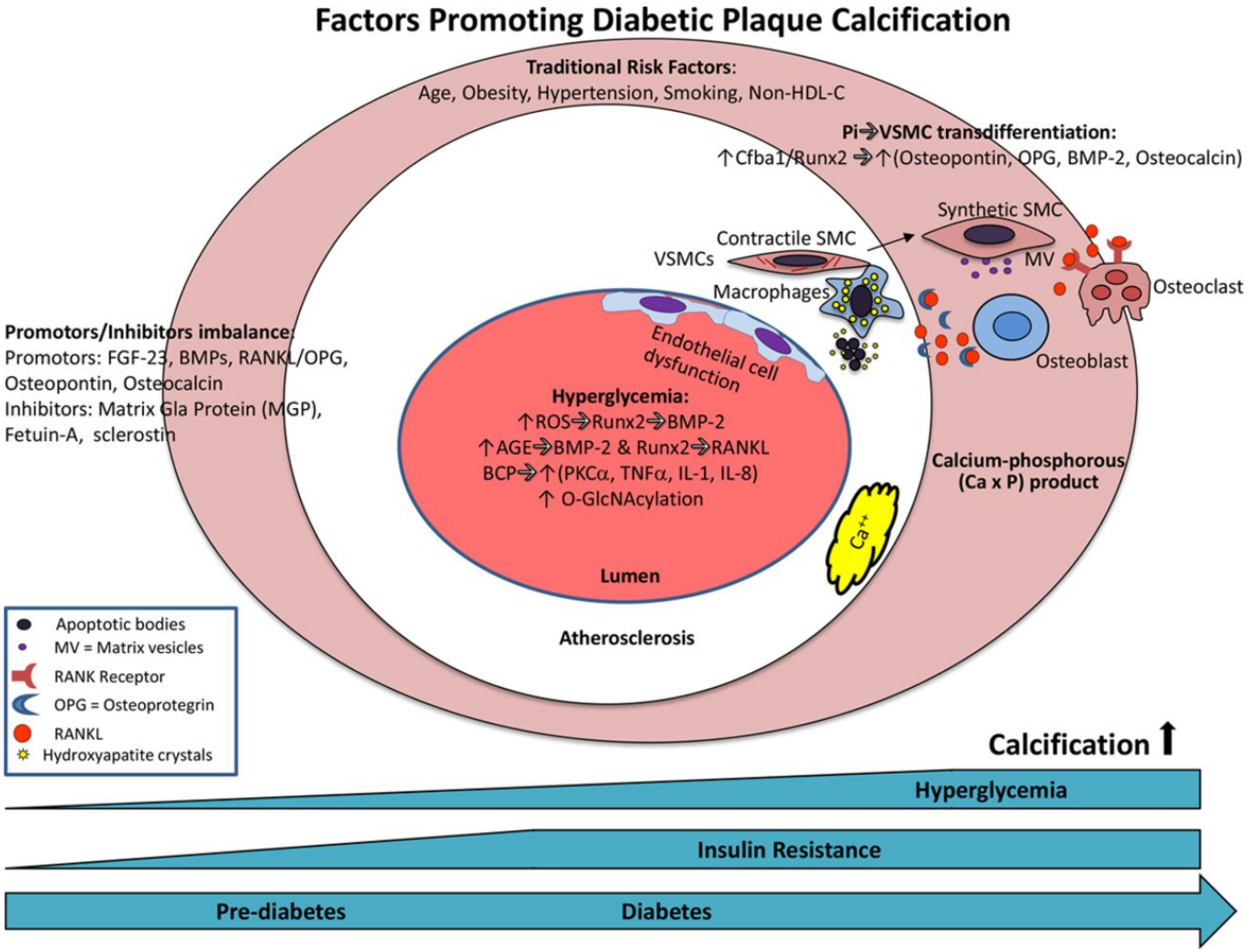




*Systemic and tissue-specific insulin resistance

Low Wang et al
Circulation. 2016;133:2459–2502.

Mechanisms of plaque calcification in diabetes mellitus.



Kazuyuki Yahagi et al. Arterioscler Thromb Vasc Biol. 2017;37:191-204

Iatrogenic hyperinsulinemia in type 1 diabetes: Its effect on atherogenic risk markers ☆

May-Yun Wang [a], Xinxin Yu [a], Young Lee [a], S. Kay McCorkle [c], Gregory O. Clark [b], Suzanne Strowig [b], Roger H. Unger [a,c], Philip Raskin [b,*]

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ABSTRACT

Aims: Insulin is lipogenic and may invoke inflammation. We wished to determine if well controlled human and mice with type 1 diabetes had iatrogenic hyperinsulinemia as an explanation for the increased rate of coronary artery disease (CAD) in type 1 diabetes.
Methods: Type 1 diabetic subjects with HbA1C less than 7.0% had plasma insulin measured before and one hour after a Boost® challenge and a dose of subcutaneously administered insulin. These levels were compared with non-diabetic humans. Plasma insulin levels in well controlled NOD mice with type 1 diabetes were measured 3h and 17h after their usual dose of insulin. Hepatic cholesterol-relevant CAD and inflammation markers were measured in the NOD mice.
Result: Marked iatrogenic hyperinsulinemia was observed in patients at levels of approximately two times higher than in non-diabetic controls. Similar findings were present in the NOD mice. Hepatic CAD risk markers were increased by insulin, but did not exceed normal expression levels in non-diabetic mice with lower insulin. In contrast, insulin-mediated stimulation of pro-inflammatory mediators TNF-α and IL-1β remained significantly higher in hyperinsulinemic NOD than non-diabetic mice.
Conclusion: Optimal insulin therapy in mice and humans with type 1 diabetes causes iatrogenic hyperinsulinemia and subsequently promotes pro-inflammatory macrophage response independent of hepatic cholesterol-relevant CAD markers. The tight glycemic control in type 1 diabetes may thus increase the risk for atherogenesis via inflammation.

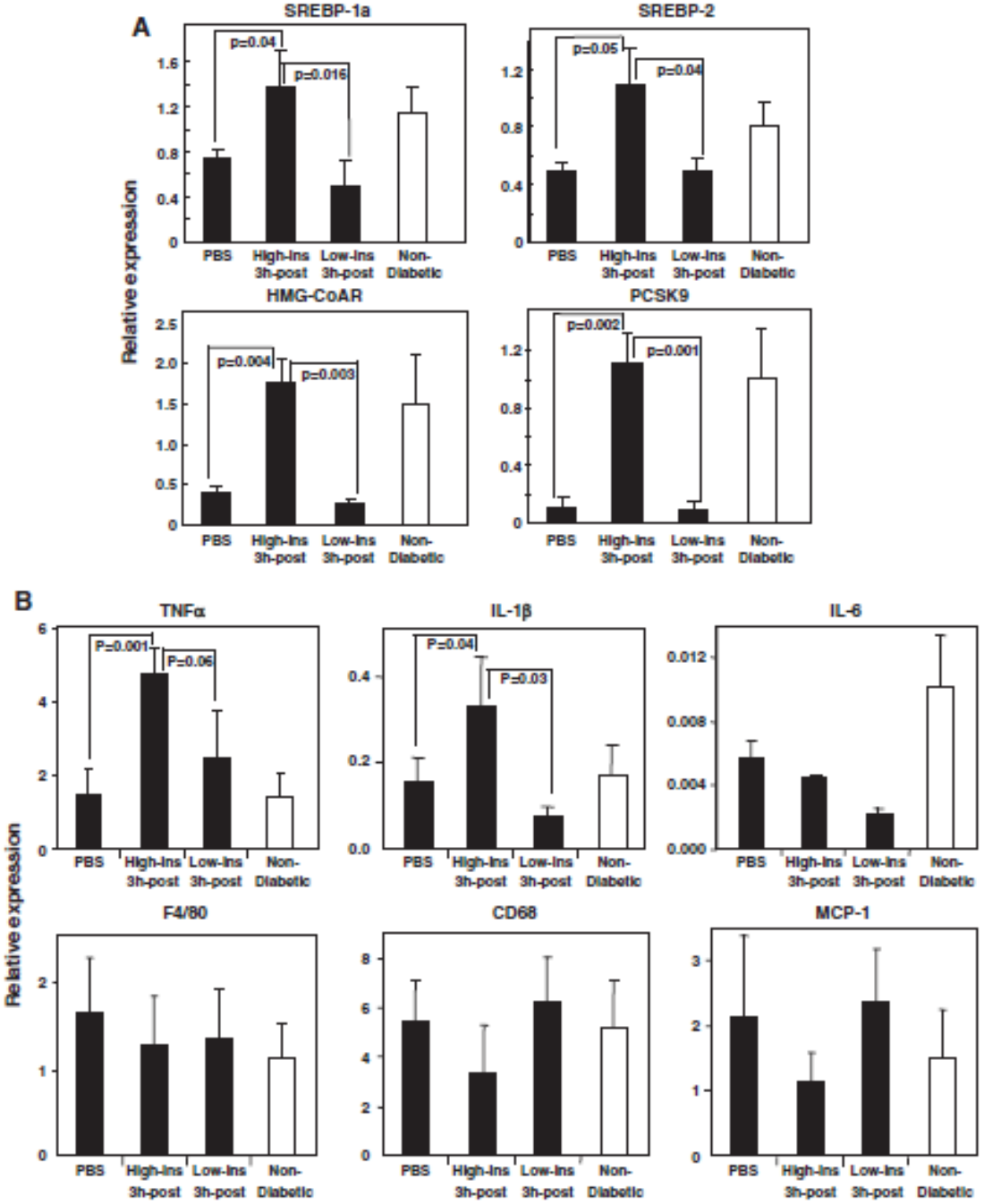


Fig 4. (A) Hepatic mRNA expression of cholesterologenic transcription factors SREBP-2 and SREBP-1a, and their targets, HMG-CoA reductase and PCSK9. Diabetic NOD mice (black) were subcutaneously injected with high (0.2 U) or low (0.02 U) insulin, or PBS twice daily for one month. Non-diabetic NOD mice (white) are used as controls ($n=12$). (B) Hepatic mRNA expression of inflammatory mediators TNF-α, IL-1β and IL6, macrophage markers F4/80 and CD68, as well as chemokine MCP-1. Mice were treated as described in Fig. 4A.

Authoritative Review

Clinical Update: Cardiovascular Disease in Diabetes Mellitus

Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus – Mechanisms, Management, and Clinical Considerations

Cecilia C. Low Wang, MD; Connie N. Hess, MD, MHS; William R. Hiatt, MD; Allison B. Goldfine, MD

Abstract—Cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus. Diabetes mellitus exacerbates mechanisms underlying atherosclerosis and heart failure. Unfortunately, these mechanisms are not adequately modulated by therapeutic strategies focusing solely on optimal glycemic control with currently available drugs or approaches. In the setting of multifactorial risk reduction with statins and other lipid-lowering agents, antihypertensive therapies, and antihyperglycemic treatment strategies, cardiovascular complication rates are falling, yet remain higher for patients with diabetes mellitus than for those without. This review considers the mechanisms, history, controversies, new pharmacological agents, and recent evidence for current guidelines for cardiovascular management in the patient with diabetes mellitus to support evidence-based care in the patient with diabetes mellitus and heart disease outside of the acute care setting. (*Circulation*. 2016;133:2459–2502. DOI: 10.1161/CIRCULATIONAHA.116.022194.)

