

CONVEGNO SID AMD UMBRIA

Nel Cuore del Diabete: cardio-diabetologia, approccio integrato, multidisciplinarietà, nuove tecnologie, engagement del paziente/operatore

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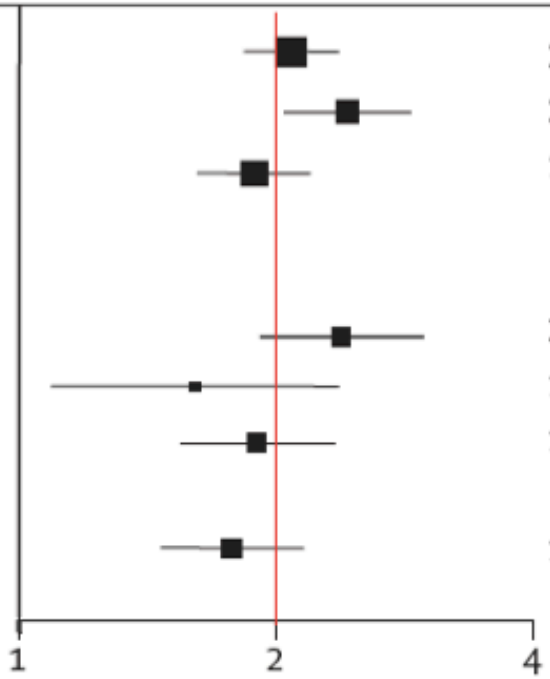
Metformina, sulfoniluree, pioglitazone

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974 ANNO DI FONDAZIONE

SID fondata nel 1964 Società Italiana di Diabetologia

Cardiovascular risk in diabetes

	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26 505	2·00 (1·83–2·19)	64 (54–71)
Coronary death	11 556	2·31 (2·05–2·60)	41 (24–54)
Non-fatal myocardial infarction	14 741	1·82 (1·64–2·03)	37 (19–51)
Stroke subtypes*			
Ischaemic stroke	3799	2·27 (1·95–2·65)	1 (0–20)
Haemorrhagic stroke	1183	1·56 (1·19–2·05)	0 (0–26)
Unclassified stroke	4973	1·84 (1·59–2·13)	33 (12–48)
Other vascular deaths	3826	1·73 (1·51–1·98)	0 (0–26)



Analyses based on 530,083 participants from 102 prospective studies.
HRs adjusted for age, smoking status, body-mass index and systolic blood pressure, and, where appropriate, stratified by sex and trial arm.

Emerging Risk Factors Collaboration. *Lancet* 2010; 375: 2215-22

Reducing risk for complications

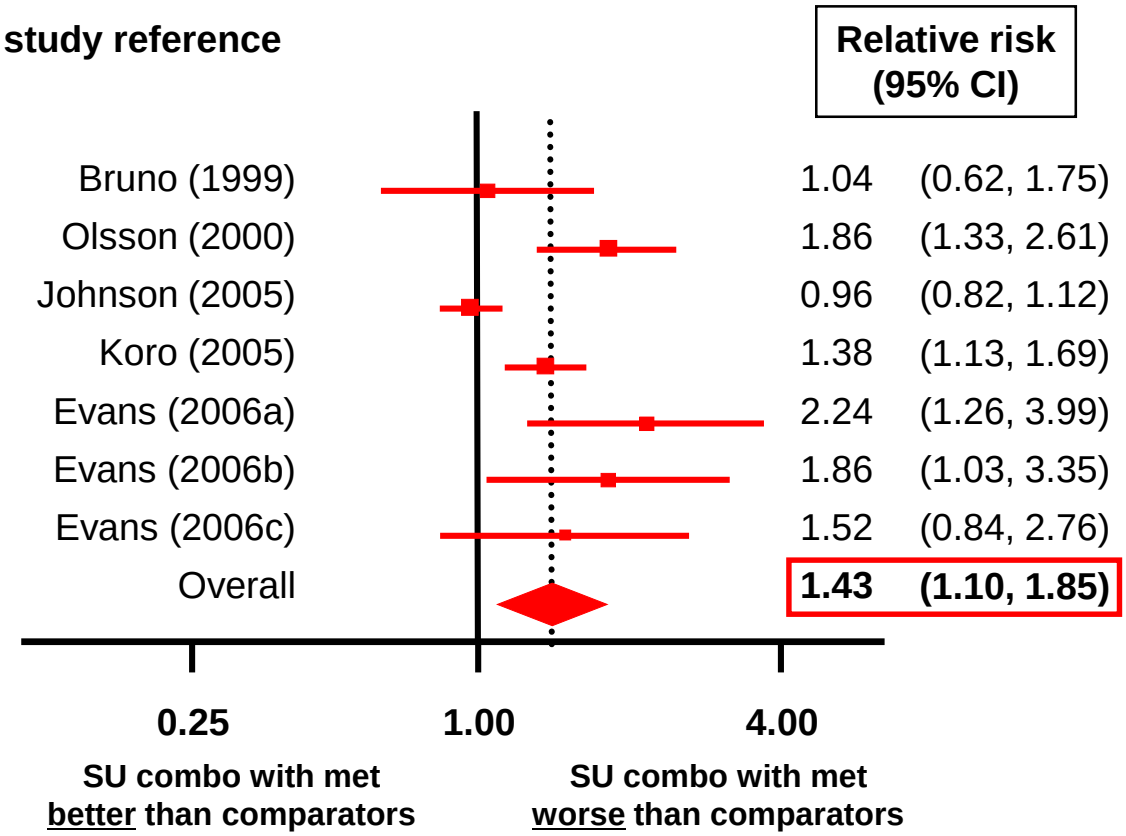
- Microvascular
  - **Glucose**
  - **Blood pressure (esp retinopathy, nephropathy)**
  - Lipids
  - Smoking cessation
- Macrovascular
  - **Blood pressure**
  - **Lipids**
  - **Antiplatelet agents**
  - Smoking cessation
  - Glucose

