CONVEGNO SID AMD UMBRIA

Quali scelte terapeutiche nel paziente in area critica e nel postcritico

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AHA Scientific Statement

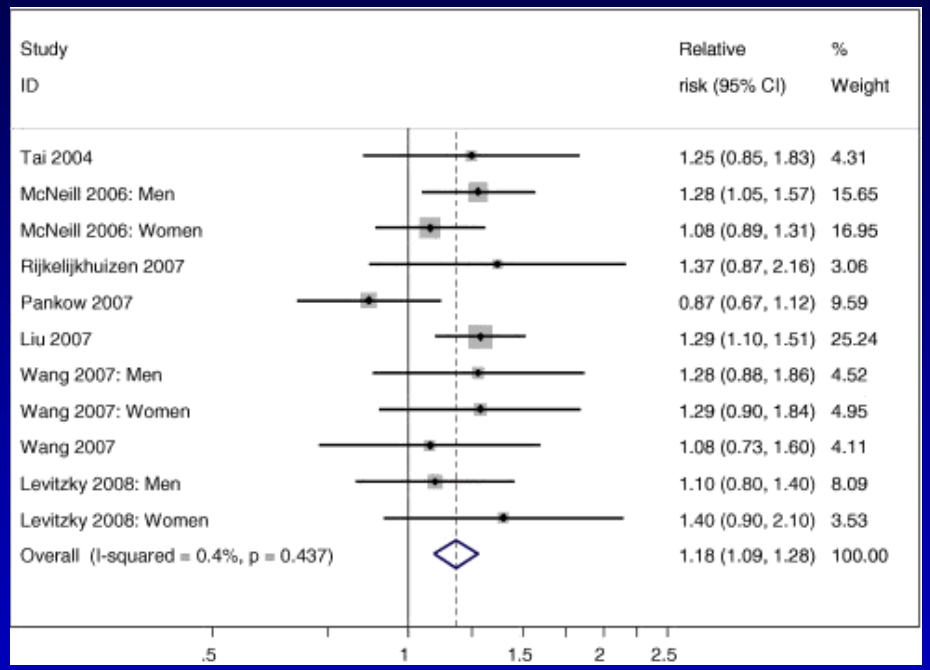
Is Blood Glucose the Instigator or Innocent Bystander of adverse outcomes in Acute Coronary Syndrome?

..

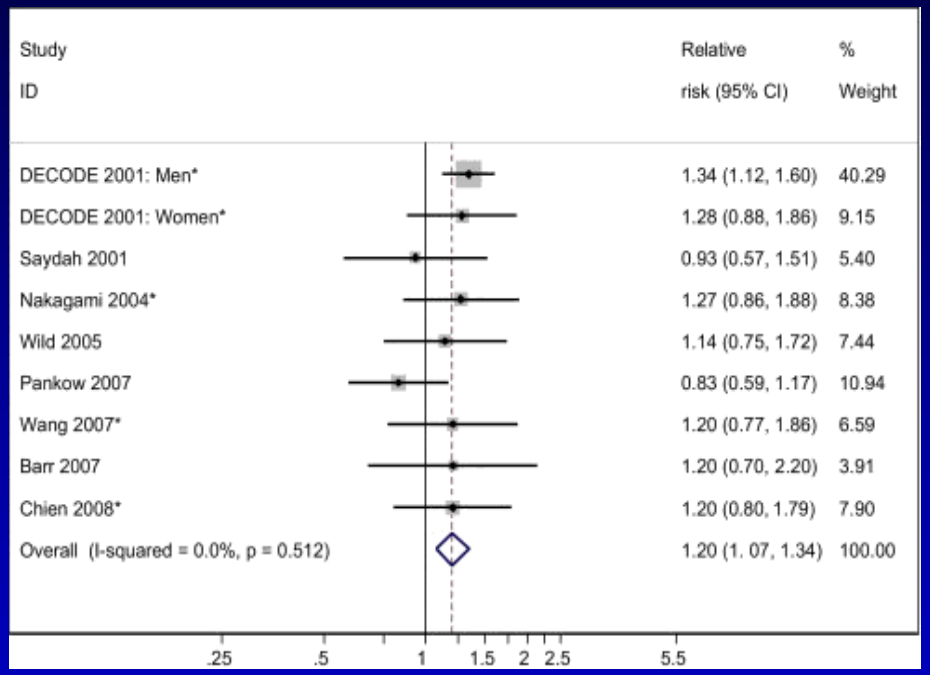
"diabetes is a cardiovascular disease" .....

Pre-Diabetic Conditions:
Risk of Cardiovascular Disease

Meta-analysis of 18 clinical trials



Impaired Fasting Glucose (IFG)



Impaired Glucose Tolerance (IGT)

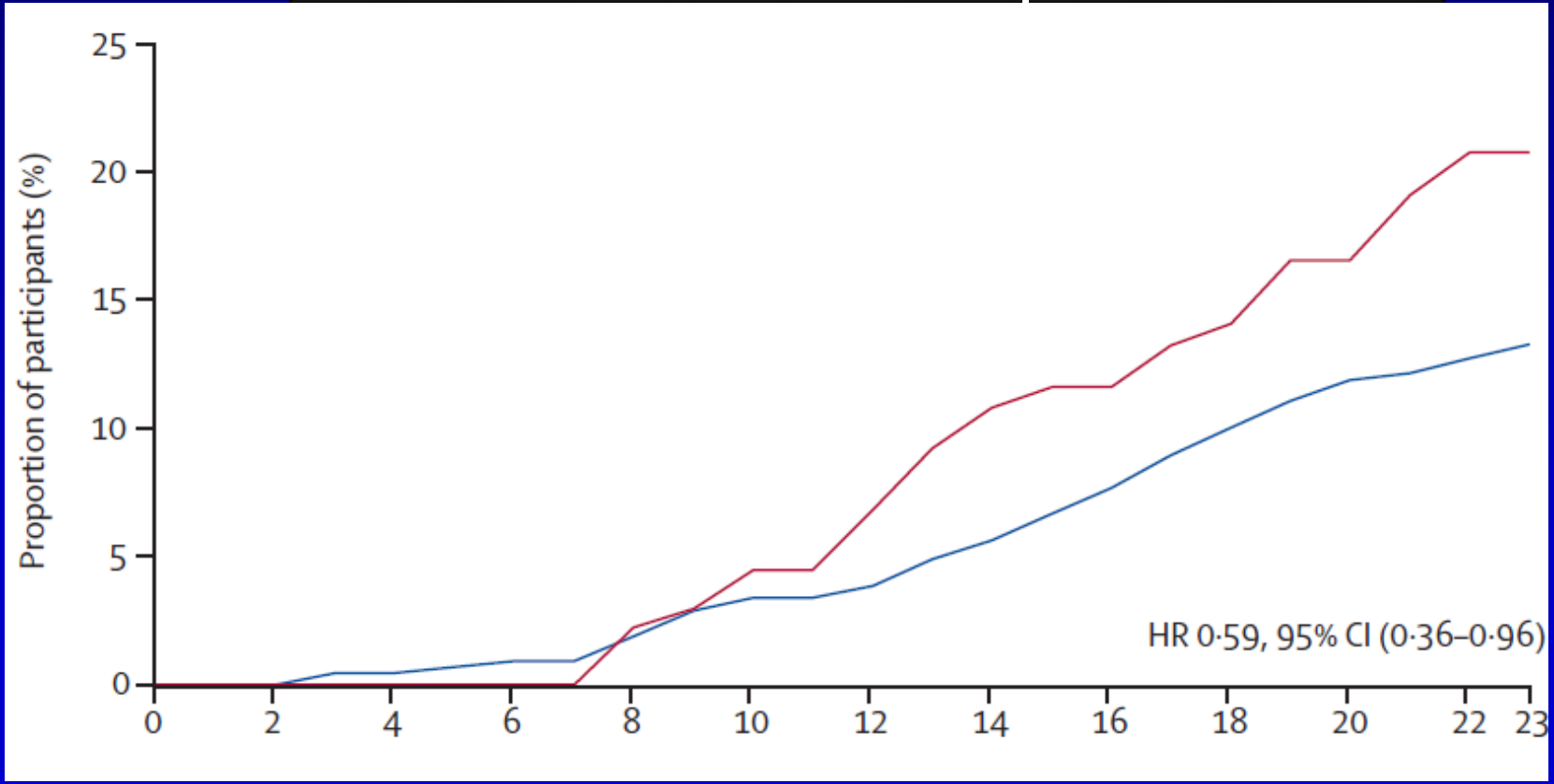
- The RR of CVD for IFG: 1.20 (95% CI, 1.12-1.28), when using a FBG of 110-125 mg/dl and 1.18 (95% CI, 1.09-1.28) at FBG level of 100-125 mg/dl;
- The RR of CVD for IGT was 1.20 (95% CI, 1.07-1.34)

Ford ES et al. JACC 2010;55:1310-1317

Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study

Lancet Diabetes Endocrinol 2014

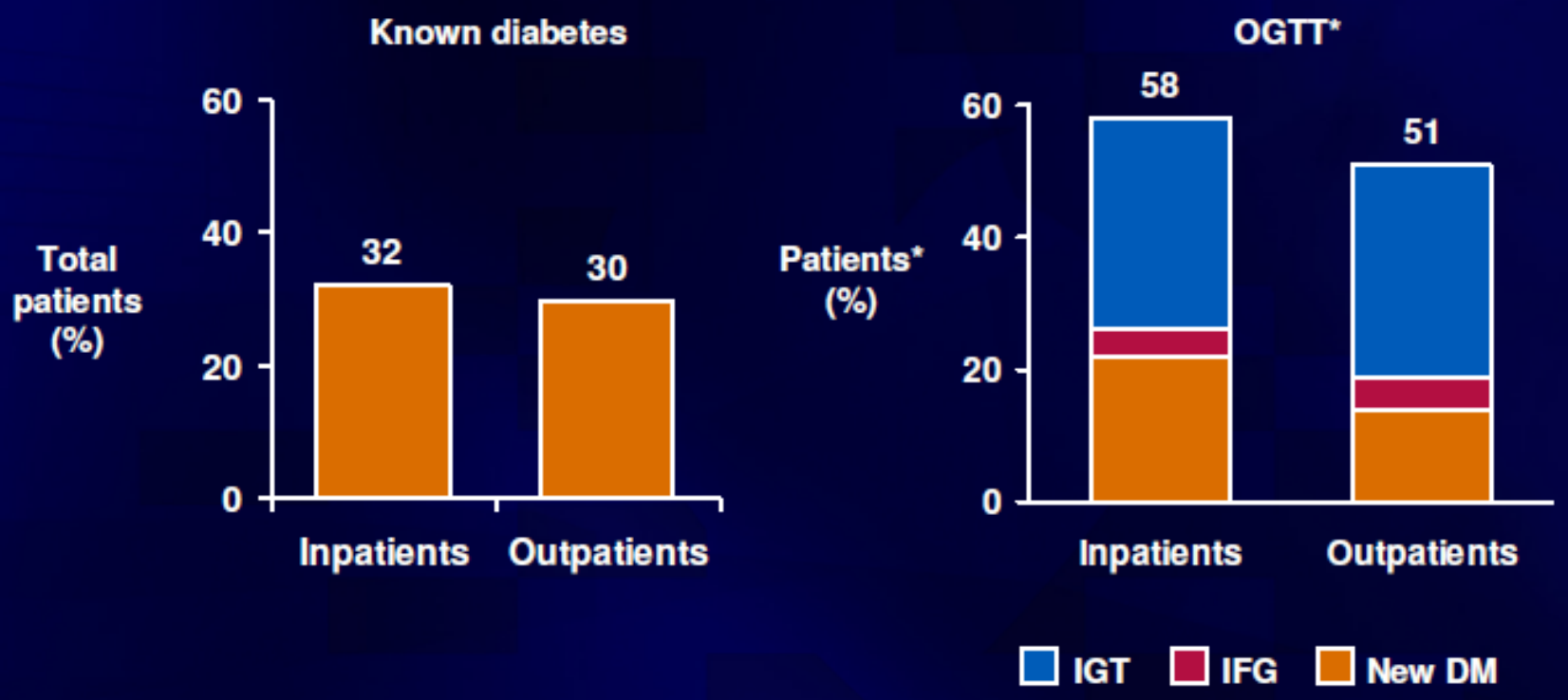
Mortality for Cardiovascular Disease



Abnormal glucose metabolism in CAD:

The Euro Heart Survey on diabetes and the heart

n = 2107 inpatients with acute CAD; n = 2854 outpatients with stable CAD



*n = 1920 without known diabetes
OGTT = oral glucose tolerance test;
IGT = impaired glucose tolerance; IFG = impaired fasting glucose

Bartnik M et al.
Eur Heart J. 2004;25:1880-90.