Key Words: cardiovascular diseases ■ diabetes mellitus ■ drugs ■ heart failure ■ trials

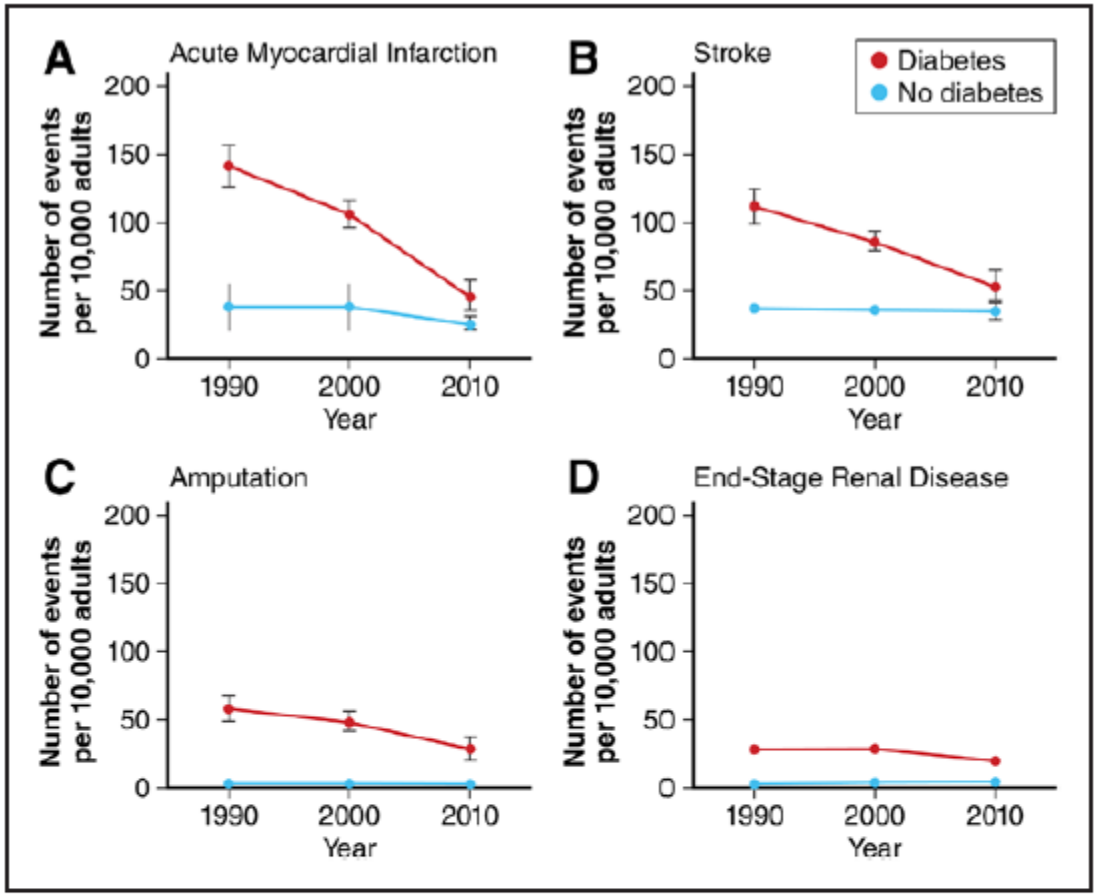


Figure 1. Rates of vascular diseases are decreasing in persons with diabetes mellitus but are still higher than in persons without diabetes mellitus: 20 years of surveillance. Age-standardized rates of selected vascular diseases in individuals with or without diabetes mellitus in the years 1990, 2000, and 2010. **A**, Acute myocardial infarction. **B**, Stroke. **C**, Amputation. **D**, End-stage renal disease. Red indicates individuals with diabetes mellitus; blue, individuals without diabetes mellitus. Error bars indicate 95% confidence intervals. Adapted from Gregg et al with permission of the publisher. Copyright ©2014, Massachusetts Medical Society.

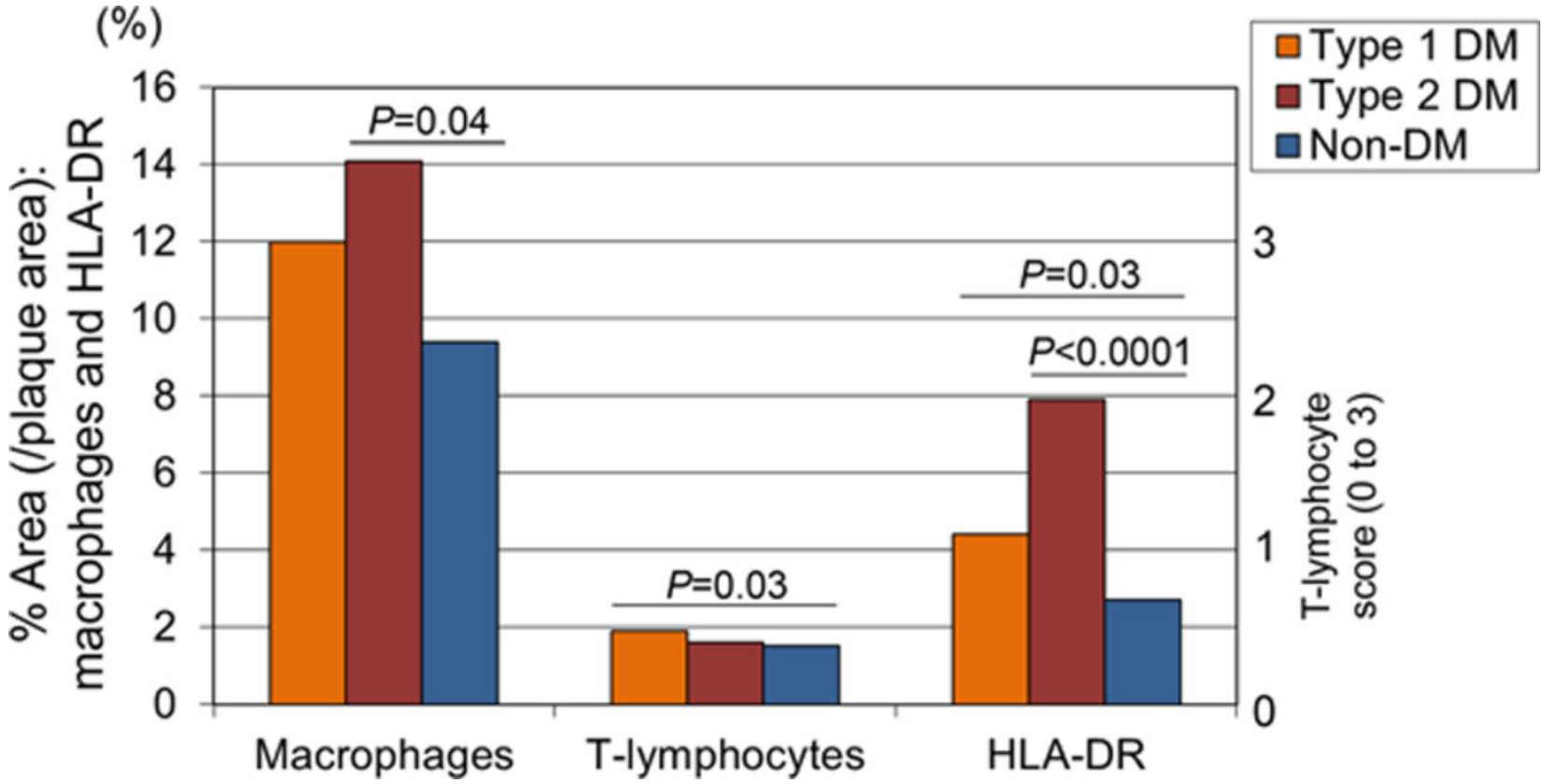
Low Wang et al
Circulation. 2016;133:2459–2502.

Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes MellitusHighlights

by Kazuyuki Yahagi, Frank D. Kolodgie, Christoph Lutter, Hiroyoshi Mori, Maria E. Romero, Aloke V. Finn, and Renu Virmani

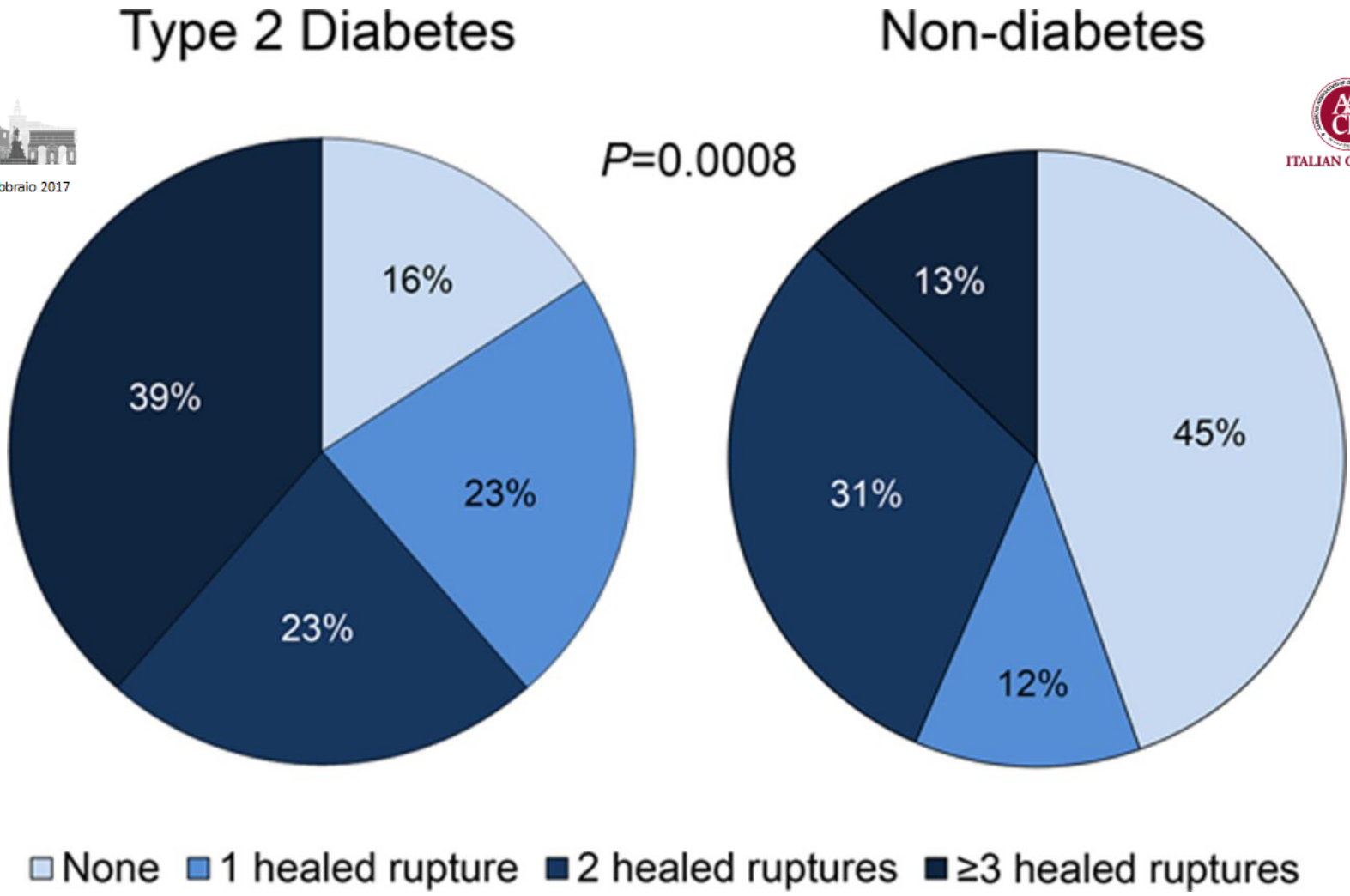
Arterioscler Thromb Vasc Biol
Volume 37(2):191-204
January 25, 2017

Inflammation in diabetic coronary arteries.



Kazuyuki Yahagi et al. Arterioscler Thromb Vasc Biol. 2017;37:191-204

The pie charts reflect the percentage of healed ruptures (HPR) per heart relative to diabetic status at autopsy.