Hypoglycemic therapy and CV risk

Combination of SUs and Metformin may be Linked to Higher Risk for CVD and All-cause Mortality*

Meta-analysis data from 9 clinical studies

Risk ratios for composite end point of CVD hospitalizations or CVD mortality*

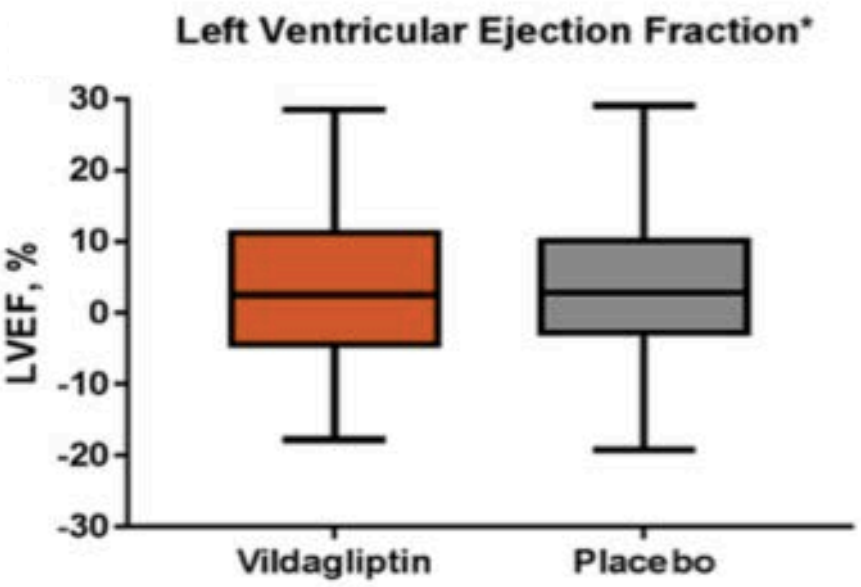


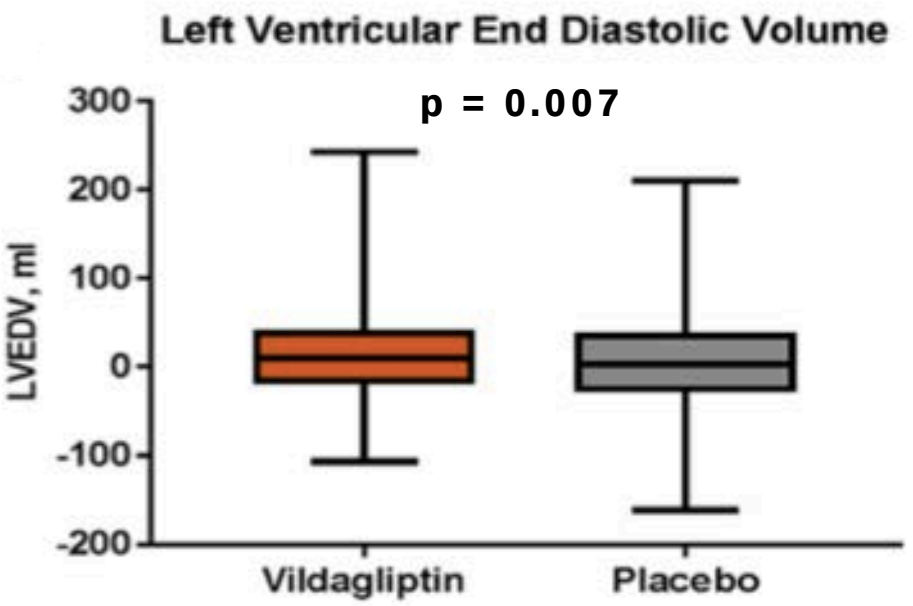
CI=confidence interval; CVD=cardiovascular disease; met=metformin; NS=not specified; SU=sulfonylureas