Glucose metabolism after discharge from a coronary care unit and after 3 months in patients with AMI:

The Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) study

- in patients with CAD impaired glucose homeostasis is more common than normal glucose control

Bartnik M, et al. Eur Heart J 2004 ; Lenzen M, et al. Eur Heart J 2006; De Caterina R et al. Eur H J 2010

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Diabetes Care 31:1955–1959, 2008

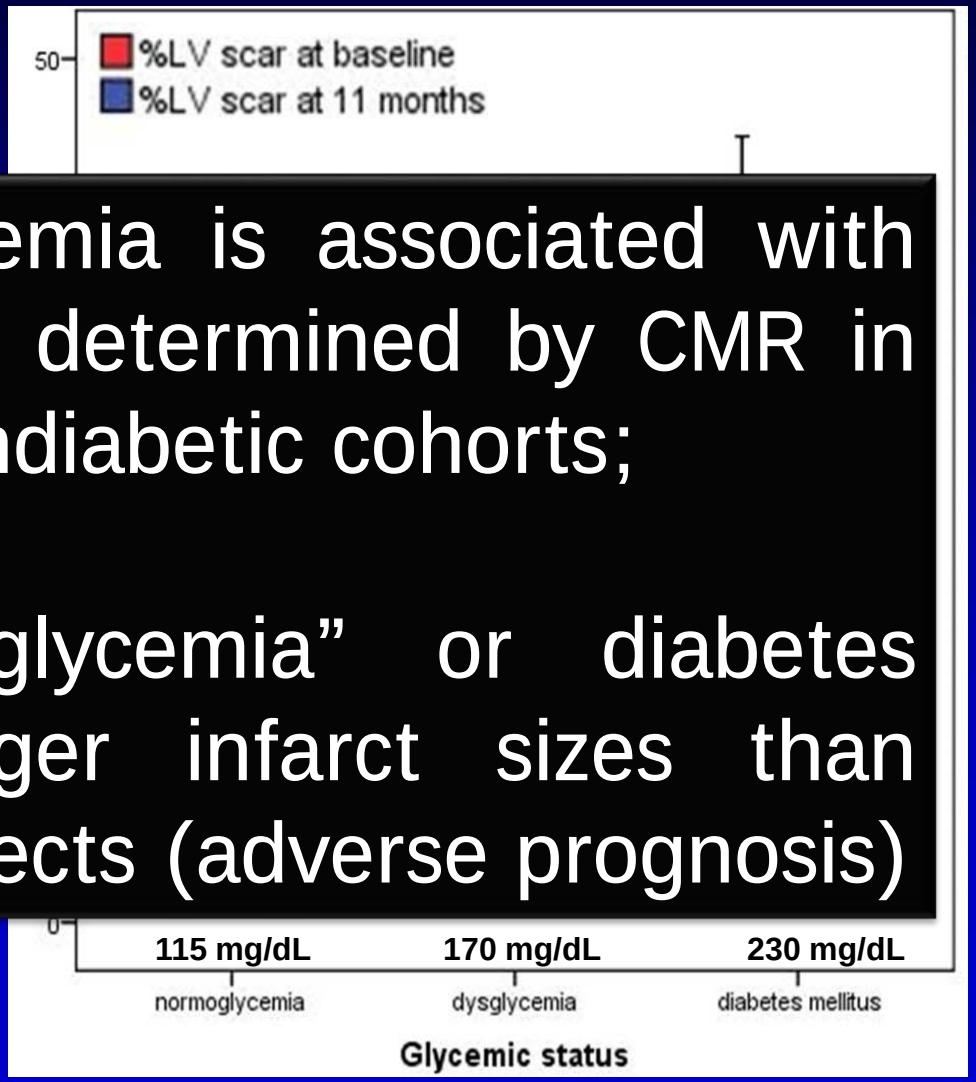
Can Admission and Fasting Glucose Reliably Identify Undiagnosed Diabetes in Patients With Acute Coronary Syndrome?

	Prevalence	Sensitivity	Specificity	PPV
FPG ≥5.6 mmol/l	48	81.6	64.7	46.3
APG ≥7.8 mmol/l	30	65.8	83.3	59.5
FPG ≥5.6 or APG ≥7.8 mmol/l	52	89.5	56.9	43.6

- Combination of **fasting** FPG ≥5.6 mmol/l **(≥100 mg/dl)** and/or **admission** APG ≥7.8 mmol/l **(≥140 mg/dl)** highly sensitive (although weakly specific) for identifying diabetes missing only 10% of diabetic pts but requiring OGTTs to be performed in 52% of pts with ACS;
- This simple algorithm could offer a practical initial screening tool at the acute setting in the high-risk population with ACS

according to OGTT criteria

Relationship of “dysglycemia” to acute myocardial infarct size as determined by CMR



- Admission hyperglycemia is associated with larger infarct size as determined by CMR in both diabetic and nondiabetic cohorts;
- Patients with “dysglycemia” or diabetes mellitus sustain larger infarct sizes than normoglycaemic subjects (adverse prognosis)

Mather et al. J Cardiovasc Magnetic Res 2010,

Diabetic Cardiomiopathy:

mechanism(s) and clinical translational

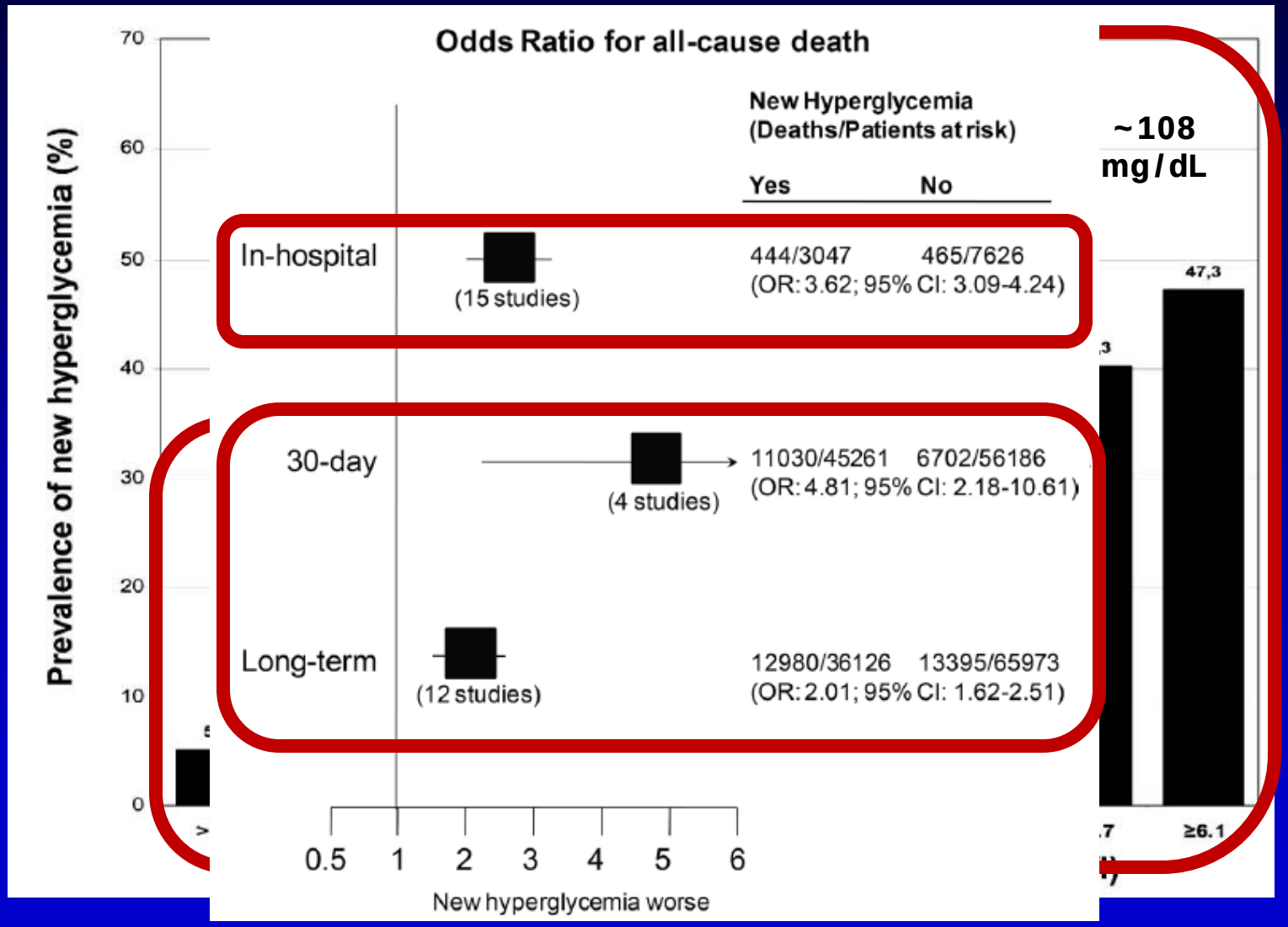
"picture worth a thousand words"

Normal control

Diabetes fibrosis

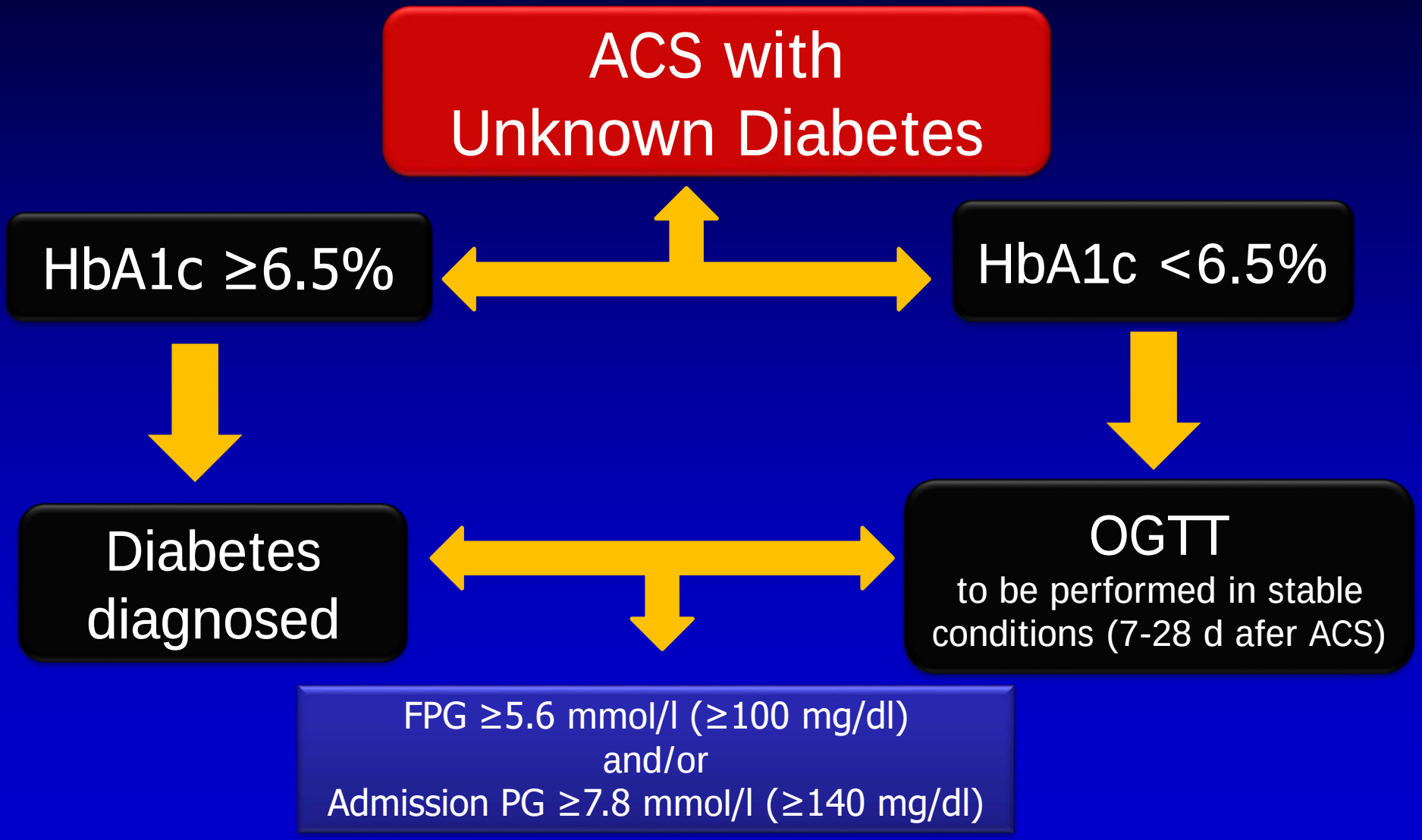
Regan TJ. *J Clin Invest.* 1977;60:885-899.