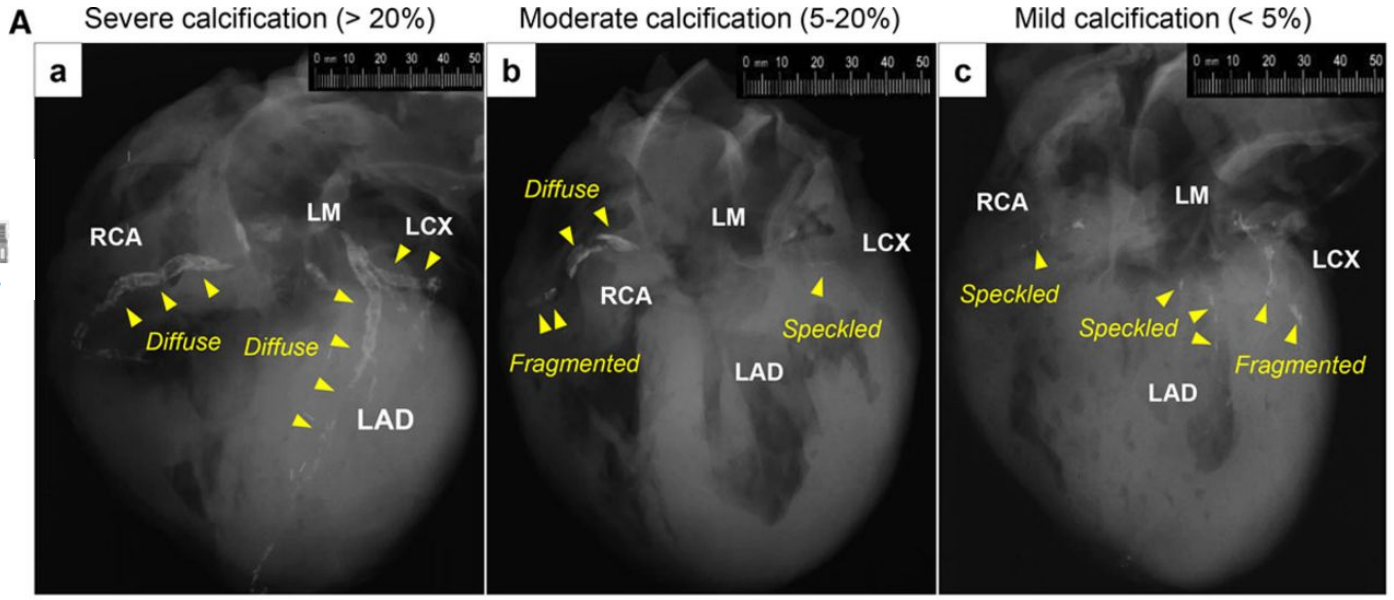


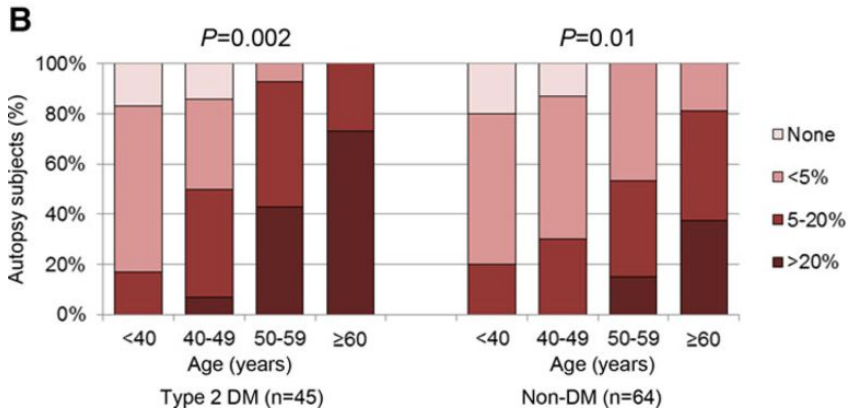
Bologna, 10-11 febbraio 2017

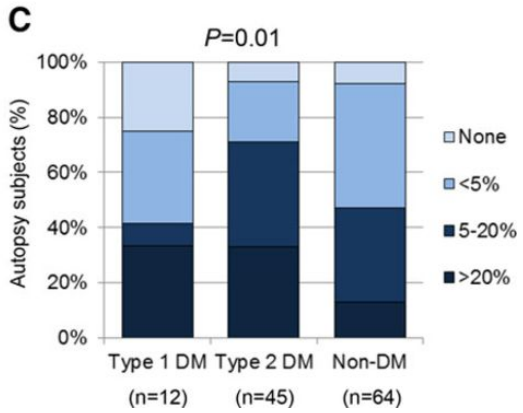
ITALIAN CHAPTER

Kazuyuki Yahagi et al. Arterioscler Thromb Vasc Biol. 2017;37:191-204

Coronary artery calcification in sudden coronary death evaluated by postmortem radiography.







Kazuyuki Yahagi et al. Arterioscler Thromb Vasc Biol. 2017;37:191-204

Figure 5. Randomized, controlled, cardiovascular outcome trials of glucose-lowering drugs or strategies in people with type 2 diabetes mellitus. ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease including myocardial infarction or ischemic stroke; CV risk, increased risk for cardiovascular disease based on risk factors, but not ischemic ASCVD; HR, hazard ratio; MACE, major adverse cardiovascular event: cardiovascular mortality, myocardial infarction, stroke; RRR, relative risk reduction; SFU, sulfonylurea; and T_2DM, type 2 diabetes mellitus. Studies: ACCORD indicates Action to Control Cardiovascular Risk in Diabetes[333]; ACCORDION, ACCORD Follow-on study[391]; ADDITION, Intensive Treatment in People With Screen Detected Diabetes (*Continued*)

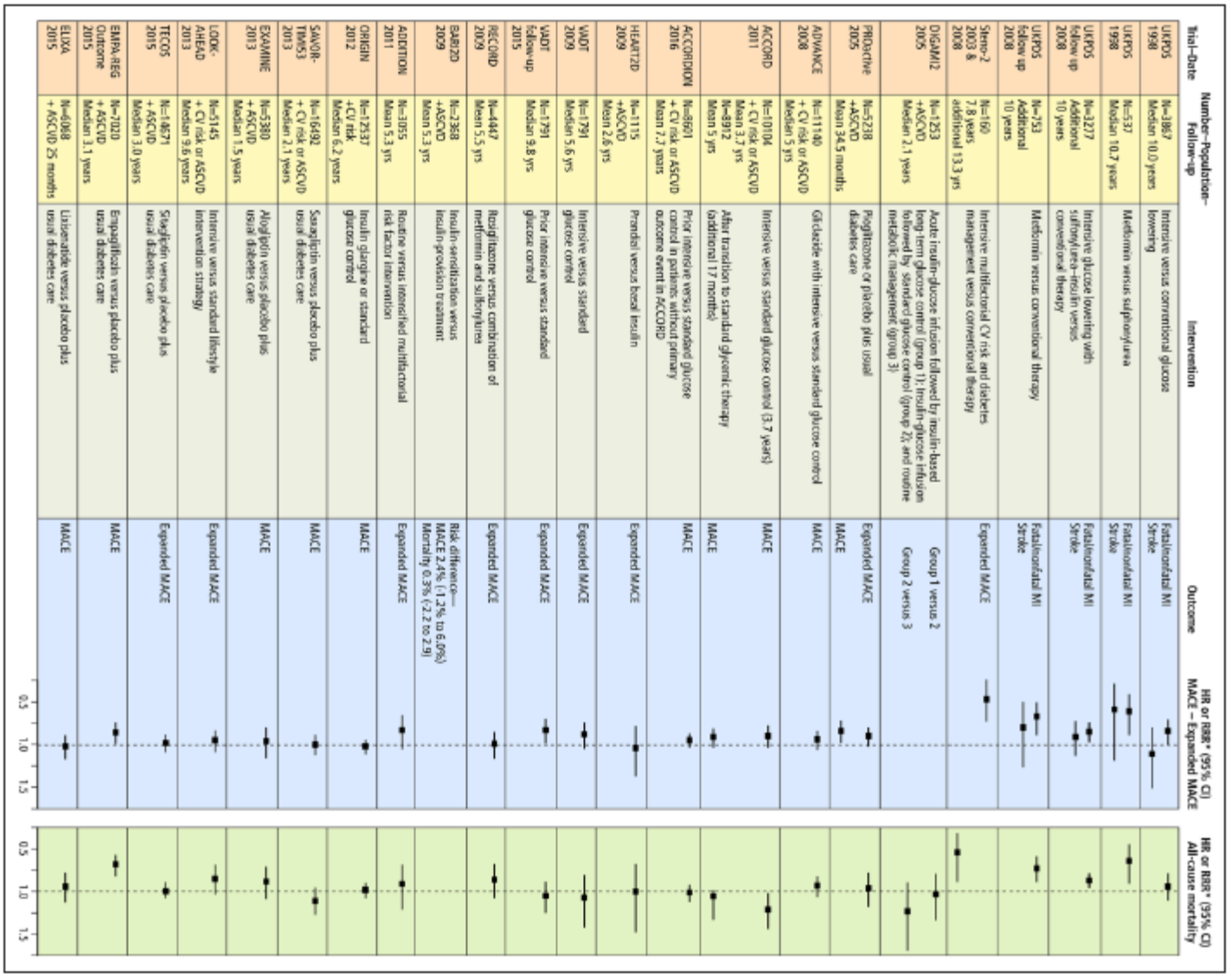


Figure 5 Continued. in Primary Care[392]; ADVANCE, Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation[334]; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes[104]; $DIGAMI_2$, Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction[393]; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide[382]; EMPA-REG OUTCOME, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients[373]; EXAMINE trial, EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care[383]; HEART2D, Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in patients with Type 2 Diabetes[394]; Look AHEAD, Action for Health in Diabetes[265]; ORIGIN, Outcome Reduction With Initial Glargine Intervention[347]; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events[102]; RECORD, Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes[102a]; SAVOR-TIMI53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53[375]; Steno-2, Multifactorial Intervention in Type 2 Diabetes at the Steno Diabetes Center[176,366]; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin[386]; UKPDS, United Kingdom Prospective Diabetes Study[41,103,199]; and VADT, Veterans Affairs Diabetes Trial.[335,345] Adapted from Holman et al[396] with permission of the publisher.

Glucose-Lowering and Vascular Benefits

- Older trials demonstrating a positive impact of tight glycemic control on macrovascular disease:
  - DCCT/EDIC
  - UKPDS
  - PROACTIVE
- More recent trials demonstrating neutral/negative effects of tight glycemic control in patients with T2DM
  - ACCORD
  - ADVANCE
  - VADT

Ryden L, et al. *Clin Ther*. 2016. In Press.

E Mannucci

G Ital Cardiol | Vol 15 | Suppl 2 al N 12 2014

Tabella 1. Trial sull'effetto del controllo glicemico nel diabete di tipo 2.

	UKPDS	ACCORD	ADVANCE	VADT
N. pazienti	4208	10 251	11 140	1791
N. eventi cardiovascolari maggiori	882	721	1147	499
Età media (anni)	54	62	66	60
Durata del diabete (media; anni)	0	10	8	11
Pazienti con pregressi eventi cardiovascolari (%)	0	32	28	31
HbA_{1c} all'endpoint nel gruppo di intervento (%)	8.1	6.4	6.5	6.9
Ipoglicemie gravi nel gruppo di intervento (n)	301	830	150	187
Effetto su eventi cardiovascolari maggiori (%)	-14	-6	-6	-11
Effetto su incidenza di infarto (%)	-19	-18	-9	-19
Effetto su mortalità cardiovascolare (%)	-19	+44	-12	+32

HbA_{1c}, emoglobina glicata.
Dati da [6-9,12]. Stime degli effetti sugli eventi da [11].

Tabella 1. Fenotipo del paziente, effetti avversi dei farmaci e loro impiego nella malattia cardiovascolare.

Farmaco	Meccanismo d'azione	Efficacia	Durabilità	Peso	Malattia CV	Controindicazioni
Metformina	↓ Rilascio epatico di glucosio ↑ Utilizzo di glucosio	++−−	+++−	−−−−	+++−	Disturbi gastrointestinali Contrastografia Insufficienza renale (GFR <30 ml/min) Malassorbimento
Sulfaniluree[a]	↑ Secrezione insulinica non-glucosio-dipendente	+++−	+−−−	++−−	−−−−	Ipoglicemie Insufficienza renale (GFR <30 ml/min) Malattia cardiovascolare Scompenso cardiaco
Glitazoni	↑ Utilizzo di glucosio	++−−	+++−	+++−	+++−	Ritenzione di liquidi Scompenso cardiaco Maculopatia diabetica
DPP4-I	↑ Secrezione insulinica glucosio-dipendente ↓ Secrezione di glucagone	++−−	++−−	−−−−	++−−	Possibilità di scompenso cardiaco in soggetti a rischio per tale patologia[b]
GLP1-RA	↑ Secrezione insulinica glucosio-dipendente ↓ Secrezione di glucagone ↓ Appetito	++++	+++−	−−−−	++−−	Rischio raro di pancreatiti Da non utilizzare per GFR <30 ml/min
SGLT2-I	↑ Escrezione urinaria di glucosio ↑ Secrezione di glucagone	+++−	+++−	−−−−	++++	Infezioni genitali e alle vie urinarie Non efficaci per GFR <50 ml/min Rischio di disidratazione in pazienti anziani in trattamento diuretico
Insulina basale	↑Utilizzo di glucosio ↓ Rilascio epatico di glucosio	++++	++++	+++−	++−−	Ipoglicemia

DPP4-I, inibitori della dipeptidil peptidasi 4; GFR, velocità di filtrazione glomerulare; GLP-1RA, agonisti recettoriali del glucagon-like peptide-1; SGLT2-I, inibitori del riassorbimento renale di glucosio.

[a]tra le sulfaniluree la gliclazide ha dimostrato una minor propensione a indurre ipoglicemie e una protezione renale nello studio ADVANCE.