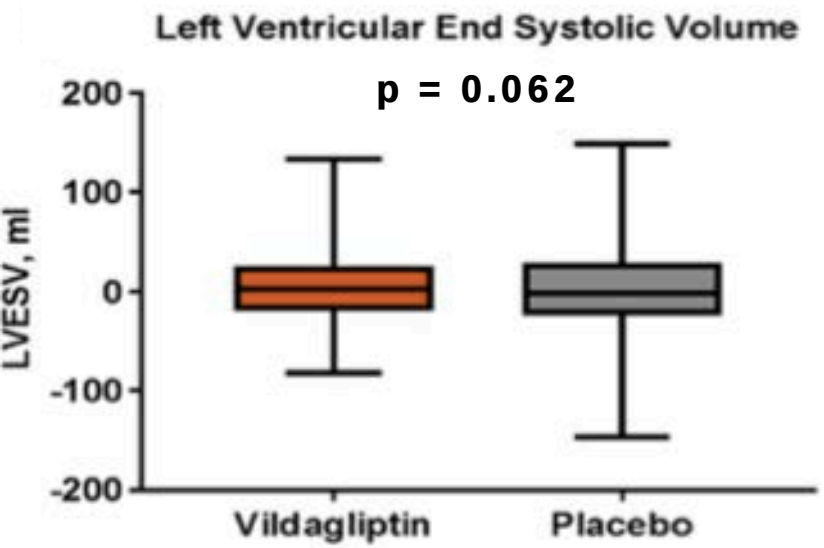
*Composite end point of CVD hospitalizations or CVD mortality – only statistically significantly increased end point.

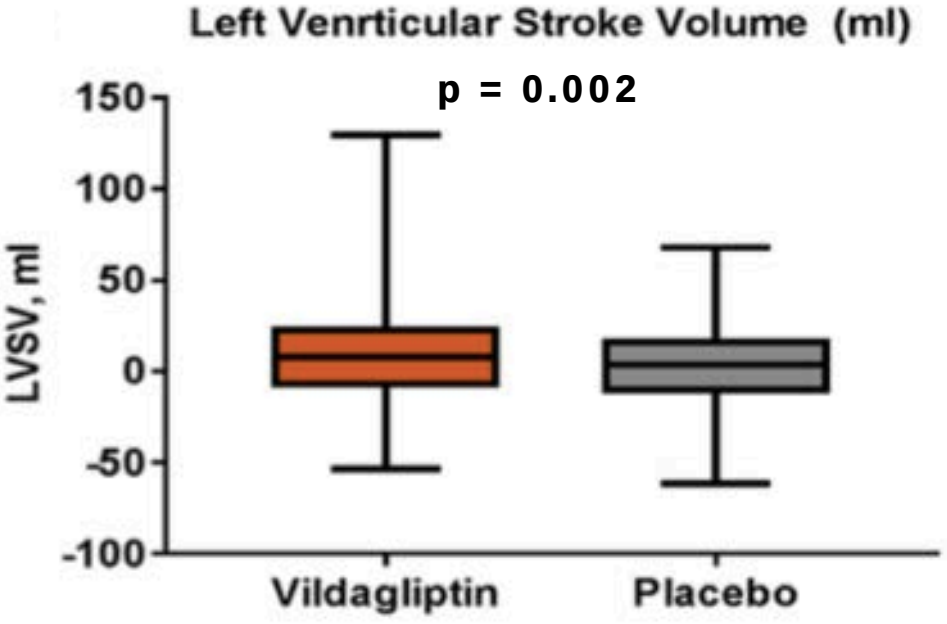
Rao A, et al. *Diabetes Care*. 2008; 31: 1672–1678.

Change From Baseline in LVEF (Primary Endpoint) and Other Echocardiographic Measurements (n=254)