New onset hyperglycemia during ACS: which threshold is harmful?



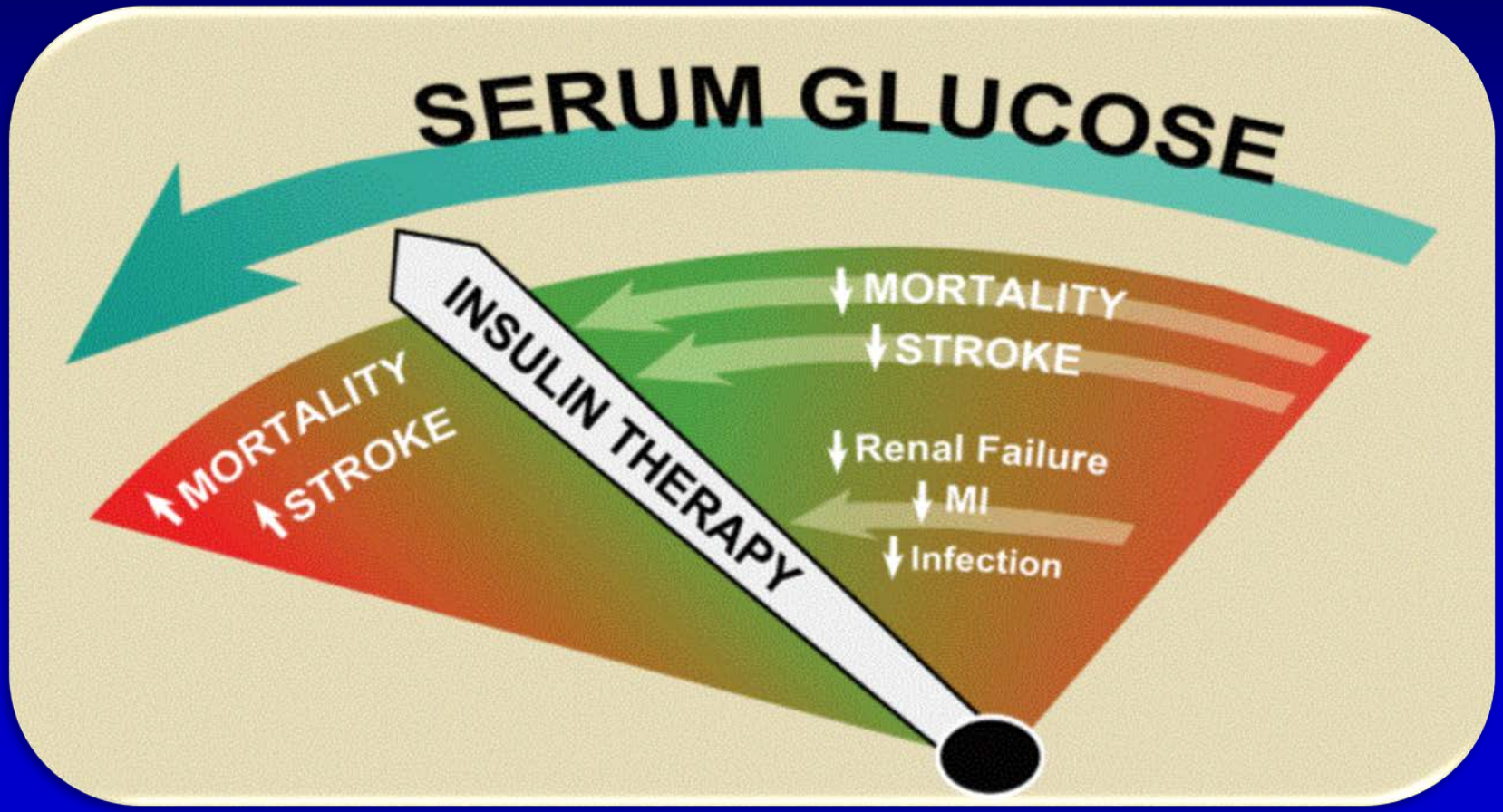
Angeli F, Reboldi G et al Curr Diabetes Review 2010; Diabetes and Metab 2013; Ther Adv Cardiovsc Dis 2015

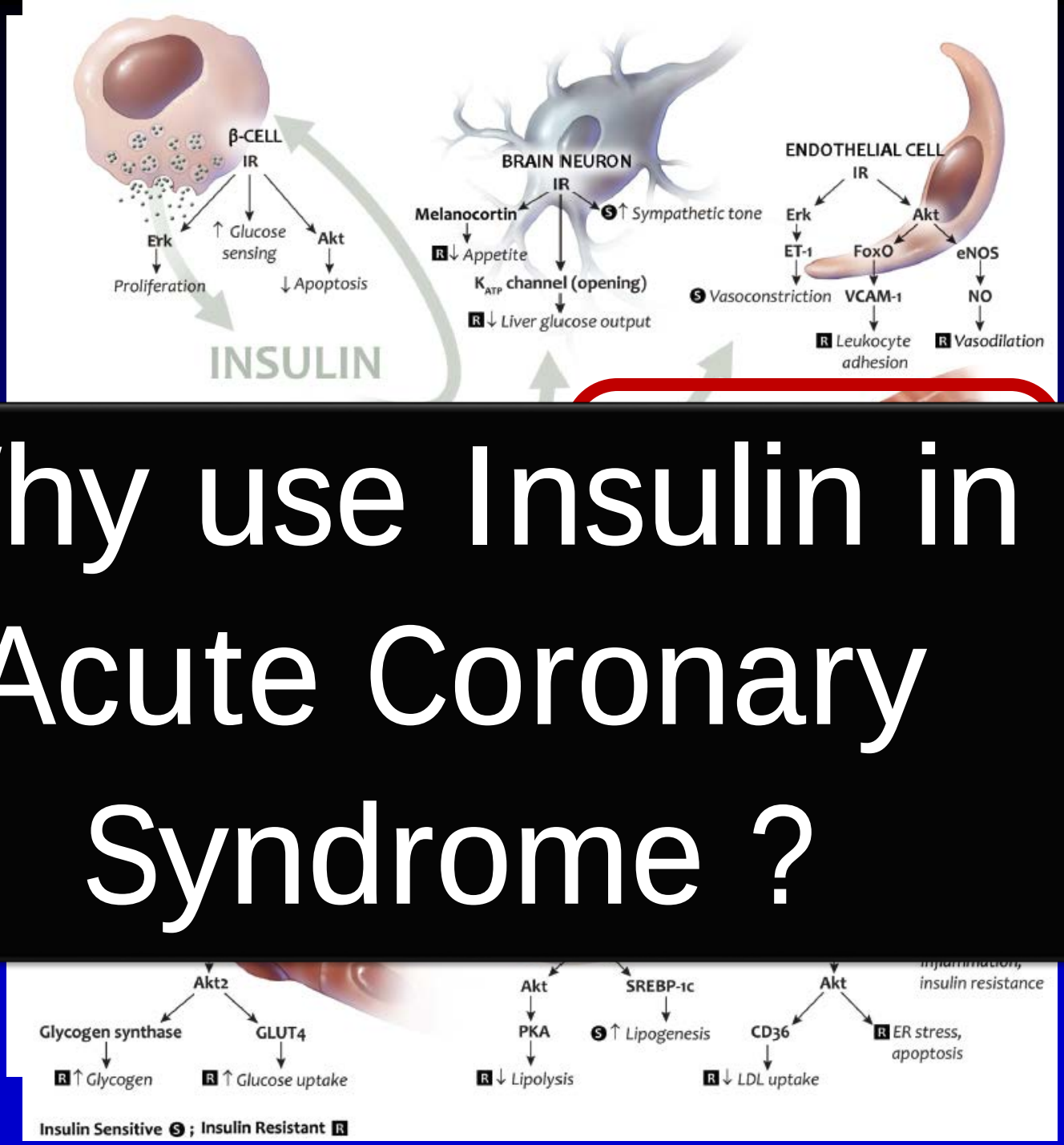
Glucose Homeostasis:
screening algorithm in patients with ACS



Does Glucose Control Matter in ACS?

Summary of Clinical Trials





Why use Insulin in Acute Coronary Syndrome ?

Rask-Madsen C ATVB. 2012

ACUTE CORONARY SYNDROMES

Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome

C Weston, L Walker, J Birkhead, National Audit of Myocardial Infarction Project, National Institute for Clinical Outcomes Research

Heart 2007;**93**:1542–1546. doi: 10.1136/hrt.2006.108696

- The UK **M**yocardial **I**nfarction **N**ational **A**udit **P**rogramme (MINAP): observational study in 201 hospitals in England and Wales;
- 38,864 pts with ACS, troponin positive, not previously known to have diabetes mellitus and whose BG on admission was >11 mmol/L (>200 mg/dL);

	No treatment		Any insulin regime					
All deaths	n	%	n	%	Relative risk*	Adjusted relative risk	95% CI	p Value
7 days	290/1761	16.5	101/868	11.6	1.42	1.56	1.22 to 2.0	<0.001
30 days	389/1761	22.1	137/868	15.8	1.40	1.51	1.22 to 1.86	<0.001
Deaths on day of admission excluded								
1–7 days	228/1682	13.6	80/841	9.5	1.43	1.43	1.09 to 1.89	0.011
1–30 days	327/1682	19.4	116/841	13.8	1.41	1.41	1.11 to 1.78	0.004

Diabetes and Insulin-Glucose Infusion in Acute MI Study (DIGAMI)

- Prospective, randomized trial of 620 patients with acute MI

- Glycemic Control in Patients With Acute MI is “cost effective”;
- Importance of early and aggressive glucose control, regardless of prior diabetes status;
- For every 9 patients treated with intensive insulin regimen, one life was saved

0 1 2 3 4 5 0 1 2 3 4 5

Follow-up (years) Follow-up (years)

Malmberg K, et al. J Am Coll Cardiol. 1995; BMJ. 1997;314:1512–1515.

DIGAMI-2 and CREATE-ECLA outcomes show need for glucose control

Study (Year)	N	Treatment*	Outcomes
DIGAMI 1 (1995)	620 DM	IV GIK ≥24 hr + multidose sc insulin ≥3 months	Mortality ↓18% In-hospital (NS) ↓21% 90-days (NS) ↓29% 1-year ($P < 0.05$)
DIGAMI 2 (2005)	1253 DM	IV GIK ≥24 hr ± multidose sc insulin >3 months	Mortality neutral
CREATE-ECLA (2005)	20,201	IV GIK 24 hr	Mortality, cardiac arrest, cardiogenic shock, reinfarction neutral

*vs usual care

Malmberg K et al. *J Am Coll Cardiol*. 1995.
Malmberg K et al. *Eur Heart J*. 2005.
CREATE-ECLA Trial Group Investigators. *JAMA*. 2005.