[b]solo per saxagliptina nello studio SAVOR-TIMI 53.

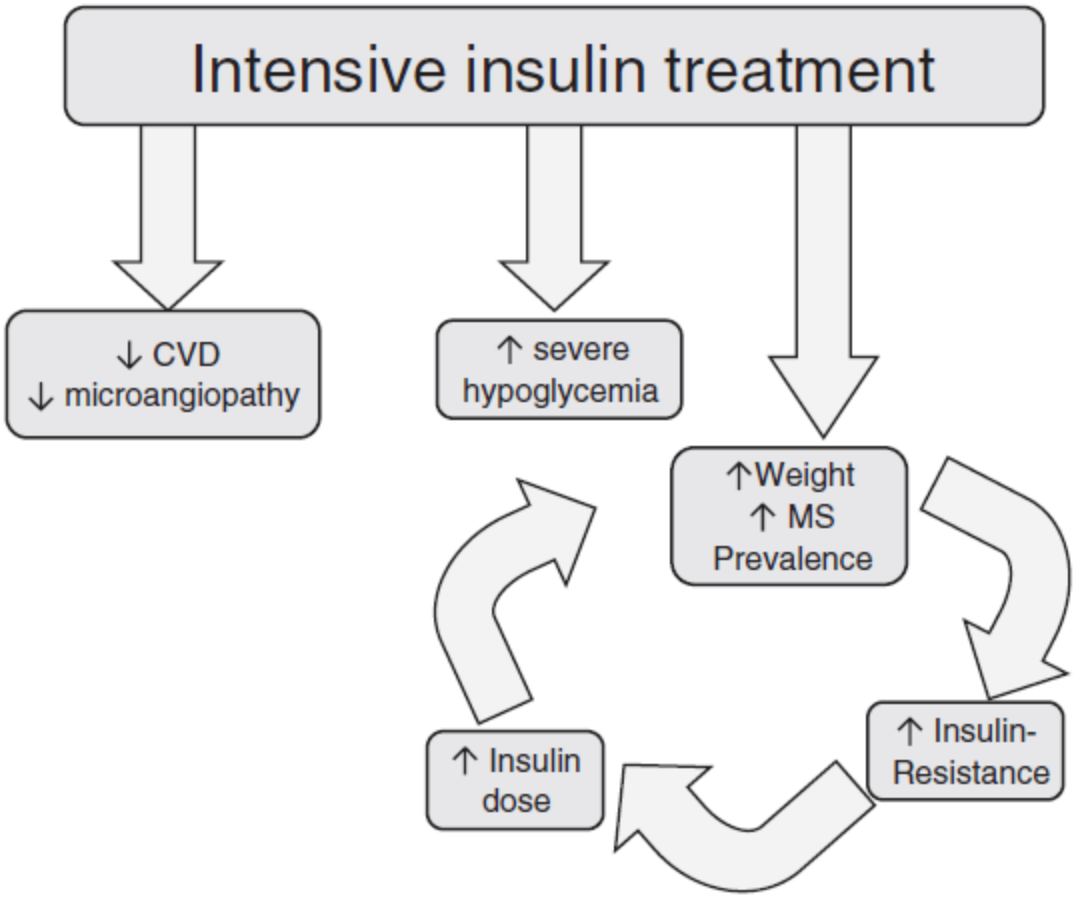


Fig. 2 – Effects of intensive insulin therapy. CVD: cardiovascular disease; MetS, metabolic syndrome.

Juan I. Chillarón

METABOLISM CLINICAL AND EXPERIMENTAL 63 (2014) 181–187

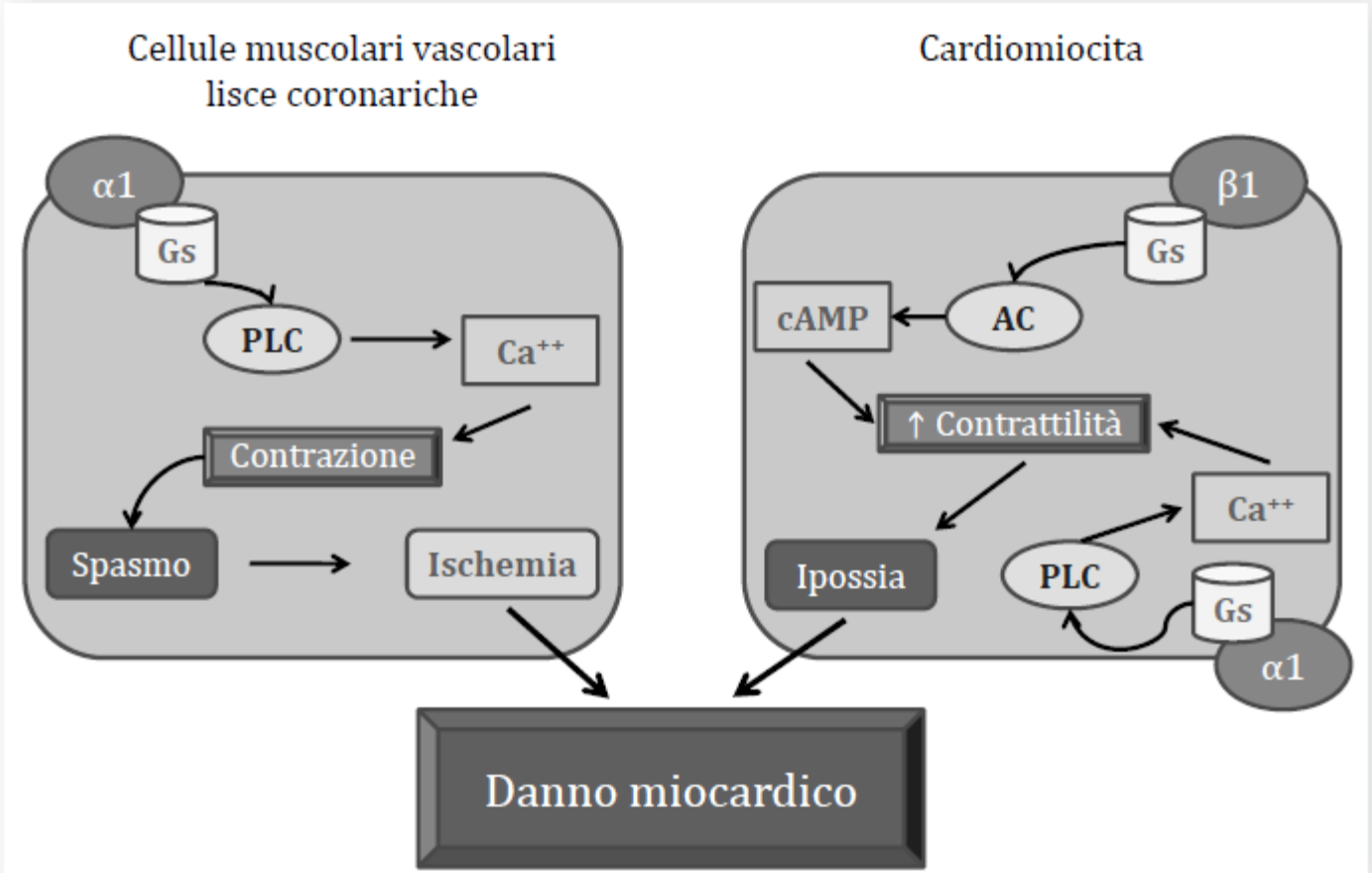


Figura 2. Rappresentazione degli effetti sulle cellule muscolari lisce e sui cardiomiociti delle catecolamine.
α_1, α_1-adrenocettore; Gs, proteina G stimolatoria; PLC, fosfolipasi C; β_1, β_1-adrenocettore; cAMP, AMP ciclico.

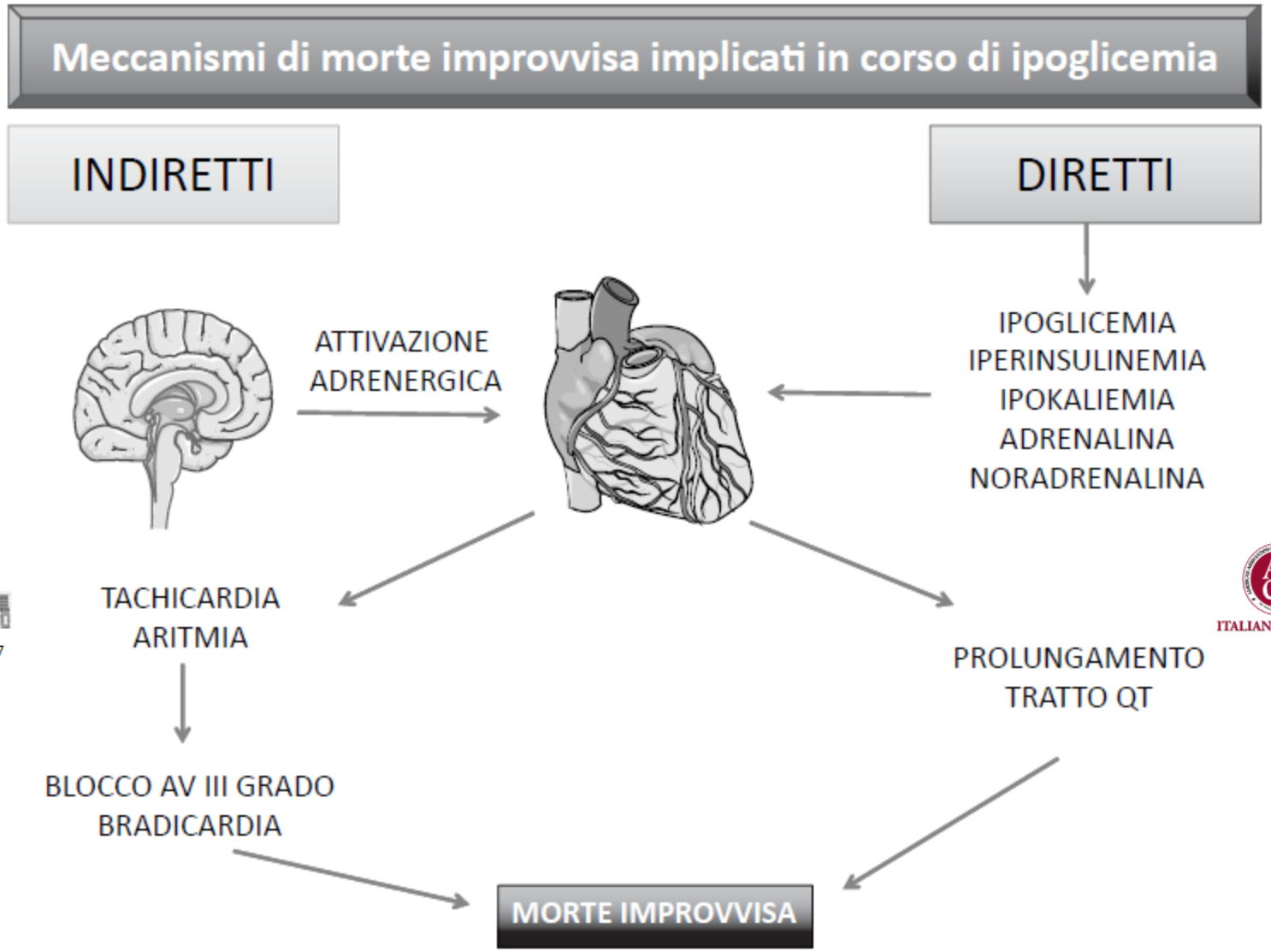


Figura 3. Rappresentazione dei meccanismi fisiopatologici che legano l'ipoglicemia alla morte improvvisa.

World Journal of Diabetes

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DOI: 10.4239/wjd.v6.i1.30

World J Diabetes 2015 February 15; 6(1): 30-36
ISSN 1948-9358 (online)

TOPIC HIGHLIGHT

WJD 5th Anniversary Special Issues (4): Diabetes-related complications

Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes

Hidekatsu Yanai, Hiroki Adachi, Hisayuki Katsuyama, Sumie Moriyama, Hidetaka Hamasaki, Akahito Sako

with the development of severe hypoglycemia. In patients treated with insulin, the intensified insulin therapy is more frequently associated with severe hypoglycemia than the conventional insulin therapy and continuous subcutaneous insulin infusion. Among the underlying clinical factors for development of severe hypoglycemia, low socioeconomic status, aging, longer duration of diabetes, high HbA1c and low body mass index, comorbidities are precipitating factors for severe hypoglycemia. Poor cognitive and mental functions are also associated with severe hypoglycemia.