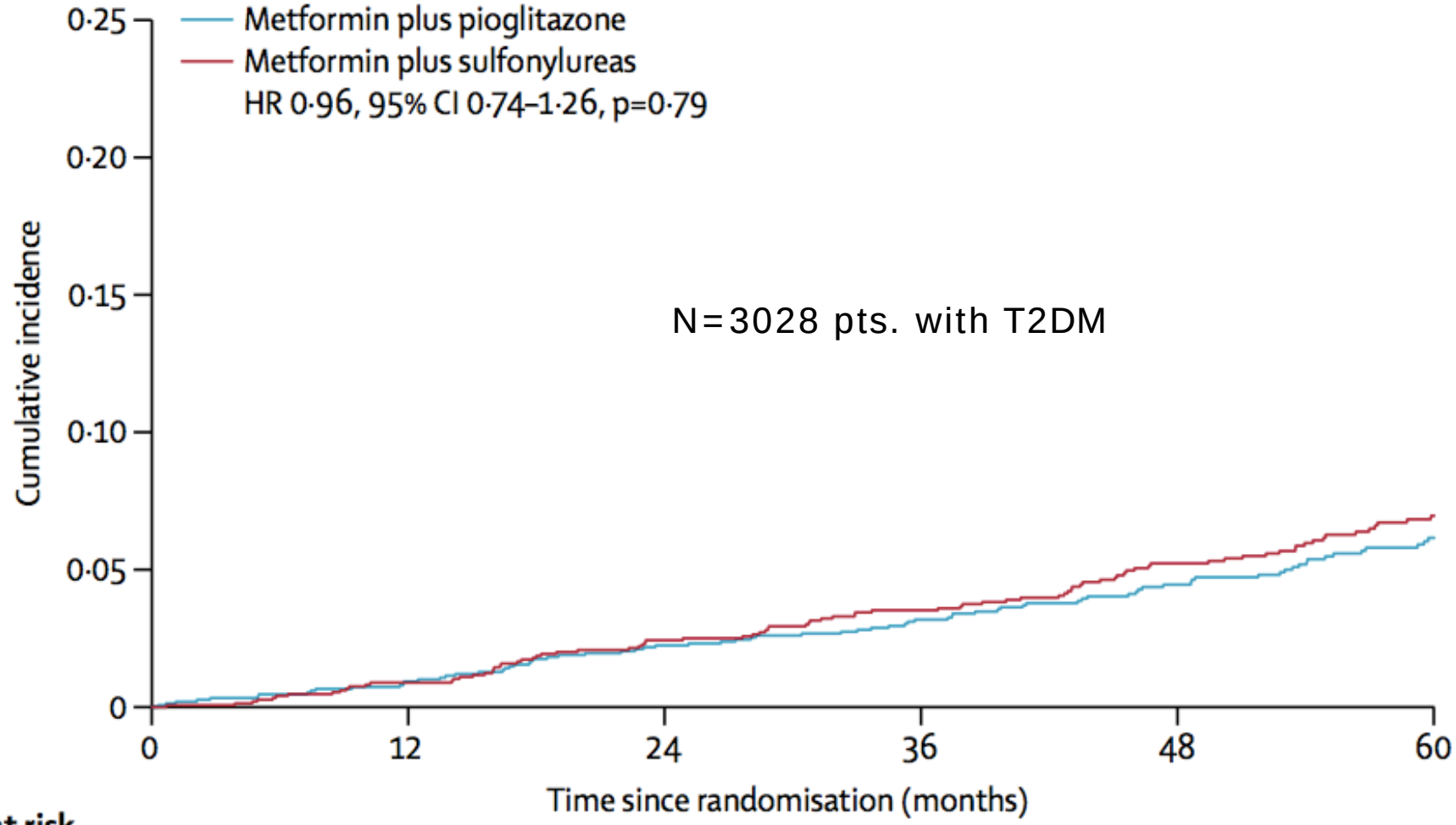






J Am Coll Cardiol HF 2017

First occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, or urgent coronary revascularisation



Number at risk (events)					
Metformin plus pioglitazone	1535 (14)	1462(19)	1393 (14)	1317 (16)	1097 (17)
Metformin plus sulfonylureas	1493 (14)	1432 (24)	1368 (15)	1291 (21)	1085 (17)

Lancet Diabetes Endocrinol 2017

Cardiovascular history of patients in TOSCA and VIVIDD

Previous cardiovascular history		
Previous cardiovascular disease*	187 (12%)	148 (10%)
Previous acute myocardial infarction	109 (7%)	86 (6%)
Previous stroke	28 (2%)	13 (1%)
Previous acute coronary syndrome	39 (3%)	40 (3%)
Carotid artery revascularisation	14 (1%)	12 (1%)
Coronary artery revascularisation	105 (7%)	101 (7%)