ESC
European Society of Cardiology
European Heart Journal (2017) **00**, 1–66
doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

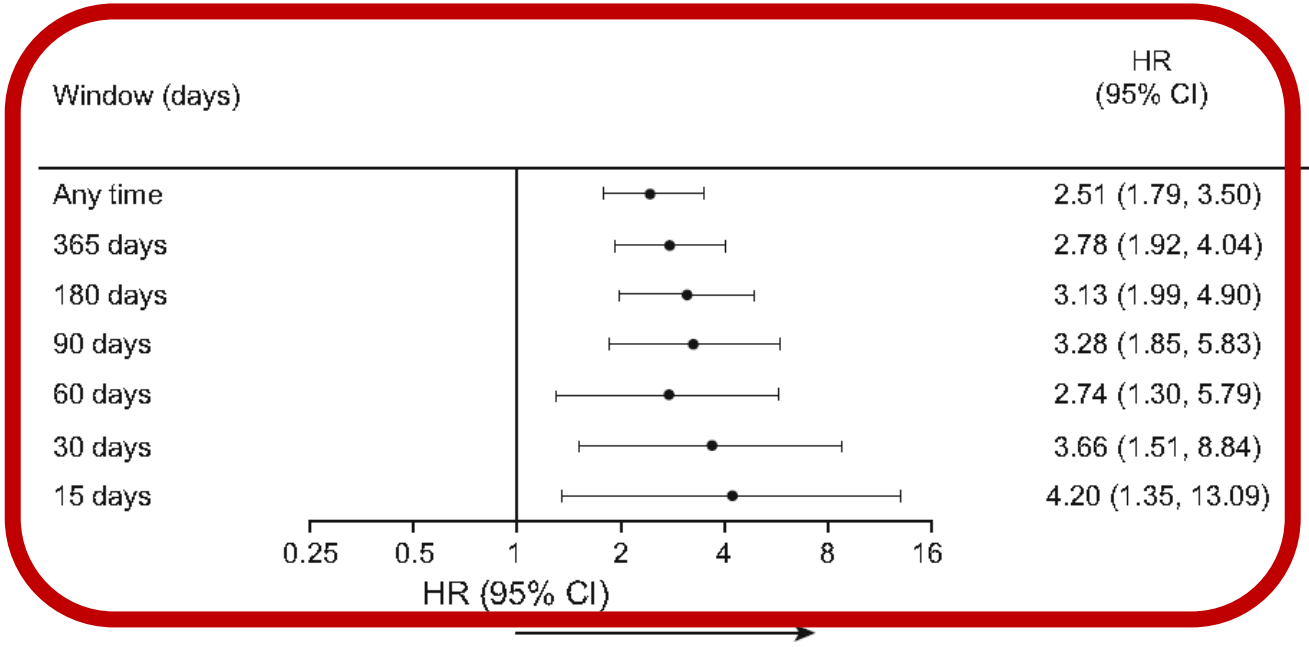
2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

- It is recommended to evaluate glycaemic status in all STEMI pts with and without a known history of diabetes or hyperglycaemia;
- In the absence of robust data to guide the optimal glucose management (eg treatment thresholds and glucose targets) in STEMI patients, a close but not too strict glucose control seems the best approach;
- In the acute phase, it is reasonable to manage hyperglycaemia (ie maintain a BG concentration ≤11.0mmol/L or 200 mg/dL) but absolutely avoid hypoglycaemia (< 70 mg/dL)

Diabetologia
DOI 10.1007/s00125-017-4422-0

ARTICLE

DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality



Window (days)	HR (95% CI)	All-cause mortality with prior severe hypoglycaemia in window		All-cause mortality without prior severe hypoglycaemia in window	
		n	Rate	*n*	Rate
Any time	2.51 (1.79, 3.50)	38	7.32	385	2.64
365 days	2.78 (1.92, 4.04)	30	7.78	393	2.67
180 days	3.13 (1.99, 4.90)	20	8.56	403	2.71
90 days	3.28 (1.85, 5.83)	12	8.95	411	2.74
60 days	2.74 (1.30, 5.79)	7	7.40	416	2.77
30 days	3.66 (1.51, 8.84)	5	9.84	418	2.77
15 days	4.20 (1.35, 13.09)	3	11.23	420	2.78

Higher risk of all-cause mortality any time following severe hypoglycaemia

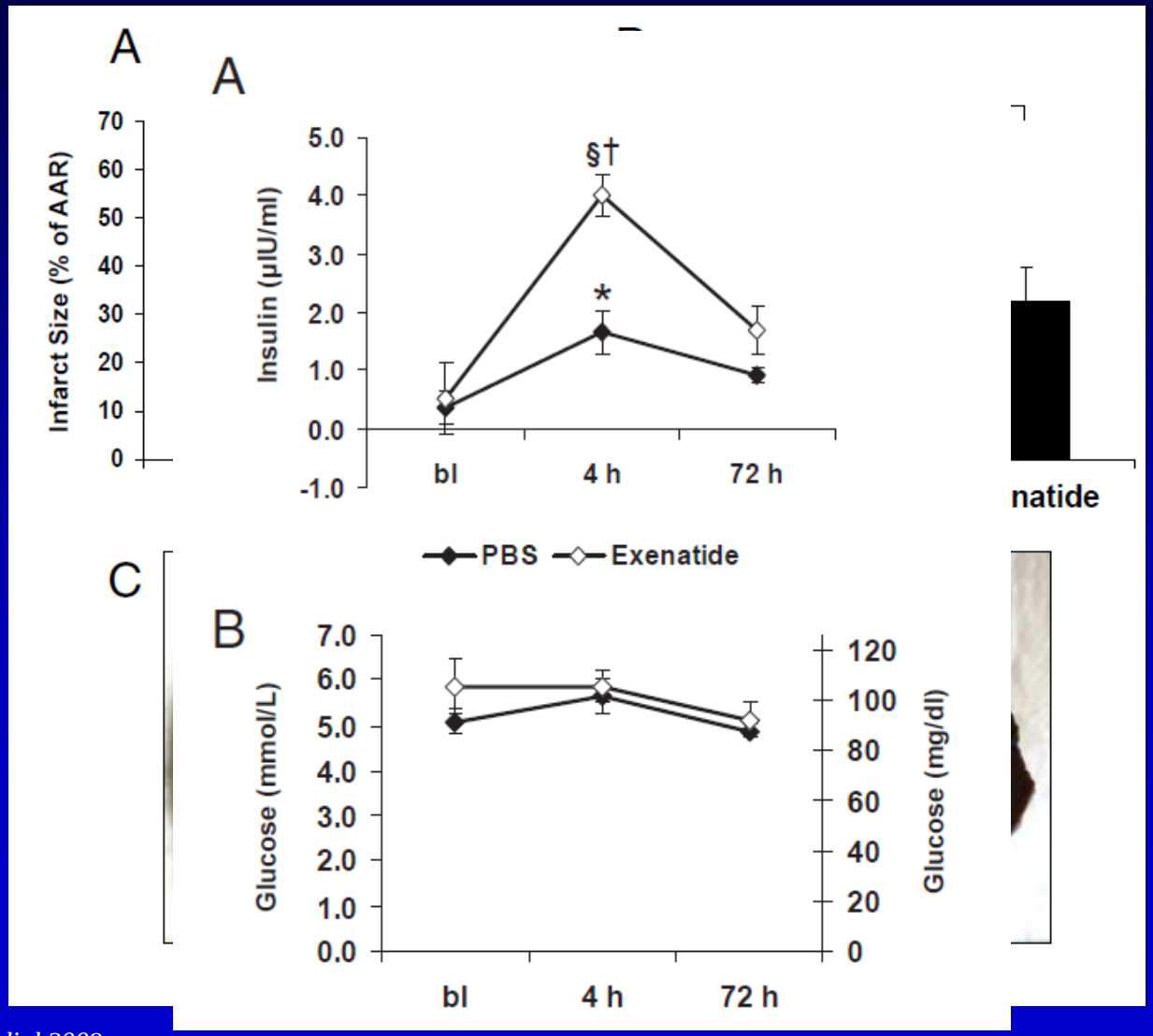
Desouza CV et al. Diab Care 2010; 33:1389-1394

Acute glucose lowering without inducing hypoglycaemia:

a possible role for GLP-1 analogues and mimetics

As normalization of hyperglycaemia is most likely beneficial in ACS, strategies that overcome the risk of hypoglycaemia might be more beneficial than insulin infusion in ACS

Exenatide Reduces Infarct Size and Improves Cardiac Function in a Porcine Model of Ischemia and Reperfusion Injury

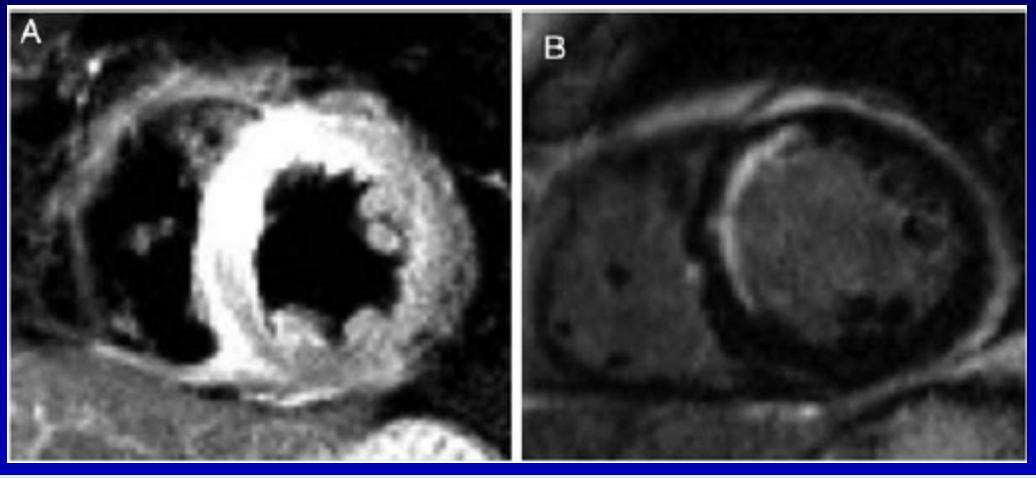


Timmers L et al. J Am Coll Cardiol 2009

European Heart Journal (2012) **33**, 1491–1499
doi:10.1093/eurheartj/ehr309

CLINICAL RESEARCH
Acute coronary syndromes

Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction



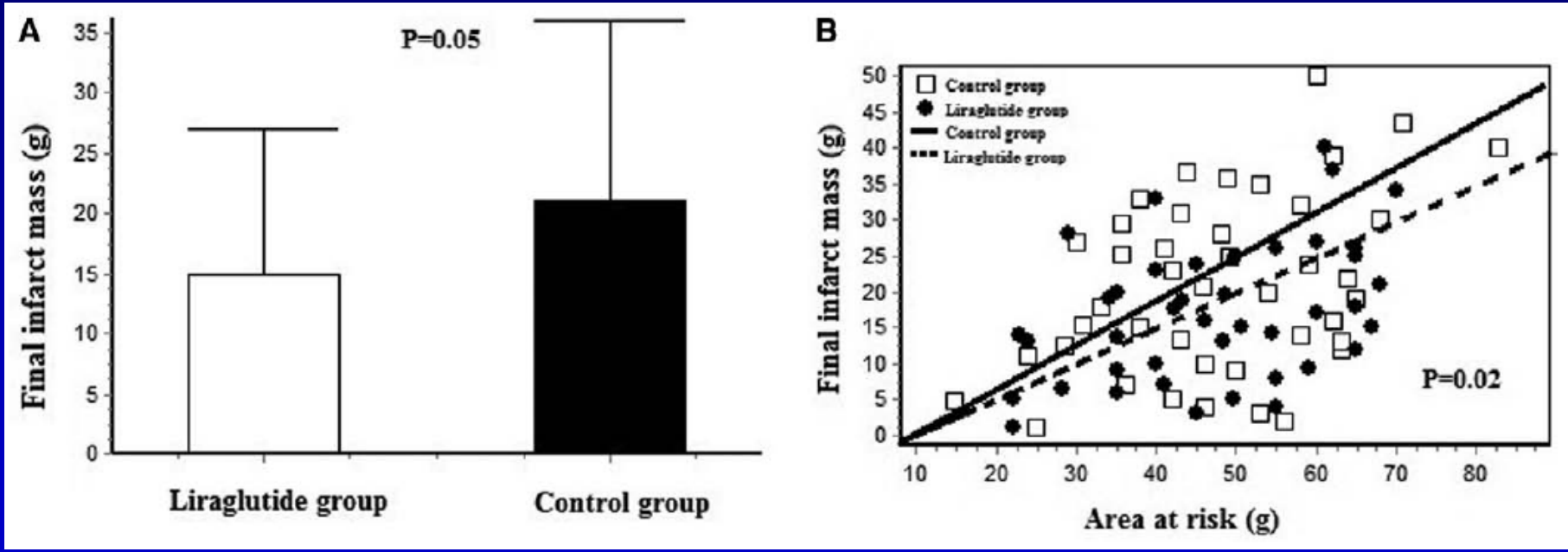
	n	Exenatide	*n*	Placebo	*P*-value
Overall study population					
Salvage index[a]	54	0.71 ± 0.13	51	0.62 ± 0.16	0.003
Infarct size (g)/area at risk (g)	54	0.30 ± 0.15	51	0.39 ± 0.15	0.003