Table 1 Published articles about the drug-induced hypoglycemia in patients with diabetes

Ref.	Subjects	Year	Nation	Setting	OAD	Insulin	Combination
Kim *et al*[27]	Type 2 (*n* = 298)	2004-2009	South Korea	The Emergency Department of two general hospitals	Glimepiride (24.2%) Gliclazide (5.4%) Glibenclamide (8.4%)	NPH/RI (38.3%) Premixed (11.1%) Glargine/Detemir (13.1%)	
Tsujimoto *et al*[28]	Type 1 (*n* = 85)	2006-2012	Japan	Retrospective cohort study in one medical center		Insulin (100%)	
	Type 2 (*n* = 305)				SU (42.3%) Others (6.6%)	Insulin (51.1%)	
Signorovitch *et al*[29]	Type 2 not treated with insulin (*n* = 5582)	1998-2010	United States	US-based employer claims database	SU (38.2%) Biguanides (56.3%) a-GI (0.9%) Sitagliptin (1.0%) Incretin mimetics (0.5%) TZD (14.9%)		
Moisan *et al*[30]	Not determined (*n* = 3575)	2000-2008	Canada	Inception cohort study using the database of the Quebec health insurance board and the Quebec registry of hospitalizations	SU (32.1%) Metformin (45.0%) SU + Metformin (12.3%) Others (2.1%)	Insulin (8.5%)	
Hsu *et al*[31]	Type 2 (*n* = 500)	1998-2009	Taiwan	A nationwide population-based study using the National Health Insurance Research Database	SU (67.8%) Others (61.4%)	Insulin (24.2%)	
Holstein *et al*[32]	Type 1 (*n* = 92)	1997-2000	German	A longitudinal population-based study		Conventional (27.2%) Intensified (69.6%) CSII (3.3%)	
	Type 1 (*n* = 121)	2007-2010				Conventional (6.6%) Intensified (79.3%) CSII (13.2%)	
	Type 2 (*n* = 148)	1997-2000			SU (30.4%)	Conventional (52.7%) Intensified (0%) CSII (0%)	SU + Insulin (16.9%)
	Type 2 (*n* = 225)	2007-2010			SU (29.8%) Metformin (0.9%)	Conventional (40.8%) Intensified (21.8%) CSII (0%)	SU + Insulin (6.7%)
Ha *et al*[33]	Not determined (*n* = 320)	2006-2009	South Korea	Retrospective analysis of hypoglycemic patients presented to emergency room of Uijeongbu St. Mary's Hospital	Glimepiride (29.7%) Glibenclamide (4.7%) Gliclazide (4.7%) Gliquidone (1.3%) Glipizide (0.9%) Others (24.7%)	Insulin (29.1%)	SU + Insulin (5.0%)
Geller *et al*[34]	Not determined (*n* = 8100)	2007-2011	United States	Nationally representative public health surveillance of adverse drug events among insulin-treated patients seeking emergency department care		Insulin (83.4%)	Insulin + Biguanide (8.5%) SU (6.6%) TZD (3.6%) DPP-4 inhibitors (1.3%) GLP-1 analogues (0.2%) Others (0.9%)
Ben-Ami *et al*[35]	Type 1 and 2 (*n* = 99)	1986-1992	Israel	Retrospective analysis of the medical record in Rambam Medical Center	Glyburide (51.5%) Glyburide + Metformin (10.2%)	Insulin (23.2%)	Insulin + Glyburide (13.1%) Insulin + Metformin (2.0%)
Quilliam *et al*[36]	Type 2 (*n* = 536581)	2004-2008	United States	Retrospective cohort designed to assess the rate and costs of hypoglycemia among working-age patients with type 2 diabetes in the MarketScan database	SU (42.3%) Metformin (75.7%) TZD (33.3%) Other oral agents (4.4%)	Insulin (6.0%) Other injectable agents (2.7%)	
Parsaik *et al*[37]	Type 1 (*n* = 210)	2003-2009	United States	Population-based study		Simple insulin (10.0%) MDI (67.0%) CSII(18.0%)	OAD + Insulin (1.0%)
	Type 2 (*n* = 503)				OAD (23.0%)	Simple insulin (27.0%) MDI (37.0%) CSII (1.0%)	OAD + Insulin (11.0%)

a-GI: a-glucosidase inhibitors; CSII: Continuous subcutaneous insulin infusion; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide
MDI: Multiple daily insulin injection; NPH: Neutral protamine Hagedorn; OAD: Oral anti-diabetic drug; RI: Regular insulin; SU: Sulfonylurea; TZ
Thiazolidinediones.

Table 3 Summary of the underlying clinical factors for the development of hypoglycemia in patients with diabetes

1 Socioeconomic status (education, race)
2 Aging
3 State of diabetes (duration, HbA1c, body mass index)
4 Cognitive and mental function
5 Comorbidity
6 Failure of organ which influence on clearance of insulin and oral anti-diabetic drugs (Heart, liver, renal failure)
7 Hypoglycemia-associated autonomic failure

Yanai H *et al.*
World J Diabetes 2015 February 15; 6(1): 30-36

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ITALIAN CHAPTER

Insulin-Requiring Versus Noninsulin-Requiring Diabetes and Thromboembolic Risk in Patients With Atrial Fibrillation

PREFER in AF

Giuseppe Patti, MD,[a] Markus Lucerna, PhD,[b] Ilaria Cavallari, MD,[a] Elisabetta Ricottini, MD,[a] Giulia Renda, MD, PhD,[c] Ladislav Pecen, PhD,[d] Fabio Romeo, MD,[e] Jean-Yves Le Heuzey, MD,[f] Josè Luis Zamorano, MD, PhD,[g] Paulus Kirchhof, MD,[h,i] Raffaele De Caterina, MD, PhD[c,j]

ABSTRACT

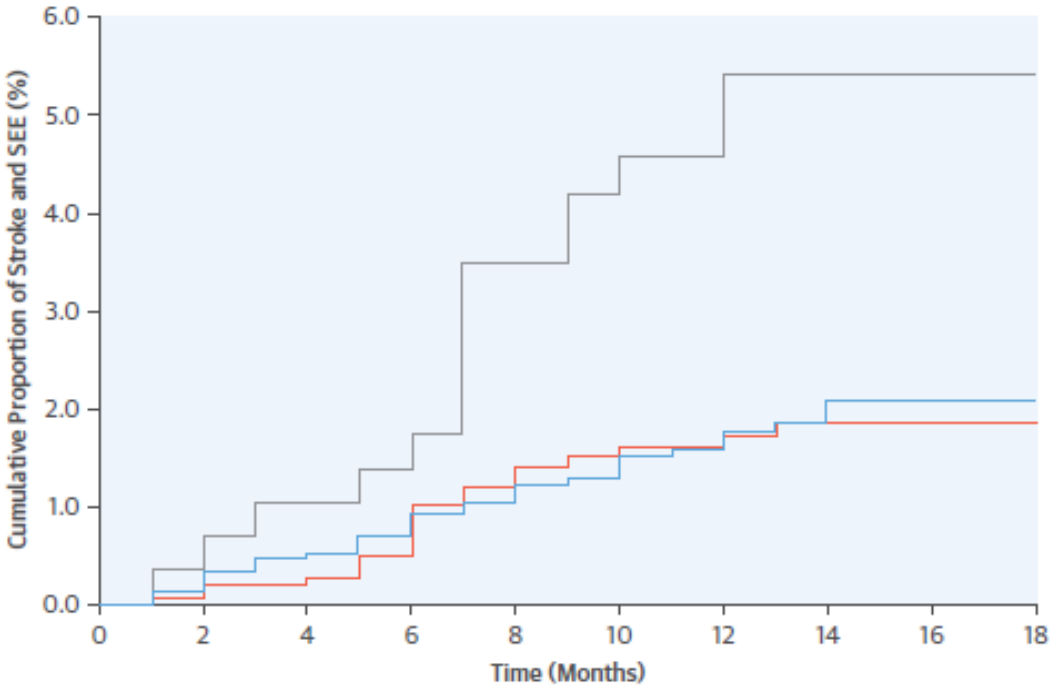
BACKGROUND Diabetes is a known risk predictor for thromboembolic events in patients with atrial fibrillation (AF), but no study has explored the prognostic weight of insulin in this setting.

either no diabetes (5.2% vs. 1.9%; hazard ratio: 2.89; 95% confidence interval: 1.67 to 5.02; p = 0.0002) or diabetes without insulin treatment (5.2% vs. 1.8%; hazard ratio: 2.96; 95% confidence interval: 1.49 to 5.87; p = 0.0019). Notably, rates of stroke/embolism were similar in patients with diabetes not receiving insulin versus patients without diabetes (hazard ratio: 0.97; 95% confidence interval: 0.58 to 1.61; p = 0.90). The selective predictive role of insulin-requiring diabetes was independent of potential confounders, including diabetes duration, and was maintained in various subpopulations, including the subgroup receiving anticoagulant therapy.

CONCLUSIONS In this cohort of anticoagulated patients with AF, the sole presence of diabetes not requiring insulin did not imply an increased thromboembolic risk. Conversely, insulin-requiring diabetes contributed most, if not exclusively, to the overall increase of thromboembolic risk in AF. (J Am Coll Cardiol 2017;69:409–19) © 2017 by the American College of Cardiology Foundation.

CONCLUSIONS In this cohort of anticoagulated patients with AF, the sole presence of diabetes not requiring insulin did not imply an increased thromboembolic risk. Conversely, insulin-requiring diabetes contributed most, if not exclusively, to the overall increase of thromboembolic risk in AF. (J Am Coll Cardiol 2017;69:409–19) © 2017 by the American College of Cardiology Foundation.

CENTRAL ILLUSTRATION Diabetes and Thromboembolism in Atrial Fibrillation



No diabetes	4,429	4,409	4,384	4,365	4,326	4,280	3,854	1,642	148	27
Non-insulin DM	1,000	998	994	987	973	963	868	320	33	5
Insulin DM	288	287	285	284	270	260	230	72	5	1

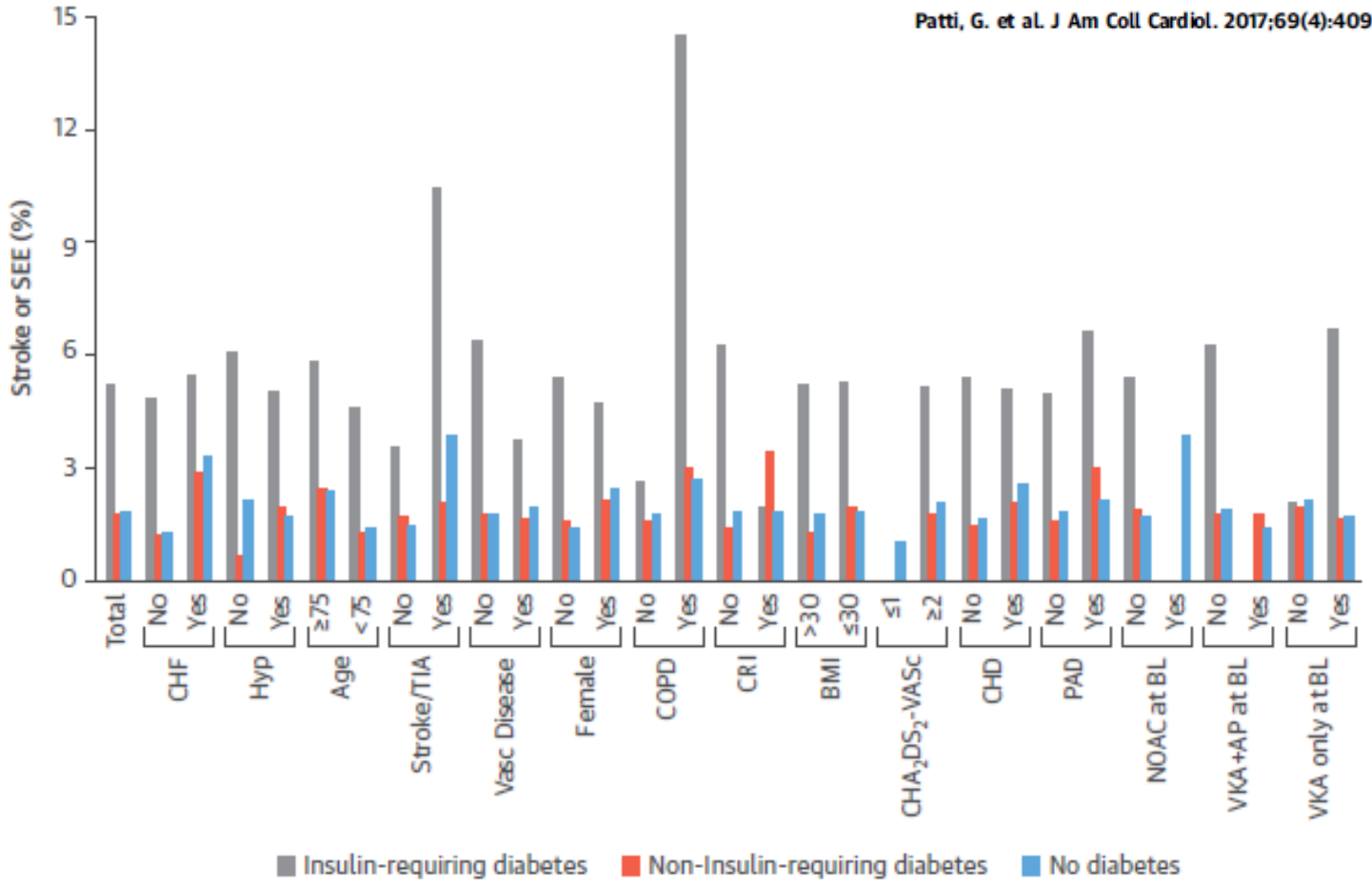
No diabetes — Non-insulin-requiring diabetes — Insulin-requiring diabetes

- Diabetic patients on insulin therapy had a >2.5-fold higher risk of thromboembolic events versus patients without diabetes or diabetic patients not receiving insulin treatment
- Similar thromboembolic risk was observed in nondiabetic patients and in patients with noninsulin-requiring diabetes

Patti, G. et al. J Am Coll Cardiol. 2017;69(4):409-19.