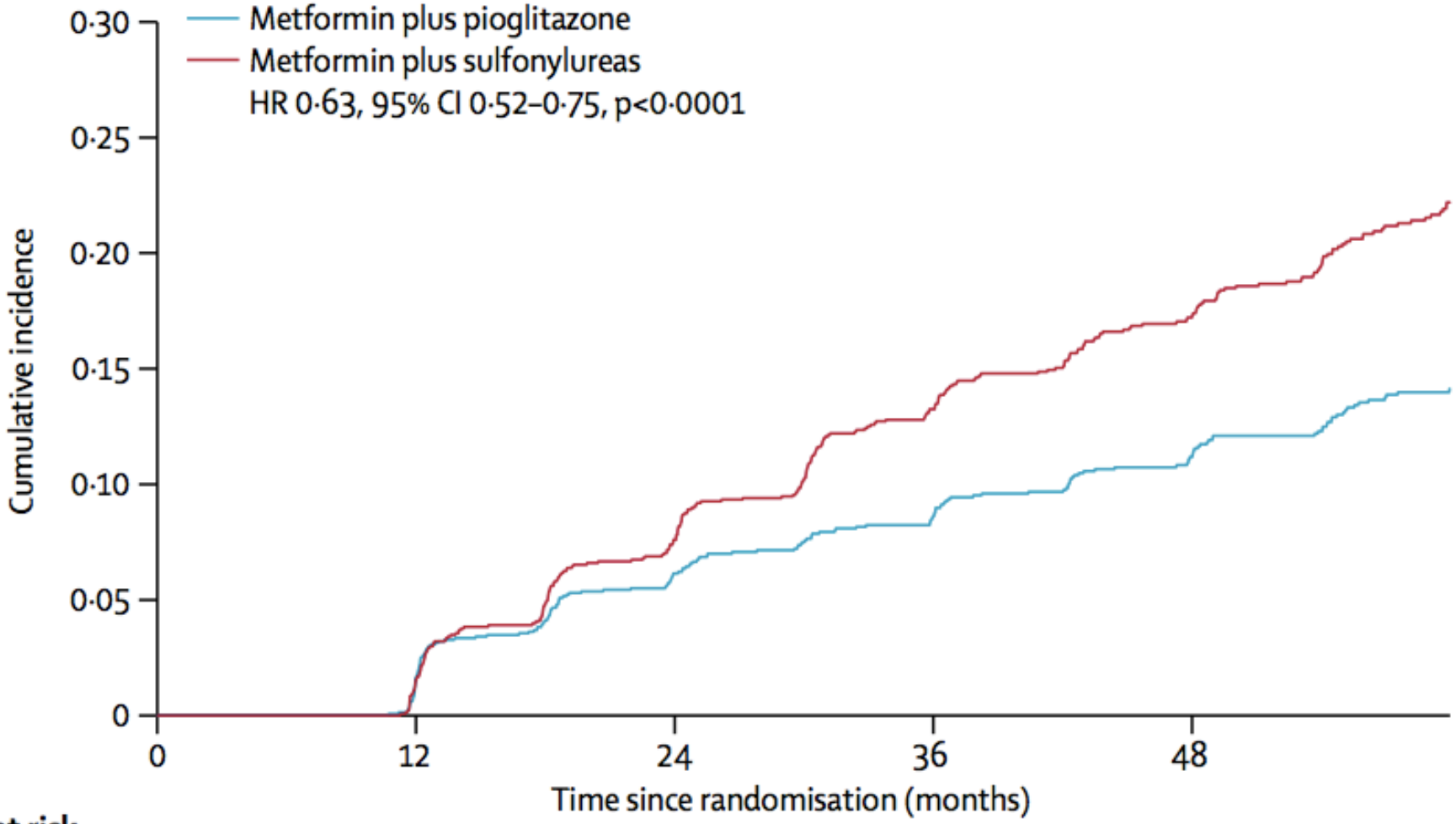
History		
Myocardial infarction	82 (64.1)	80 (63.5)
Angina pectoris	55 (43.0)	48 (38.1)
CABG	30 (23.4)	30 (23.8)
PCI	24 (18.8)	22 (17.5)
Stroke	12 (9.4)	11 (8.7)
Atrial fibrillation	29 (22.7)	34 (27.0)

	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Hazard ratio (95% CI)	p value
	n (%)	n per 100 patient-years	n (%)	n per 100 patient-years		
On-treatment analysis (post hoc)						
Primary composite outcome*	73 (5%)	1·2	99 (7%)	1·5	0·82 (0·60–1·10)	0·19
All-cause death	43 (3%)	0·7	45 (3%)	0·7	1·08 (0·71–1·65)	0·70
Non-fatal myocardial infarction (including silent myocardial infarction)	13 (1%)	0·2	23 (2%)	0·4	0·63 (0·32–1·24)	0·18
Non-fatal stroke	11 (1%)	0·2	18 (1%)	0·3	0·67 (0·32–1·42)	0·30
Urgent coronary revascularisation	18 (1%)	0·3	32 (2%)	0·5	0·62 (0·35–1·11)	0·11
Key secondary outcome†	48 (3%)	0·8	79 (5%)	1·2	0·67 (0·47–0·96)	0·03
Expanded composite outcome‡	122 (8%)	2·1	147 (10%)	2·3	0·90 (0·71–1·15)	0·41

	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Incidence rate ratio (95% CI)	p value
	Patients	Events	Patients	Events		
Severe hypoglycaemic events	1 (<1%)	2	24 (2%)	33	0·06 (0·01–0·25)	<0·0001
Moderate hypoglycaemic events	147 (10%)	515	484 (32%)	1868	0·27 (0·24–0·30)	<0·0001

Lancet Diabetes Endocrinol 2017

Failure of hypoglycaemic treatment was defined as HbA1c of 8% (64 mmol/mol) or above on two consecutive visits 3 months apart