In patients with STEMI undergoing pPCI, administration of exenatide at the time of reperfusion increases myocardial salvage

Coronary Artery Disease

Circ Cardiovasc Imaging. 2016;

Effects of Liraglutide on Reperfusion Injury in Patients With ST-Segment–Elevation Myocardial Infarction



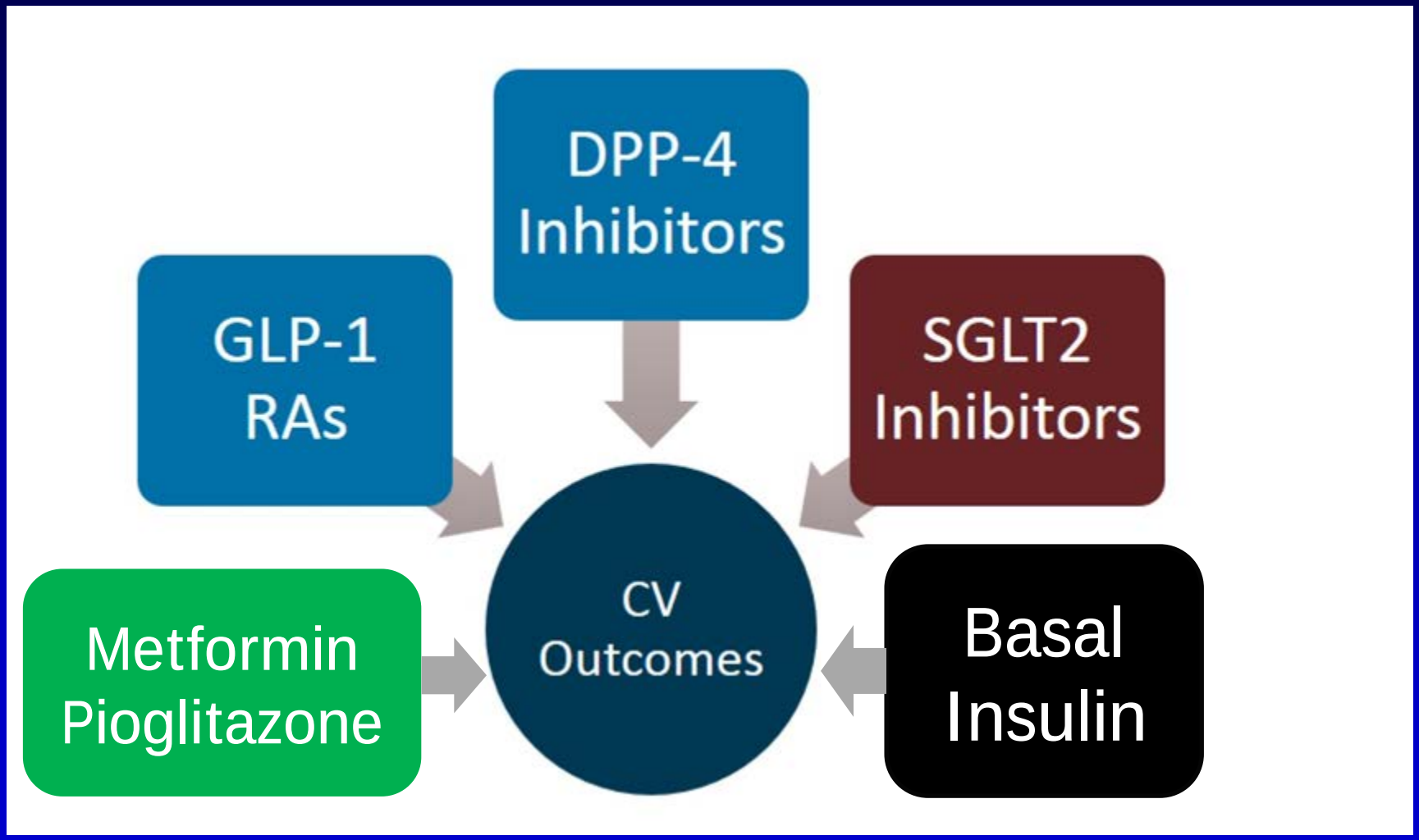
Liraglutide improves myocardial salvage and infarct size after STEMI, possibly by reducing reperfusion injury

AREA CRITICA: SUM-UP

- Screening glicemico: un “must” in tutti i pz con sindrome coronarica acuta;
- Trattamento precoce con insulina migliora gli outcomes a patto di prevenire l’ipoglicemia (obiettivi rationali ma non rigorosi);
- Ruolo dei GLP-1 RAs in fase acuta (↓ area ischemica?)

Cosa Fare nel periodo post-critico?

CV Outcomes with Glucose Lowering Agents



Cheng JWM, et al. Curr Med Res Opin 2017

SID
Società Italiana
di Diabetologia

POSITION STATEMENT

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

Enzo Bonora, Antonio Bossi, Daniela Bruttomesso, Angelo De Pascale, Gabriella Gruden, Davide Lauro, Frida Leonetti, Edoardo Mannucci, Roberto Miccoli, Annalisa Natalicchio, Gianluca Perseghin, Francesco Purrello, Ferdinando Sasso, Giorgio Sesti

Box 1 *- Al momento attuale i farmaci ipoglicemizzanti che sulla base di RCTs posseggono documentati benefici cardiovascolari sono metformina (prevenzione primaria e secondaria), empagliflozin, canaglifozin, liraglutide e pioglitazone (prevenzione secondaria).*

SGLT2 Inhibitors
CV Benefit a Class Effect?

- CVD-REAL: real-world study, across 6 countries, broad population of patients with T2D (87% did not have known CVD); N>300,000
- Largely, driven by canagliflozin in the United States and dapagliflozin in Europe

Primary Analysis: HHF SGLT2is vs other GLDs

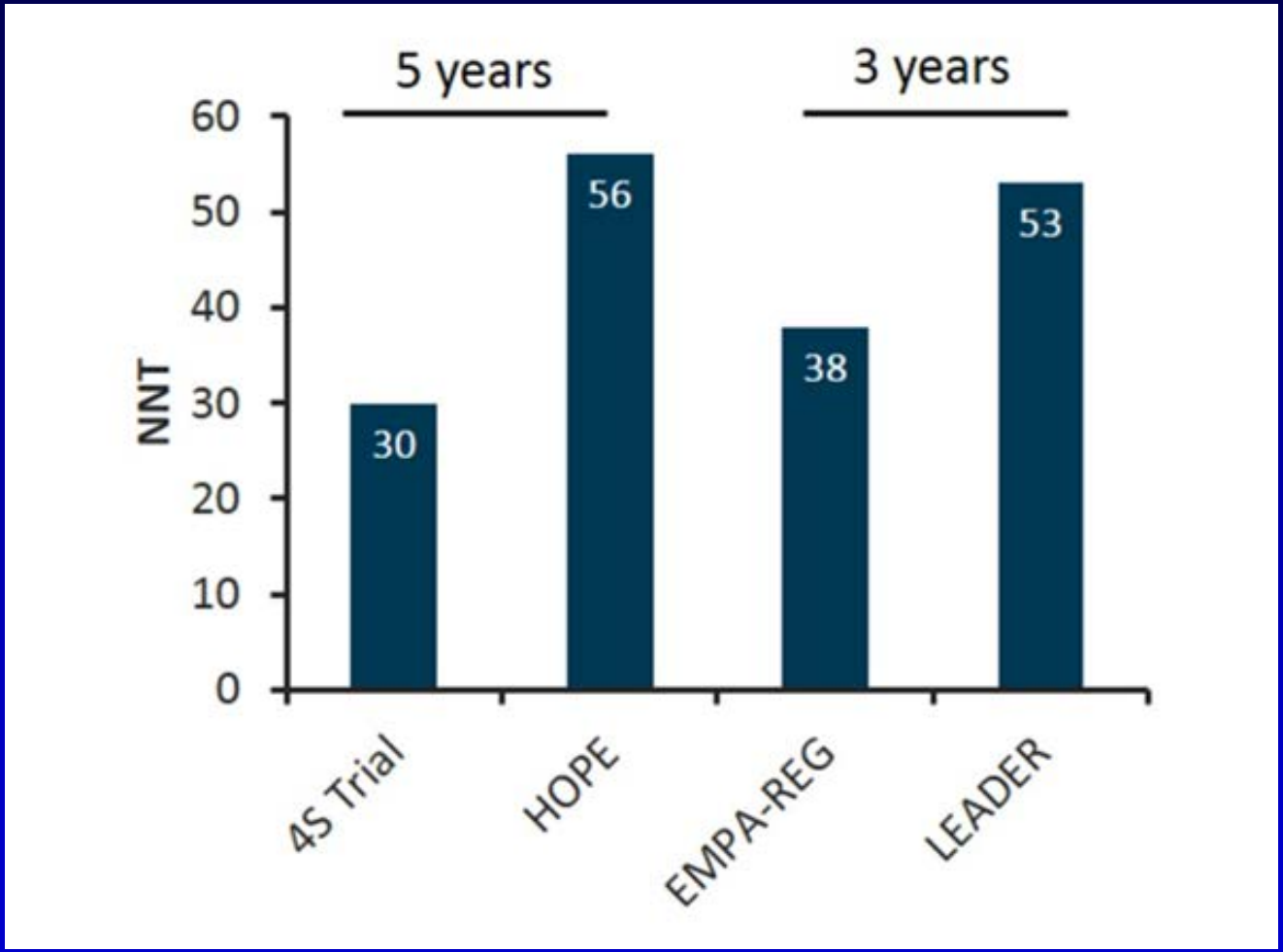
Database	N	No. of Events	HR (95% CI)
USA	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	**309,056**	**961**	**0.61 (0.51, 0.73)**

Secondary Outcome: Risk of All-Cause Mortality SGLT2is vs other GLDs

Database	N	No. of Events	HR (95% CI)
USA	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	**215,622**	**1334**	**0.49 (0.41, 0.57)**

Kosiborod M. *Circulation*. 2017;136:249-259.