Patients with diabetes mellitus on insulin therapy had a significantly higher incidence of thromboembolic events, including stroke, at 1 year compared with those without insulin and patients without diabetes; conversely, the thromboembolic risk was similar in patients with diabetes not requiring insulin treatment and in those without diabetes. DM = diabetes mellitus; SEE = systemic embolic events.

FIGURE 2 1-Year Stroke or Systemic Embolism By Subpopulations



This analysis confirmed in all subgroups the study's main findings that insulin-requiring diabetes largely contributes to the overall increase of thromboembolic risk in atrial fibrillation, whereas the mere presence of diabetes without insulin treatment does not convey a negative prognostic value. CHA_2DS_2-VASc score ≤1 is female sex-corrected (i.e., CHA_2DS_2-VASc ≤1 for males and CHA_2DS_2-VASc ≤2 for females). AP = antiplatelet; BL = baseline; BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); CHD = coronary heart disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRI = chronic renal impairment; Hyp = systemic hypertension; NOAC = non-vitamin K antagonist oral anticoagulants; PAD = peripheral artery disease; SEE = systemic embolic events; TIA = transient ischemic attack; Vasc = vascular; VKA = vitamin K antagonist.

OPEN

Relationship between frequency of hypoglycemic episodes and changes in carotid atherosclerosis in insulin-treated patients with type 2 diabetes mellitus

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The effect of hypoglycemia on the progression of atherosclerosis in patients with type 2 diabetes mellitus (T2DM) remains largely unknown. This is a post hoc analysis of a randomized trial to investigate the relationship between hypoglycemic episodes and changes in carotid intima-media thickness (IMT). Among 274 study subjects, 104 patients experienced hypoglycemic episodes. Increases in the mean IMT and left maximum IMT of the common carotid arteries (CCA) were significantly greater in patients with hypoglycemia compared to those without hypoglycemia. Classification of the patients into three groups according to the frequency of hypoglycemic episodes showed that high frequency of hypoglycemic events was associated with increases in mean IMT-CCA, and left max-IMT-CCA and right max-IMT-CCA. In addition, repetitive episodes of hypoglycemia were associated with a reduction in the beneficial effects of sitagliptin on carotid IMT. Our data suggest that frequency of hypoglycemic episodes was associated with changes in carotid atherosclerosis.

While type 2 diabetes mellitus (T2DM) is a risk factor for cardiovascular disease (CVD), which is one of the major causes of morbidity and mortality in these patients[1], large randomized clinical trials did not show the benefits of strict glycemic control on CVD in patients with established atherosclerosis or longstanding T2DM[2–4]. On the other hand, a recent study reported that the occurrence of hypoglycemia was associated with increased risk of CVD and all-cause mortality in insulin-treated patients with type 1 diabetes mellitus (T1DM) and T2DM[5].

Hypoglycemia is a common adverse effect of management for diabetes, especially insulin therapy, and a barrier to optimal glycemic control. Hypoglycemia affects blood constituents[6,7], inflammatory cytokine levels[8,9], and coagulation and fibrinolysis factors[10,11], all of which might promote the progression of atherosclerosis. Indeed, the acute effects of hypoglycemia, such as sympatho-adrenal activation, catecholamine release on inflammation, endothelial injury, and pro-atherothrombotic biomarkers[12,13], are well known in patients with T1DM. Also, a cross sectional study demonstrated that repeated episodes of hypoglycemia were associated with preclinical atherosclerosis evaluated by carotid and femoral echography and measurement of flow-mediated brachial dilatation

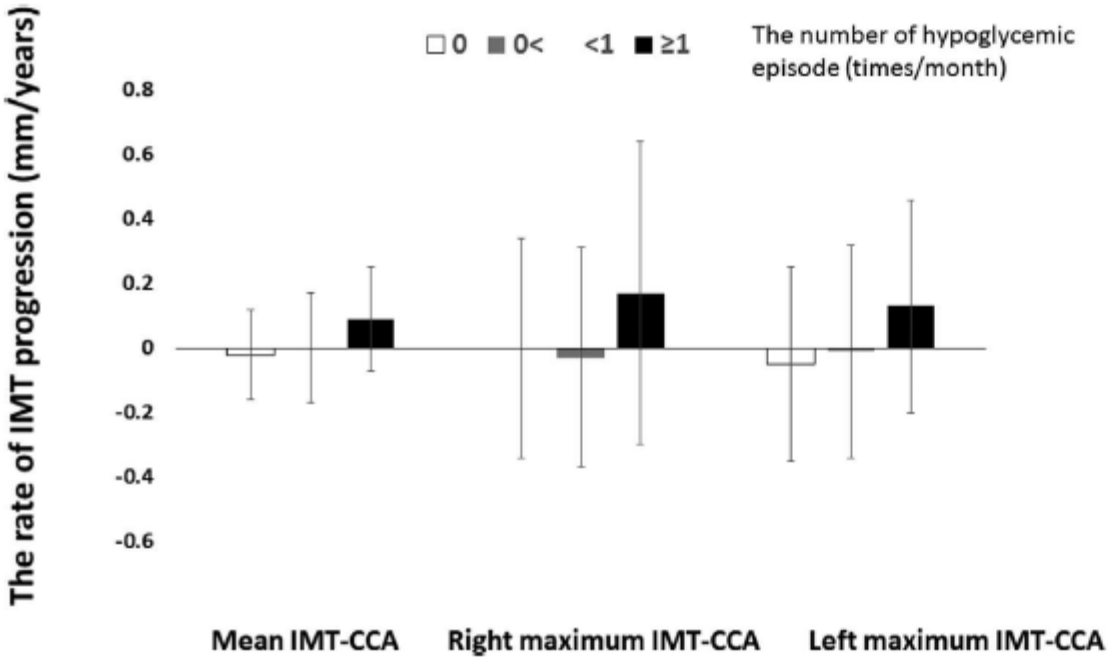

Figure 1. Changes in IMT according to the frequency of hypoglycemic episodes. Data are mean ± SD.

Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes

Craig J. Currie, Chris D. Poole, Marc Evans, John R. Peters, and Christopher LI. Morgan

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Context: The safety of insulin in the treatment of type 2 diabetes mellitus (T2DM) has recently undergone scrutiny.

Objective: The objective of the study was to characterize the risk of adverse events associated with glucose-lowering therapies in people with T2DM.

Design and Setting: This was a retrospective cohort study using data from the UK General Practice Research Database, 2000–2010.

Patients: Patients comprised 84 622 primary care patients with T2DM treated with one of five glucose-lowering regimens: metformin monotherapy, sulfonylurea monotherapy, insulin monotherapy, metformin plus sulfonylurea combination therapy, and insulin plus metformin combination therapy. There were 105 123 exposure periods.

Main Outcome Measures: The risk of the first major adverse cardiac event, first cancer, or mortality was measured. Secondary outcomes included these individual constituents and microvascular complications.

Results: In the same model, and using metformin monotherapy as the referent, the adjusted hazard ratio (aHR) for the primary end point was significantly increased for sulfonylurea monotherapy (1.436, 95% confidence interval [CI] 1.354–1.523), insulin monotherapy (1.808, 95% CI 1.630–2.005), and insulin plus metformin (1.309, 95% CI 1.150–1.491). In glycosylated hemoglobin/morbidity subgroups, patients treated with insulin monotherapy had aHRs for the primary outcome ranging from 1.469 (95% CI 0.978–2.206) to 2.644 (95% CI 1.896–3.687). For all secondary outcomes, insulin monotherapy had increased aHRs: myocardial infarction (1.954, 95% CI 1.479–2.583), major adverse cardiac events (1.736, 95% CI 1.441–2.092), stroke (1.432, 95% CI 1.159–1.771), renal complications (3.504, 95% CI 2.718–4.518), neuropathy (2.146, 95% CI 1.832–2.514), eye complications (1.171, 95% CI 1.057–1.298), cancer (1.437, 95% CI 1.234–1.674), or all-cause mortality (2.197, 95% CI 1.983–2.434). When compared directly, aHRs were higher for insulin monotherapy vs all other regimens for the primary end point and all-cause mortality.

Conclusions: In people with T2DM, exogenous insulin therapy was associated with an increased risk of diabetes-related complications, cancer, and all-cause mortality. Differences in baseline characteristics between treatment groups should be considered when interpreting these results. ***J Clin Endocrinol Metab* 98: 668–677, 2013)**

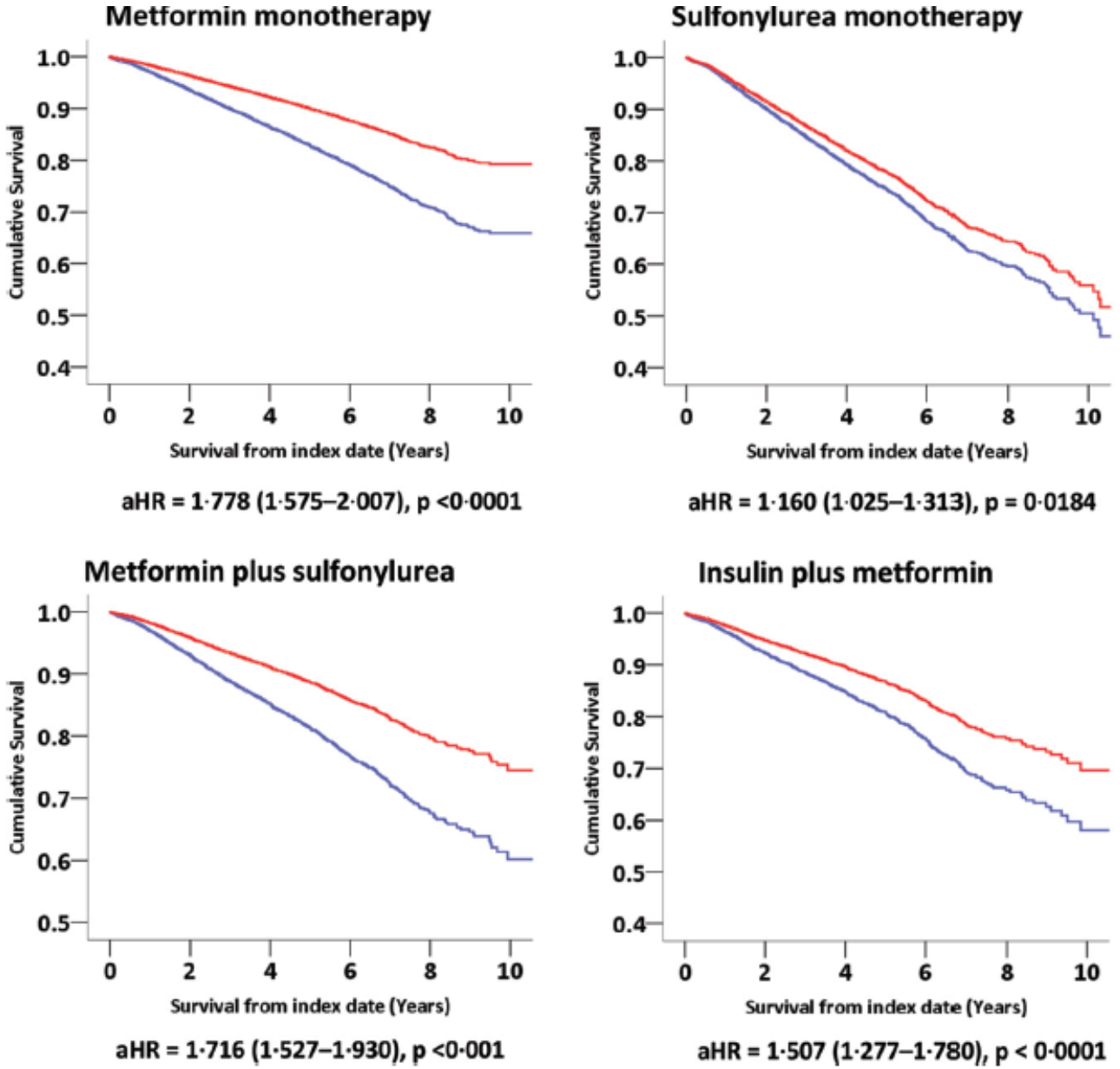


Figure 2. Adjusted survival curves for each specific regimen vs insulin monotherapy for the primary end point. Blue line indicates insulin monotherapy. Red line indicates comparator. Model specification includes the following: age, gender, smoking history, prior primary care contacts, and Charlson index.