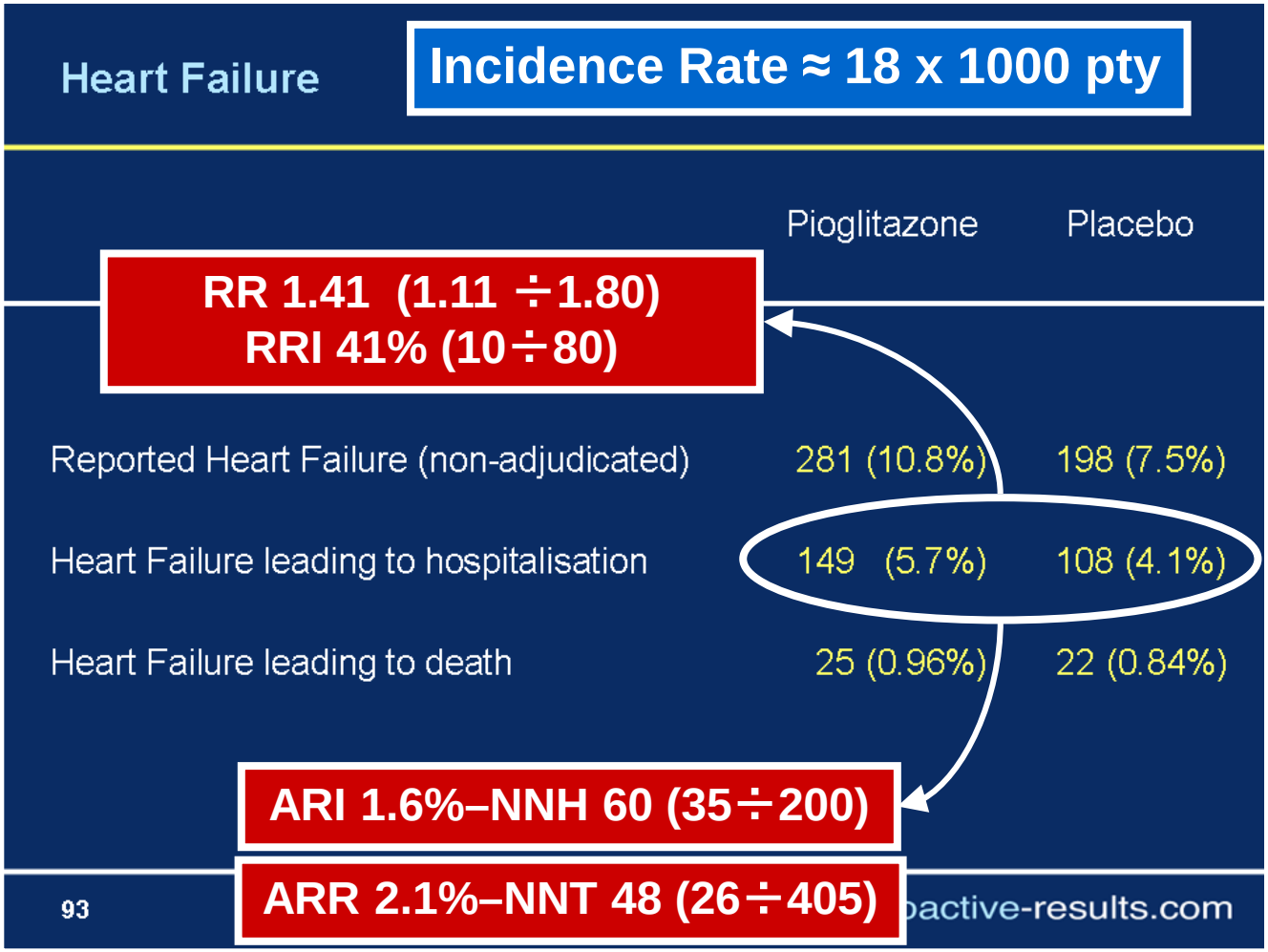
Number at risk (events)					
Metformin plus pioglitazone	1535 (19)	1449(70)	1321 (33)	1223 (33)	990 (29)
Metformin plus sulfonylureas	1493 (18)	1418 (90)	1287 (77)	1145 (49)	928 (48)

Lancet Diabetes Endocrinol 2017

Cardiovascular risk related to glitazone use in T2DM

Study	N°	CV event	OR (95% CI)
Nissen and Wolski	42	AMI	1.43* (1.03-1.98)
NEJM 356:2457, 2007	(27847)	CV death	1.64 (0.98-2.74)
Home et al.	-	AMI	1.16 (0.75-1.81)
NEJM 357:28, 2007	(4447)	CHF	2.24* (1.27-3.97)
		CV death	0.97 (0.73-1.29)
Diamond et al.	42	AMI	1.26 (0.99-1.69)
Ann Int Med; 147:578, 2007	(27847)	CV death	1.17 (0.77-1.77)
Singh et al.	4	AMI	1.42* (1.06-1.91)
JAMA 298:1189, 2007	(14291)	CHF	2.09* (1.52-2.88)
		CV death	0.90 (0.63-1.26)
Lincoff et al.	19	MACE	0.82* (0.72-0.94)
JAMA 298:1180, 2007	(16390)	CHF	1.41* (1.14-1.76)
Lago et al.	7	CHF	1.72* (1.21-2.42)
Lancet 370:1129, 2007	(20191)	CV death	0.93 (0.67-1.29)

Congestive Heart Failure in the PROACTIVE Study



Potenziali down-sides cardiovascolari delle sulfoniluree, glinidi e pioglitazone nel diabete mellito tipo 2

Potenziale problema	Evitare o riconsiderare l'uso di
Incremento ponderale	Sulfoniluree e glinidi, TZD
Ipoglicemia	Sulfoniluree e glinidi
Ritenzione idrica/edema, alterata natriuresi	Pioglitazone
Disfunzione endoteliale	Sulfoniluree (esclusa gliclazide)
Scompenso cardiaco	Pioglitazone
Ridotta funzione renale	Sulfoniluree

Ryden L, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88-136.