High Risk CV Outcomes: NNT to Save 1 CV Event



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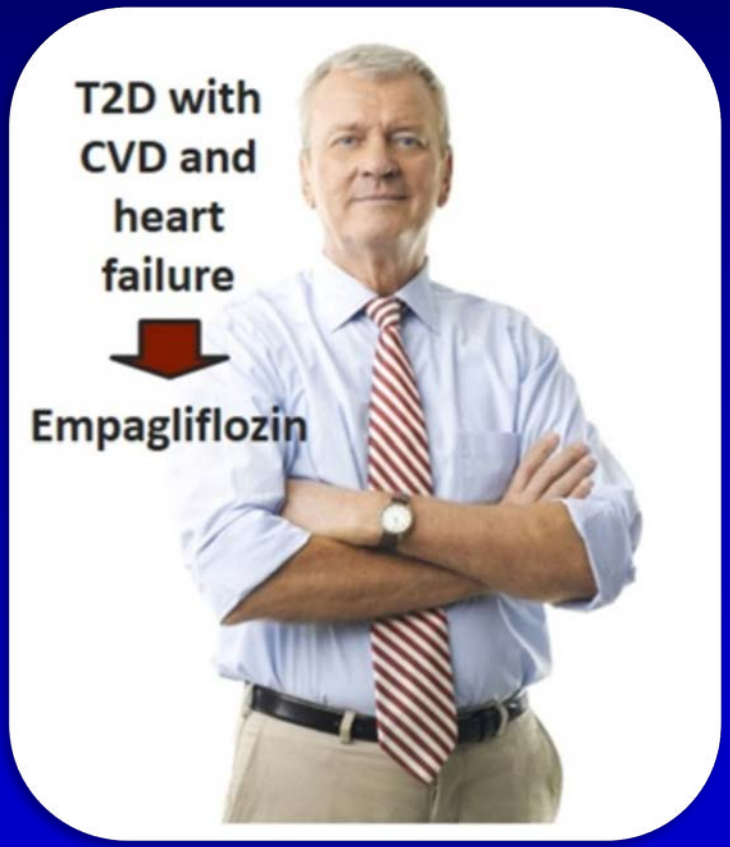
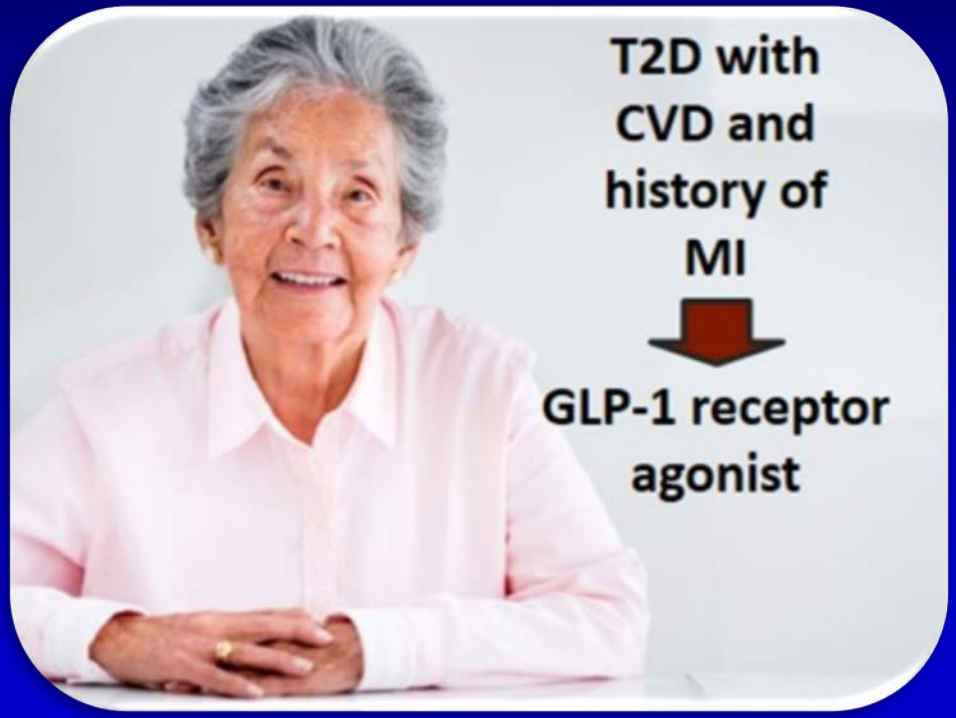
Box 3 *- In pazienti con pregressa malattia cardiovascolare la terapia ipoglicemizzante dovrebbe includere inibitori di SGLT2 , in particolare empaglifozin, canaglifozin e liraglutide anche in presenza di buon controllo glicemico con la terapia in corso.*

Box 4 *– I risultati dei CVOT non sembrano suggerire un effetto classe per quanto riguarda gli agonisti del recettore di GLP-1.*
L'effetto classe degli inibitori di SGLT-2 sui MACE sembra essere suggerito dagli studi EMPA-REG OUTCOME (empagliflozin) e CANVAS (canagliflozin), anche se emergono delle differenze nel profilo di sicurezza tra le varie molecole.

Box 2 *- L'associazione di inibitori di SGLT2 , in particolare empaglfozin e canaglifozin, e liraglutide potrebbe essere una opzione terapeutica per i pazienti con pregressa malattia cardiovascolare.*

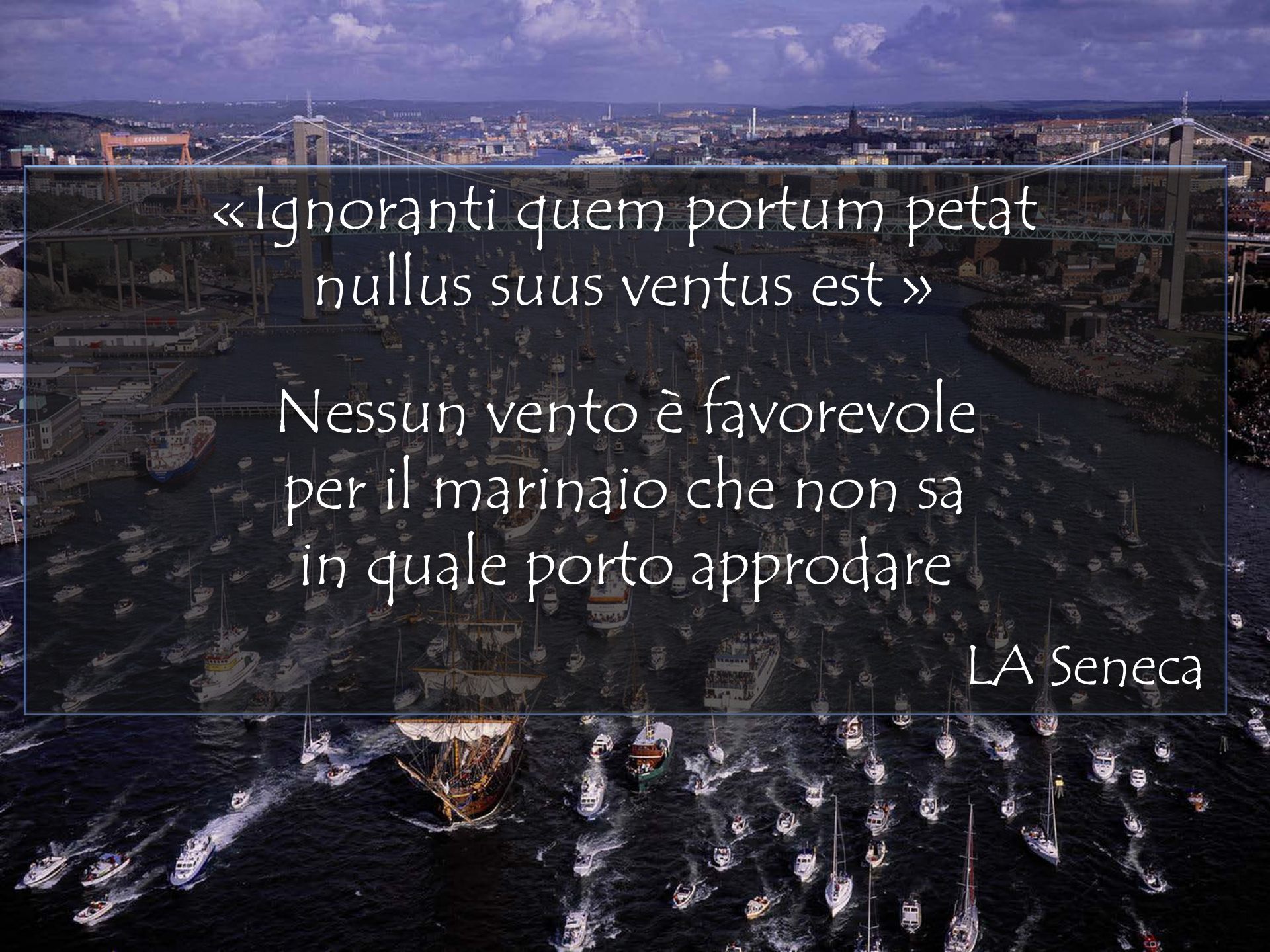
Quale Molecola per Quale Paziente?





Conclusions

- Hyperglycemia is a common finding in ACS but still many gaps in knowledge exist (glucose threshold);
- In acute setting insulin treatment is cost-effective, as far as hypoglycemia is avoided, while the role of GLP-1RAs in limiting infarct area deserves attention;
- Emerging glucose-lowering agents (GLP-1RAs and SGLT2-I) demonstrate significant improvement in CV outcomes, but each agent has its own CV benefit profile (“precision medicine”)

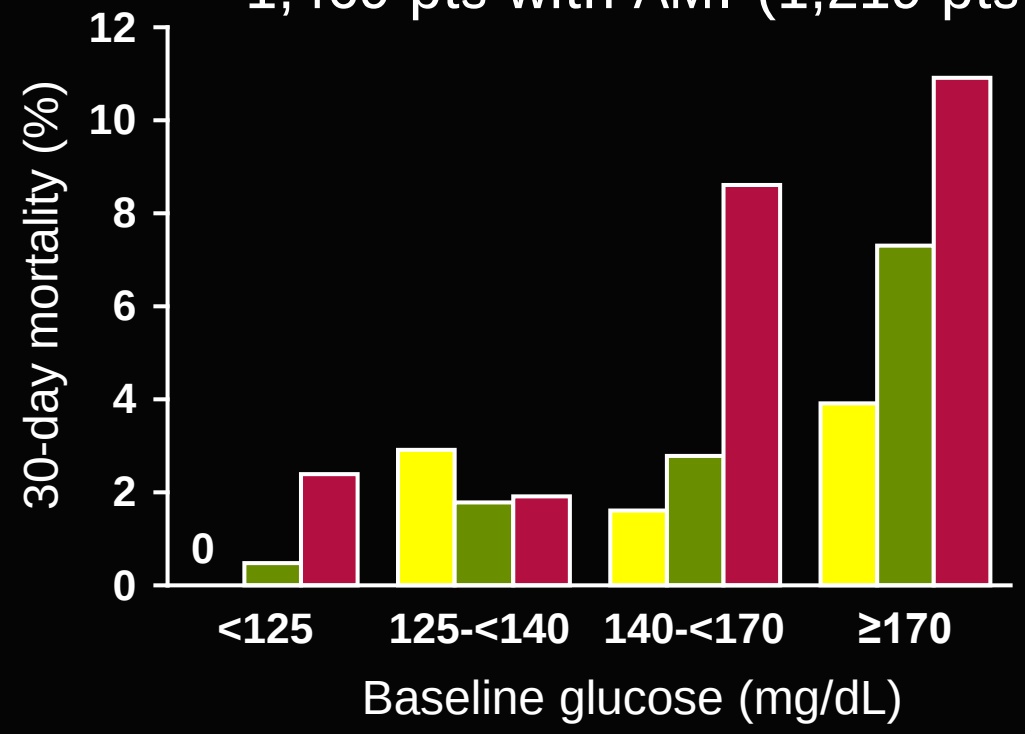


«Ignoranti quem portum petat
nullus suus ventus est »

Nessun vento è favorevole
per il marinaio che non sa
in quale porto approdare

LA Seneca

Admission glucose and glucose change within 24 hours predict mortality risk



↓ 9% in 30-day mortality per ↓11 mg/dL glucose in first 24 h (P = 0.002)*

***Multivariate analysis**

ΔGlucose (24 hr vs baseline)