Currie et al J Clin Endocrinol Metab, February 2013, 98(2):668–677

Long-Term Outcome of PCI Versus CABG in Insulin and Non–Insulin-Treated Diabetic Patients

Results From the FREEDOM Trial

George D. Dangas, MD, PhD,* Michael E. Farkouh, MD,* Lynn A. Sleeper, ScD,† May Yang, MPH,† Mikkel M. Schoos, MD, PhD,* Carlos Macaya, MD, PhD,‡ Alexandre Abizaid, MD, PhD,§ Christopher E. Buller, MD,‖ Gerard Devlin, MD,¶ Alfredo E. Rodriguez, MD, PhD,# Alexandra J. Lansky, MD,** F. Sandra Siami, MPH,† Michael Domanski, MD,* Valentin Fuster, MD, PhD,* for the FREEDOM Investigators

ABSTRACT

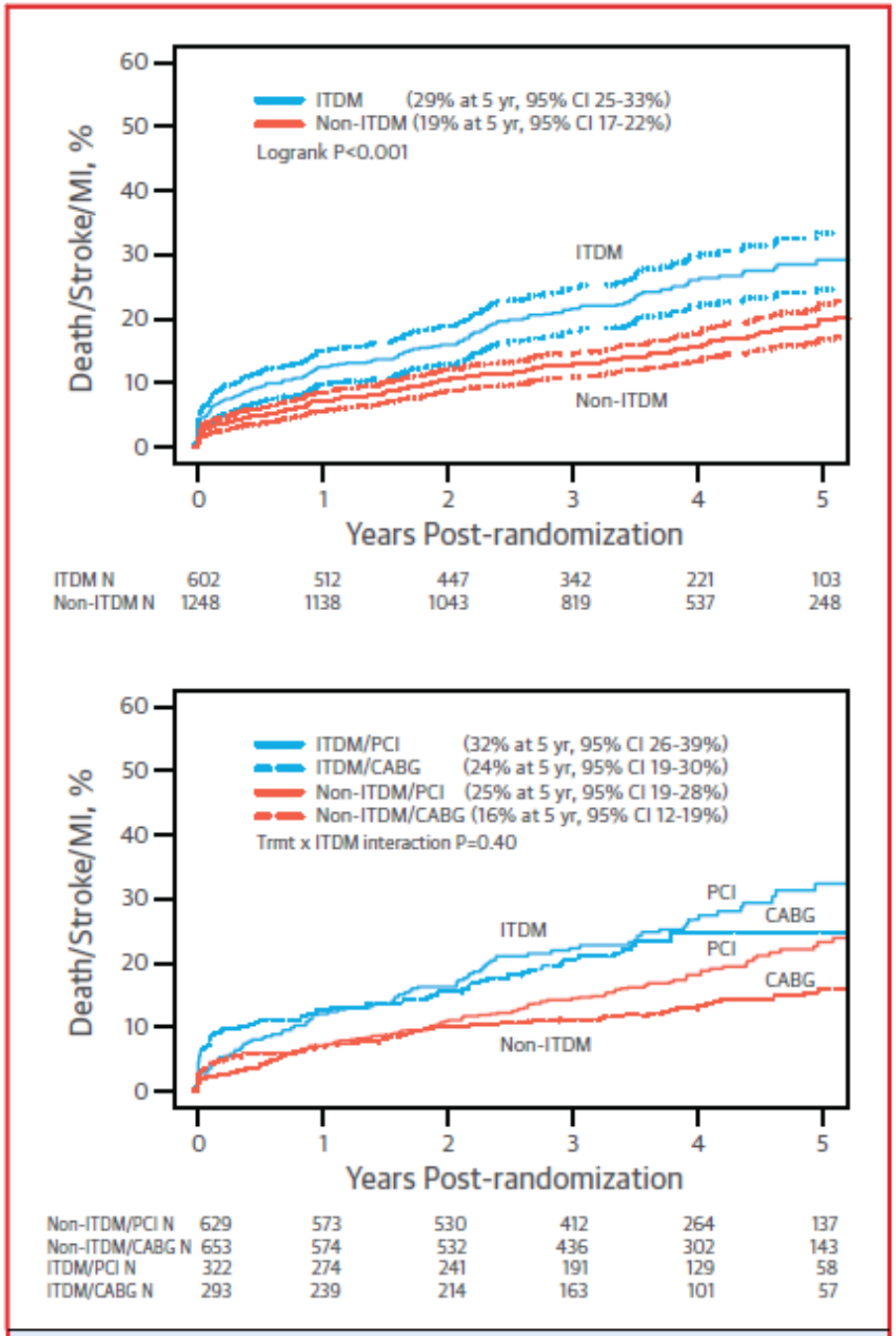
BACKGROUND The prospective, randomized FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial found coronary artery bypass graft surgery (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease, managed with or without insulin.

OBJECTIVES In this subgroup analysis of the FREEDOM trial, we examined the association of long-term clinical outcomes after revascularization in patients with insulin-treated diabetes mellitus (ITDM) compared with patients not treated with insulin.

METHODS A total of 1,850 FREEDOM subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 patients (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. Analyses were performed for the primary outcome composite of death/stroke/myocardial infarction (MI) using all available follow-up data.

RESULTS The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, $p < 0.001$), which persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.06 to 1.73, $p = 0.014$). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction $p = 0.40$) for ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event is 12.7 in ITDM and 13.2 in non-ITDM.

CONCLUSIONS In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin. (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes [FREEDOM]; NCT00086450) (J Am Coll Cardiol 2014;64:1189–97) © 2014 by the American College of Cardiology Foundation.



CENTRAL ILLUSTRATION **Estimates of the Primary Endpoint by Treatment Received and Insulin Use**

(Top) Kaplan-Meier estimated percentage of subjects achieving the primary composite outcome by insulin use, with point-wise 95% confidence bands (**salmon** = non-ITDM; **blue** = ITDM). **(Bottom)** Kaplan-Meier estimated percentage of subjects achieving the primary composite outcome by treatment received and insulin use (interaction p = 0.40). The median follow-up was somewhat lower in the CABG survivors within the ITDM cohort (42.7 months) compared with the other 3 groups (median 48.0 months for PCI ITDM; 47.6 months for PCI non-ITDM; 48.0 for CABG non-ITDM). CABG = coronary artery bypass graft surgery; CI = confidence interval; ITDM = insulin-treated diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; Trmt = treatment.

Dangas *et al.*
(J Am Coll Cardiol 2014;64:1189–97)

Bologna, 10-11 febbraio 2017

Medicine®

ITALIAN CHAPTER

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Comparing the Clinical Outcomes Between Insulin-treated and Non-insulin-treated Patients With Type 2 Diabetes Mellitus After Coronary Artery Bypass Surgery

A Systematic Review and Meta-analysis

Krishna Munnee, MS, Pravesh K. Bundhun, MD, Hongzhi Quan, MD, PhD, and Zhangui Tang, MD, PhD

Abstract: Several studies have shown c
(CABG) to be beneficial in patients w
(T2DM) and multivessel coronary artery
lin-treated T2DM (ITDM) are usually
control and are expected to suffer more
patients with non-insulin-treated T2D
adverse clinical outcomes in patients w
CABG are still not very clear. Hence, t
compare the short-and long-term adver
larger number of patients with ITDM and NITDM after CABG,
respectively

According to this study, patients with ITDM had a significantly higher rate of mortality and MAEs compared with patients with NITDM after CABG. Stroke was also significantly higher in patients with ITDM during a long-term follow-up period. However, since the result for the long-term mortality had a higher heterogeneity as compared with the other subgroups, and because a similar revascularization rate was observed between the ITDM and NITDM groups after CABG maybe because of a limited number of patients analyzed, further studies still need to be conducted to completely solve this issue.

(*Medicine* 95(10):e3006)

Bologna, 10-11 febbraio 2017

ITALIAN CHAPTER

Coronary artery bypass surgery compared with percutaneous coronary interventions in patients with insulin-treated type 2 diabetes mellitus: a systematic review and meta-analysis of 6 randomized controlled trials

Pravesh Kumar Bundhun, Zi Jia Wu and Meng-Hua Chen*

Abstract

Background: Data regarding the long-term clinical outcomes in patients with insulin-treated type 2 diabetes mellitus (ITDM) revascularized by either coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) are still controversial. We sought to compare the long-term (≥1 year) adverse clinical outcomes in patients with ITDM who underwent revascularization by either CABG or PCI.

Methods: Randomized Controlled Trials (RCTs) comparing the long-term clinical outcomes in patients with ITDM and non-ITDM revascularized by either CABG or PCI were searched from electronic databases. Data for patients with ITDM were carefully retrieved. Odd Ratio (OR) with 95 % confidence interval (CI) was used to express the pooled effect on discontinuous variables and the pooled analyses were performed with RevMan 5.3.

Results: Six RCTs involving 10 studies, with a total of 1297 patients with ITDM were analyzed (639 patients from the CABG group and 658 patients from the PCI group). CABG was associated with a significantly lower mortality rate compared to PCI with OR: 0.59, 95 % CI 0.42–0.85; P = 0.004. Major adverse cardiovascular and cerebrovascular events as well as repeated revascularization were also significantly lower in the CABG group with OR: 0.51, 95 % CI 0.27–0.99; P = 0.03 and OR 0.34, 95 % CI 0.24–0.49; P < 0.00001 respectively. However, compared to PCI, the rate of stroke was higher in the CABG group with OR: 1.41, 95 % CI 0.64–3.09; P = 0.40, but this result was not statistically significant.

Conclusion: CABG was associated with significantly lower long-term adverse clinical outcomes compared to PCI in patients with ITDM. However, due to an insignificantly higher rate of stroke in the CABG group, further researches with a larger number of randomized patients are required to completely solve this issue.