Hypoglycemia and cardiovascular events in ADVANCE

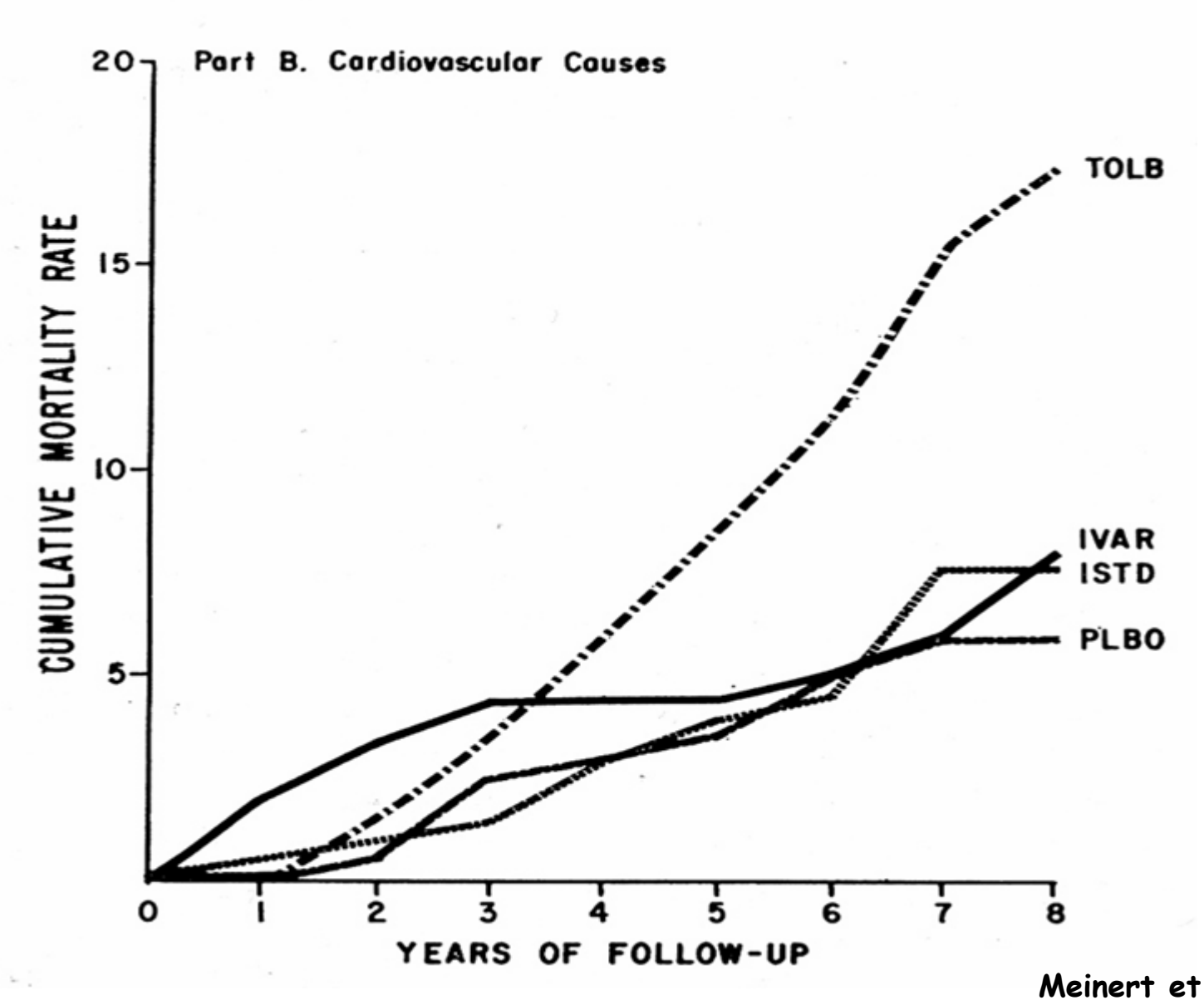
- Hypoglycemia predisposes to cardiovascular events

End point	Severe hypoglycemia, n=231 (%)	No severe hypoglycemia, n=10 909 (%)	HR (95% CI)
Major macrovascular event*	15.9	10.2	3.53 (2.41–5.17)
Major microvascular event*	11.5	10.1	2.19 (1.40–3.45)
All-cause mortality	19.5	9.0	3.27 (2.29–4.65)
Cardiovascular mortality	9.5	4.8	3.79 (2.36–6.08)
Noncardiovascular mortality	10	4.3	2.80 (1.64–4.79)

***Primary end points. Major macrovascular event=CV death, nonfatal MI, or nonfatal stroke; major microvascular event=new or worsening nephropathy or retinopathy**

Zoungas S. N Engl J Med 2010;363:1410-8..