- **≥30 mg/dL decrease**
- **No change to <30 mg/dL decrease**
- **Increase**

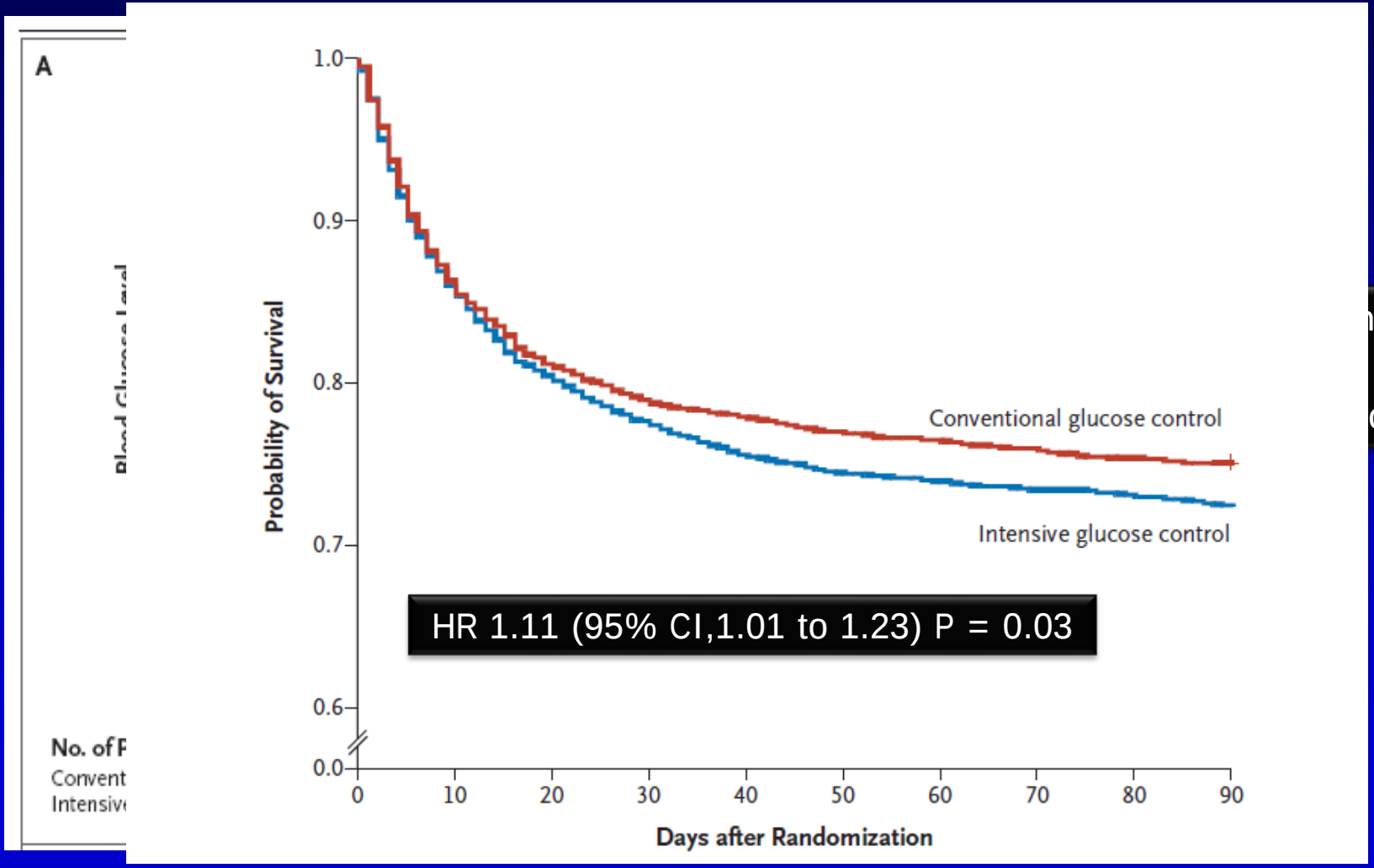
Goyal A et al. Eur Heart J. 2006;27:1289-97

ESTABLISHED IN 1812 MARCH 26, 2009 VOL. 360 NO. 13

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NEW ENGLAND JOURNAL of MEDICINE

The NICE-SUGAR Study Investigators*



ng/dL;

dL

Obiettivi glicemici nel paziente ospedalizzato: pazienti critici

	American Diabetes Association
Critically ill p.	in general < 180 mg/dL glucose range 140-180 mg/dL i.v. insulin preferred – local protocol

Moghissi E. et al. ADA/AACE recommendations 2009

Gli obiettivi glicemici

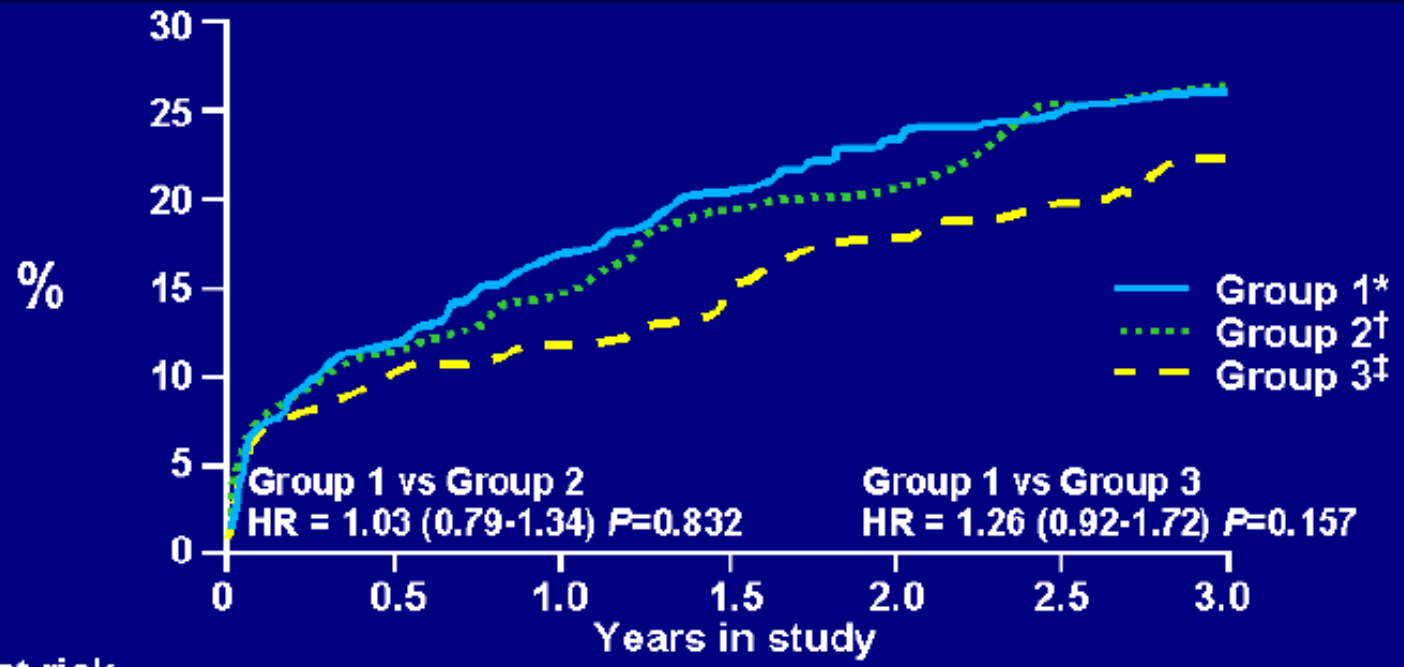
Gli obiettivi glicemici durante un ricovero ospedaliero possono essere differenziati in funzione delle diverse situazioni cliniche:

- Pazienti in situazione critica, ricoverati in Terapia Intensiva, medica o chirurgica: valori glicemici 140-180 mg/dl, in funzione del rischio stimato di ipoglicemia.

(**Livello della prova II, Forza della raccomandazione B**)

Standard italiani per la cura del diabete mellito 2009-2010
SID-AMD

DIGAMI 2



No. at risk							
Group 1	474	415	357	309	252	196	113
Group 2	473	416	358	297	256	196	100
Group 3	306	272	250	211	177	150	98

*Intensive insulin tx + insulin-based long-term glucose control
†Intensive insulin tx + standard glucose control
‡Routine management according to local practice

Malmberg K, et al. Eur Heart J 2005;26:650-61

JAMA | Original Investigation

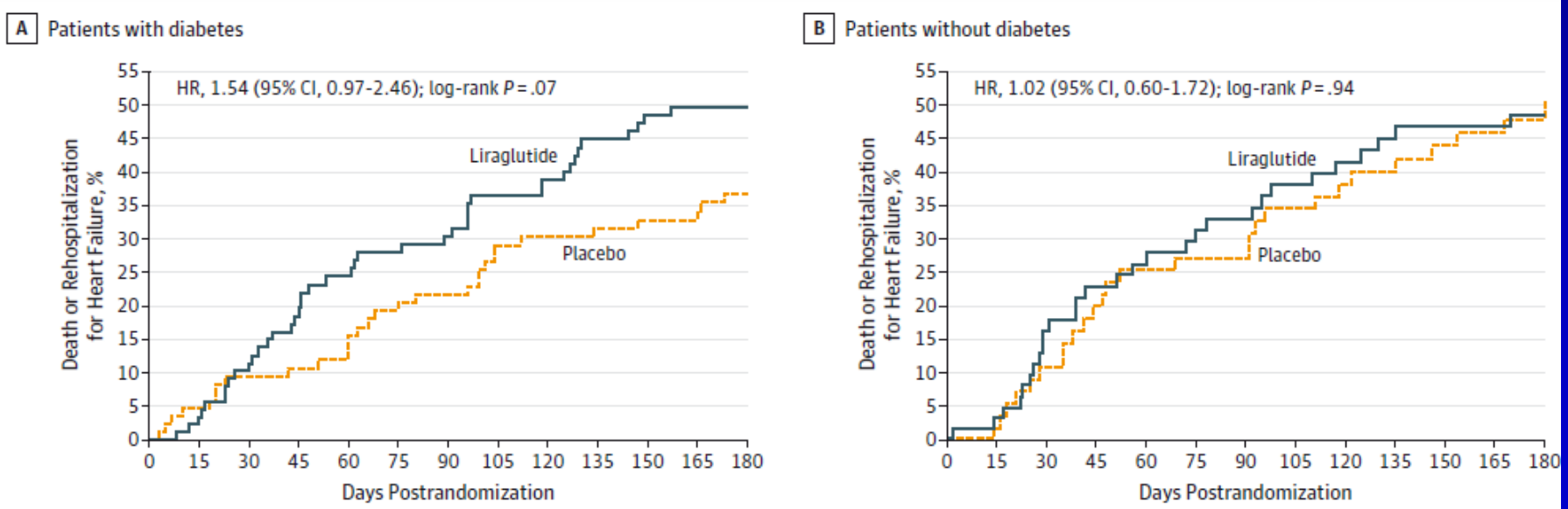
FIGHT study : **F**unctional **I**mpact of **G**LP-1 for **H**eart Failure **T**reatment