Keywords: Percutaneous coronary intervention, Coronary artery bypass surgery, Insulin-treated diabetes mellitus, Adverse clinical outcomes

Study or Subgroup	CABG Events	CABG Total	PCI Events	PCI Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.3 MACCEs						
CARDia	28	93	49	89	33.5%	0.35 [0.19, 0.65]
FREEDOM*	35	293	42	322	37.6%	0.90 [0.56, 1.46]
SYNTAX	12	87	26	88	28.9%	0.38 [0.18, 0.82]
Subtotal (95% CI)		**473**		**499**	**100.0%**	**0.51 [0.27, 0.99]**
Total events	75		117			
Heterogeneity: Tau² = 0.24; Chi² = 7.04, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)		**473**		**499**	**100.0%**	**0.51 [0.27, 0.99]**
Total events	75		117			
Heterogeneity: Tau² = 0.24; Chi² = 7.04, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Test for subgroup differences: Not applicable						

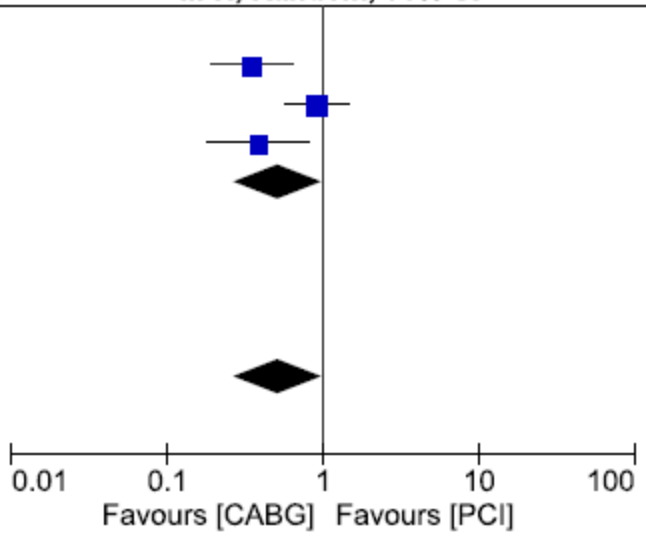


Fig. 3 Forest plot comparing major adverse cardiovascular and cerebrovascular events between the CABG and PCI groups

Adverse cardiovascular outcomes between insulin-treated and non-insulin treated diabetic patients after percutaneous coronary intervention: a systematic review and meta-analysis

ITALIAN CHAPTER

Bologna, 10-11 febbraio 2017

Pravesh Kumar Bundhun, Nuo Li and Meng-Hua Chen*

Abstract

Background: Type 2 diabetes mellitus (DM) patients have worse adverse cardiovascular outcomes after Percutaneous Coronary Intervention (PCI). However, the adverse cardiovascular outcomes between insulin-treated and non-insulin treated DM patients have been a subject of debate. We sought to compare the short-term (<1 year) and long-term (≥1 year) cardiovascular outcomes between insulin-treated and non-insulin treated DM patients after PCI.

Methods: Medline and Embase databases were searched for studies by typing 'diabetes and percutaneous coronary intervention/PCI' or 'insulin-treated and non-insulin treated diabetes mellitus and PCI'. Endpoints included adverse cardiovascular outcomes reported in these DM patients during the corresponding follow-up periods. Odd Ratio (OR) with 95 % confidence interval (CI) was used to express the pooled effect on discontinuous variables and the pooled analyses were performed with RevMan 5.3.

Results: 21 studies have been included in this meta-analysis consisting of a total of 21,759 diabetic patients (6250 insulin-treated and 15,509 non-insulin treated DM patients). Short term mortality, myocardial infarction, target lesion revascularization, major adverse cardiac effects and, stent thrombosis were significantly higher in insulin-treated

Conclusion: Insulin treatment in these DM patients was associated with a significantly higher short and long-term adverse cardiovascular outcomes after PCI compared to those DM patients not treated by insulin therapy.

Conclusion: Insulin treatment in these DM patients was associated with a significantly higher short and long-term adverse cardiovascular outcomes after PCI compared to those DM patients not treated by insulin therapy.

Keywords: Cardiovascular outcomes, Type 2 diabetes mellitus, Percutaneous coronary intervention

G ITAL CARDIOL | VOL 15 | SUPPL 2 AL N 12 2014
A AVOGARO

	GFR >60 ml/min	GFR 30-60 ml/min	GFR <30 ml/min
Non CHD	• Metformina • Sulfaniluree • Pioglitazone • AG-I • DPP4-I • GLP-1 RA • Insulina	• Metformina (↓ dose) • Gliclazide o repaglinide • Pioglitazone • AG-I • DPP4-I • GLP-1 RA • Insulina	• Gliclazide o repaglinide • Pioglitazone • DPP4-I (↓ dose)* • Insulina
CHD	• Metformina • Solo gliclazide • Pioglitazone • AG-I • DPP4-I • GLP-1 RA • Insulina	• Metformina (↓ dose) • Gliclazide • Pioglitazone • AG-I • DPP4-I • GLP-1 RA • Insulina	• Pioglitazone • DPP4-I (↓ dose)* • Insulina
Scompenso cardiaco	• Metformina • Gliclazide • DPP4-I (cautela) • AG-I • GLP-1 RA • Insulina	• Gliclazide • AG-I • DPP4-I (↓ dose) • GLP-1 RA (solo exenatide) • Insulina	• Insulina

Figura 4. Schema per la scelta degli antidiabetici orali in funzione delle comorbilità cardio-renali.
AG-I, inibitori delle alfa-glucosidasi; CHD, cardiopatia ischemica; DPP4-I, inibitori della dipeptidil peptidasi 4; GLP-1 RA, agonisti recettoriali del glucagon-like peptide 1; GFR, velocità di filtrazione glomerulare.

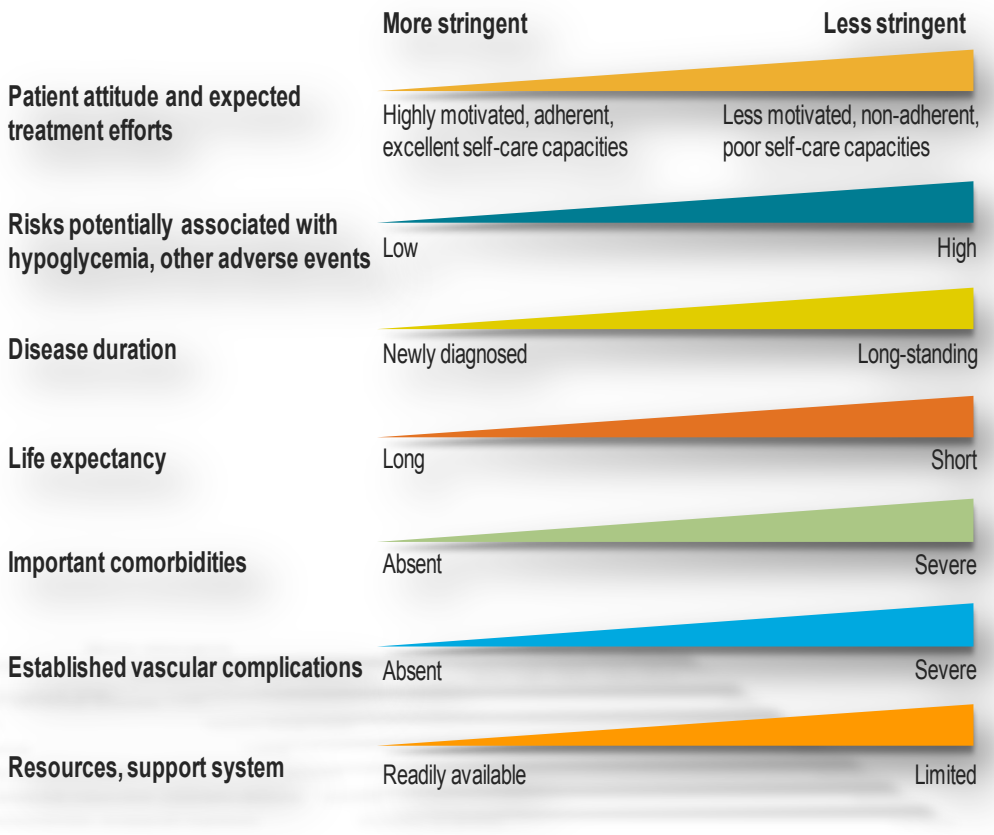
American Diabetes Association

TARGET DEL TRATTAMENTO

	TARGET GLICEMICO, HbA1c
Generale	< 7%
Più stringenti *	6 – 6.5%
Meno stringenti ^	7.5 – 8%

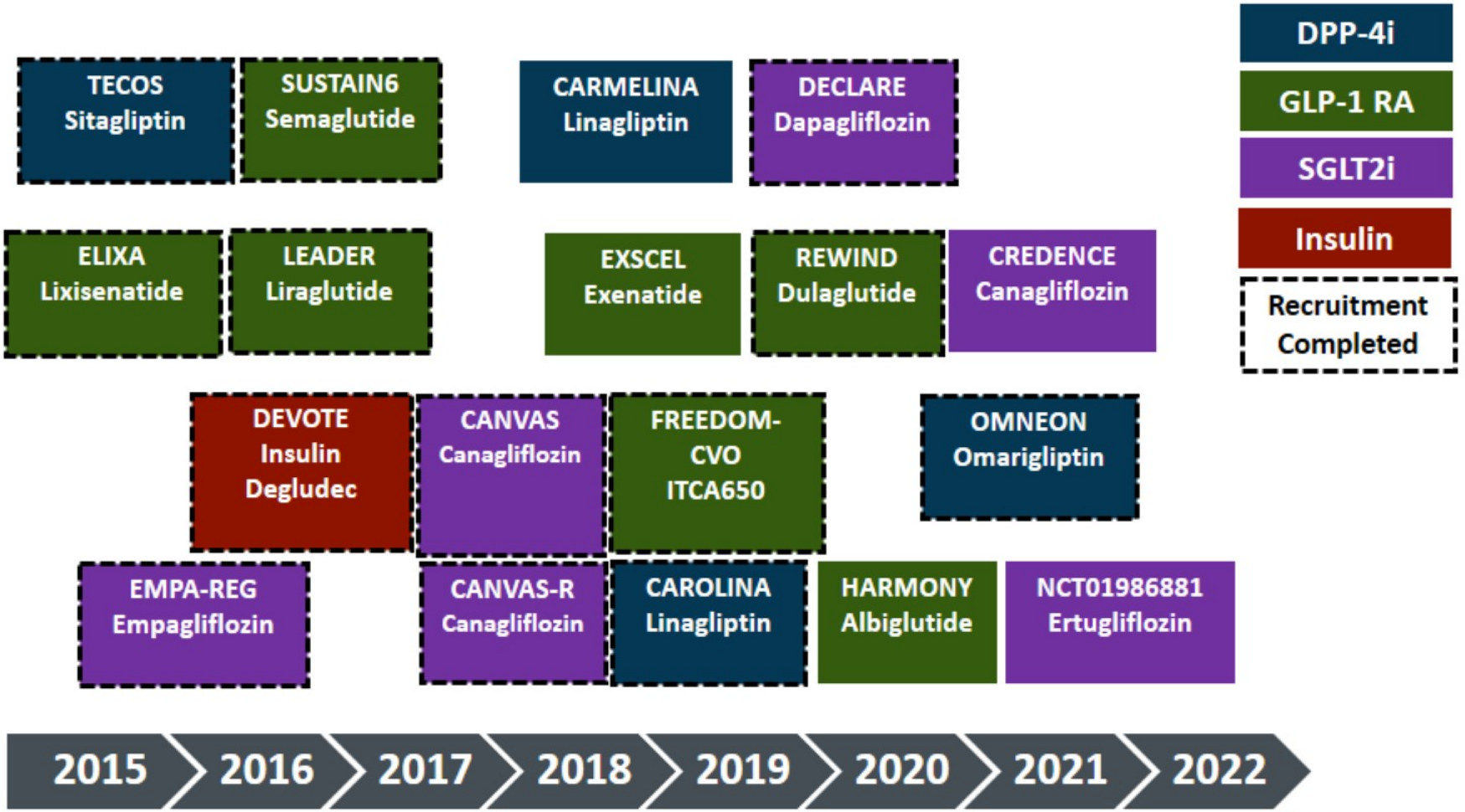
*** Criteri più stringenti: pazienti con una lunga aspettativa di vita, malattia di breve durata, no CVD**

^ Criteri meno stringenti: pazienti con storia di ipoglicemie gravi, bassa aspettativa di vita, complicanze avanzate, gravi comorbidità, scarsa aderenza al trattamento



Inzucchi SE, et al. American Diabetes Association. *Diabetes Care*. 2012;35:1364-1379;

Ongoing CVOTs in Patients With T2DM



Ryden L, et al. *Clin Ther*. 2016. In Press.

CONCLUSIONI

Per quanto riguarda il controllo glicemico, l'insieme dei risultati dei trial mostra che, almeno a lungo termine, il miglioramento del controllo glico-metabolico riduce l'incidenza di eventi cardiovascolari maggiori; inoltre, nei pazienti diabetici, la riduzione dell'iperglicemia durante una sindrome coronarica acuta migliora la prognosi. D'altro canto, le ipoglicemie si associano ad un peggioramento degli esiti cardiovascolari. La disponibilità di nuovi analoghi lenti, capaci di controllare efficacemente la glicemia a digiuno con rischio più basso di ipoglicemia, può determinare un miglioramento anche a questo riguardo, rendendo la terapia insulinica più maneggevole che in passato.

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... G R A Z I E !