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction

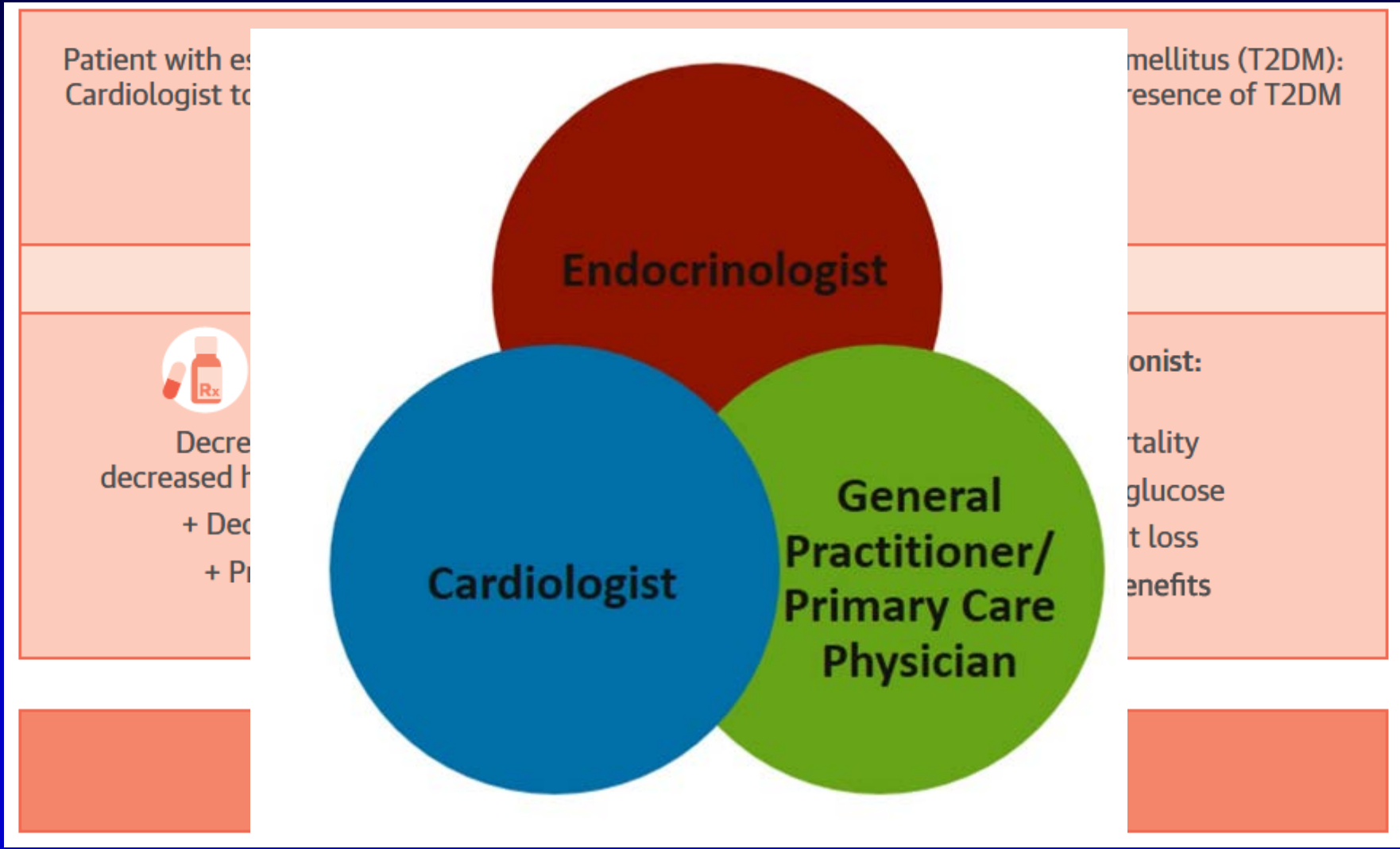
A Randomized Clinical Trial

Kenneth B. Margulies, MD; Adrian F. Hernandez, MD, MHS; Margaret M. Redfield, MD; Michael M. Givertz, MD; Guilherme H. Oliveira, MD; Robert Cole, MD; Douglas L. Mann, MD; David J. Whellan, MD, MHS; Michael S. Kiernan, MD, MS; G. Michael Felker, MD, MHS; Steven E. McNulty, MS; Kevin J. Anstrom, PhD; Monica R. Shah, MD, MSH; Eugene Braunwald, MD; Thomas P. Cappola, MD, ScM; for the NHLBI Heart Failure Clinical Research Network

Patients Who Died or Experienced Rehospitalization for Heart Failure by T2 Diabetes Status



Novel Paradigm for Care of the Patient With CV Disease and T2DM



Sattar, N. et al. J Am Coll Cardiol. 2017

FDA Warning for the DPP-4 Inhibitors Regarding HF

For Alogliptin

- Consider the risks and benefits of alogliptin prior to initiating treatment in patients at risk for HF
  - If HF develops, evaluate and manage according to current standards of care and consider discontinuation of alogliptin

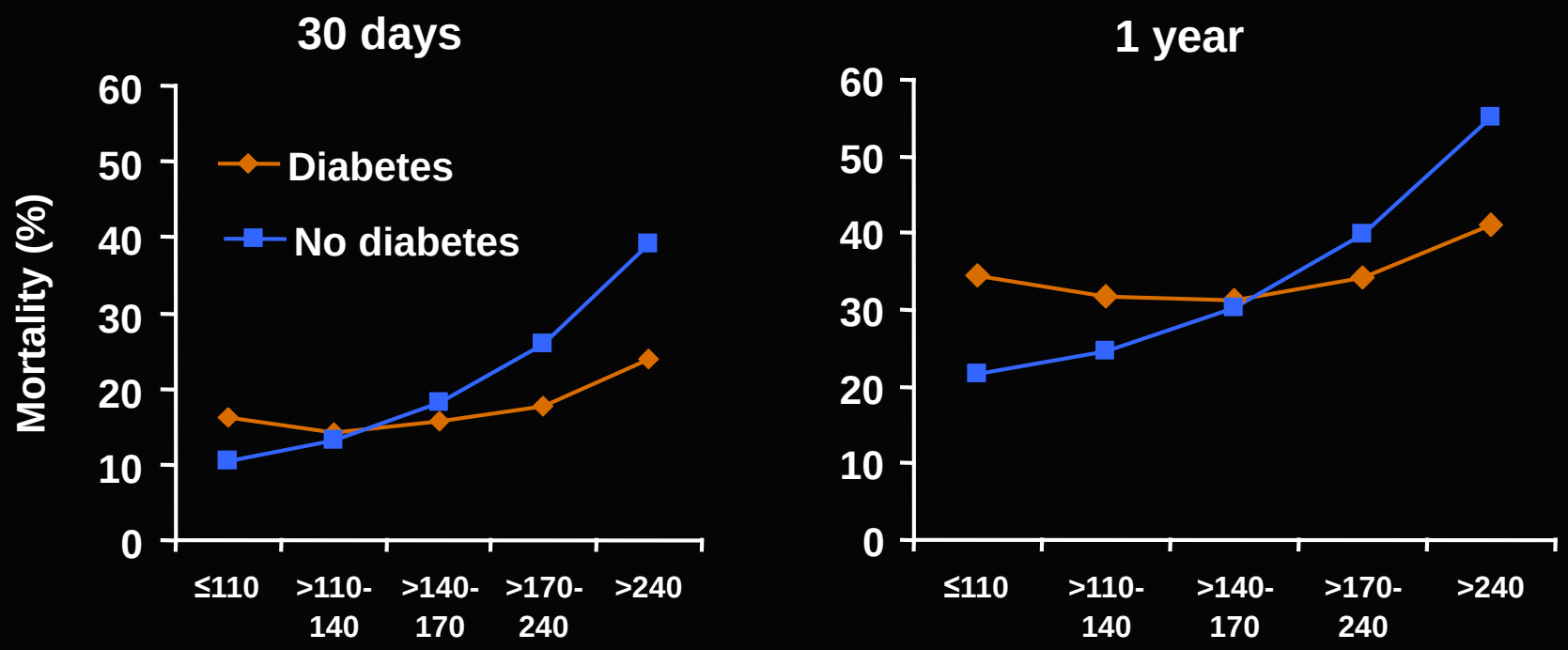
For Saxagliptin

- Consider the risks and benefits of saxagliptin prior to initiating treatment in patients at risk for HF
  - If HF develops, evaluate and manage according to current standards of care and consider discontinuation of saxagliptin

US FDA website, 2016.

Admission glucose in AMI associated with mortality, independent of T2D diagnosis

N = 141,680 hospitalized with AMI



Admission glucose (mg/dL)

Kosiborod M et al. Circulation. 2005;111:3078-86.

DIGAMI 2

	DIGAMI 1			DIGAMI 2			
	Control group (n = 314)	Insulin infusion group (n = 306)	*P*-value	Insulin infusion + insulin s.c. long-term (n = 474)	Insulin infusion alone group (n = 473)	Control group (n = 306)	*P*-value
HbA1c at randomization (%)	8.0 ± 2.0	8.2 ± 1.9	NS	7.2 ± 1.7	7.3 ± 1.7	7.3 ± 1.7	NS
HbA1c decrease	0.4 ± 1.5	1.1 ± 1.6	<0.0001	~0.5%	~0.5%	~0.5%	NS
Blood glucose (mg/dL)							
At randomization	283 ± 76	277 ± 74	NS	230 ± 81	223 ± 79	232 ± 83	NS
After 24 h	211 ± 74	173 ± 59	<0.0001	164 ± 54	164 ± 50	180 ± 65	0.0001
Δ24 h	72	104		66	59	52	

- In DIGAMI 2, the acute decrease in glycaemia during insulin infusion was modest and not different between groups;
- No difference in HbA1c could be achieved;
- Advances in the treatment of ACS might have been relevant, as the overall 1-year mortality was 65% of the mortality observed in DIGAMI 1

Malmberg K, et al. Eur Heart J 2005;26:650-61

DIGAMI:
Insulin Therapy Improves Long-term Survival in Patients With MI

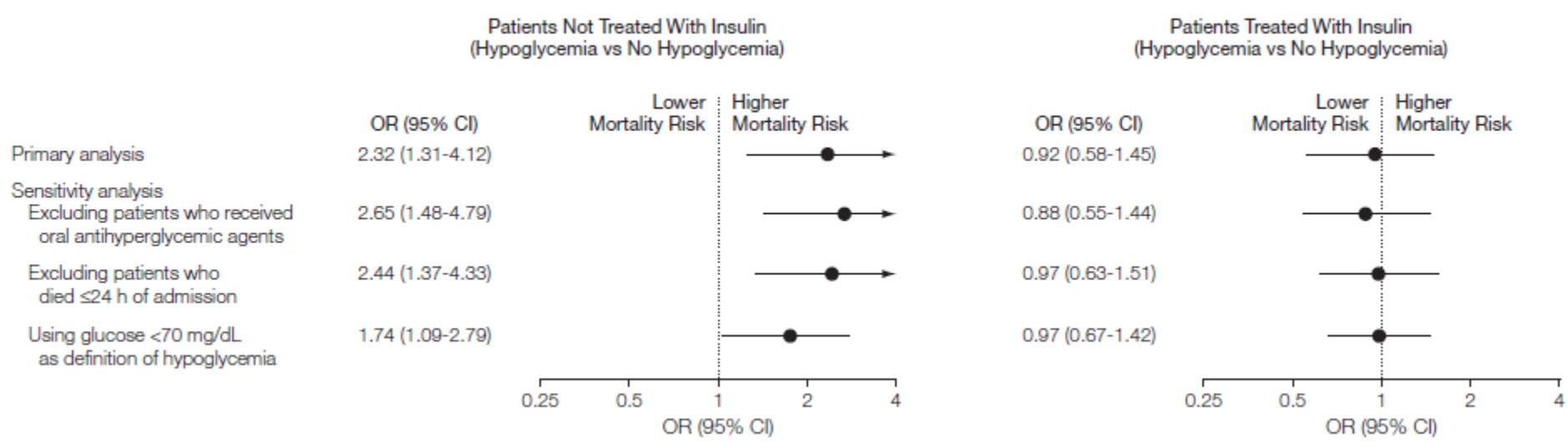
- Glycemic Control in Patients With Acute MI is cost effective;
- Importance of early and aggressive glucose control, regardless of prior diabetes status;
- For every 9 patients treated with intensive insulin regimen, one life was saved

Malmberg K, et al. J Am Coll Cardiol. 1995; BMJ. 1997;314:1512–1515.

Relationship Between Spontaneous and Iatrogenic Hypoglycemia and Mortality in Patients Hospitalized With Acute Myocardial Infarction

JAMA®

JAMA. 2009;301(15):1556-1564



while hypoglycemia is associated with increased short-term mortality in patients hospitalized with AMI, this risk is confined to pts who develop hypoglycemia spontaneously;

hypoglycemia that occurs after initiation of insulin therapy is not linked with higher mortality risk.

hypoglycemia is a marker of severe illness, rather than a direct cause of adverse outcomes.