University Group Diabetes Program

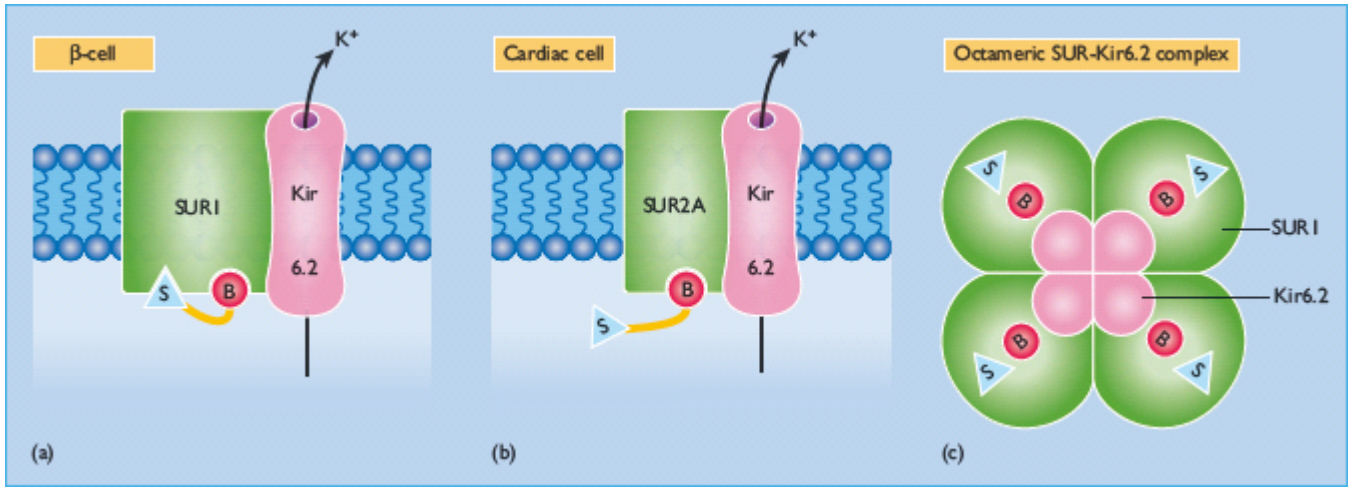


Meinert et al. 1970

Table 1 Different affinities of sulfonylurea and benzoic acid derivates for SUR subtypes

Generic name	SUR 1 (pancreatic B cells) K_i*[unit]	SUR 2A (cardiomyocytes) K_i*[unit]	Relative affinity SUR 1/SUR 2A	Reference
Tolbutamide	5.4 (3.4) µmol/l	1.7 (0.2) mmol/l	314.8	11, 12
Glibenclamide	4.2 nmol/l	27 (2) nmol/l	6.4	11
Gliclazide	50 (7) nmol/l	0.8 (0.1) mmol/l	16 000	13
Glimepiride	5.4 (0.1) nmol/l	7.3 (0.23) nmol/l	1.35	14
Meglitinide	0.26 (0.06) µmol/l	0.53 (0.11) µmol/l	2.0	11
Repaglinide	7.4 (1.2) nmol/l	8.7 (1.5) nmol/l	1.2	15
Nateglinide	7.4 (0.2) µmol/l	2.3 (1.2) mmol/l	311	16

Values are mean (SD).
*Concentration of half maximal inhibition.
SUR, sulfonylurea receptor.



MYOCARDIAL ISCHAEMIC PRE-CONDITIONING

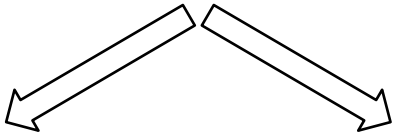
“Phenomenon by which a brief episod (s) of myocardial ischaemia increases the ability of the heart to tolerate a subsequent prolonged period of ischaemia”

‘Murry et al, 1986’

Beneficial effects of myocardial ischaemic preconditioning

- Resistance to hypoxic injury
- Slow energy metabolism
- Improve post-ischaemic function
- Protect coronary endothelium
- ↑Post-ischaemic tension in atrial trabeculae muscle
- ↓Reperfusion arrythmias

ISCHAEMIC PRE-CONDITIONING MEDIATORS

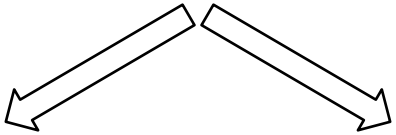


ATP sensitive K^+ channels

(K+ ATPS)

Protein Kinase C

(PKC)



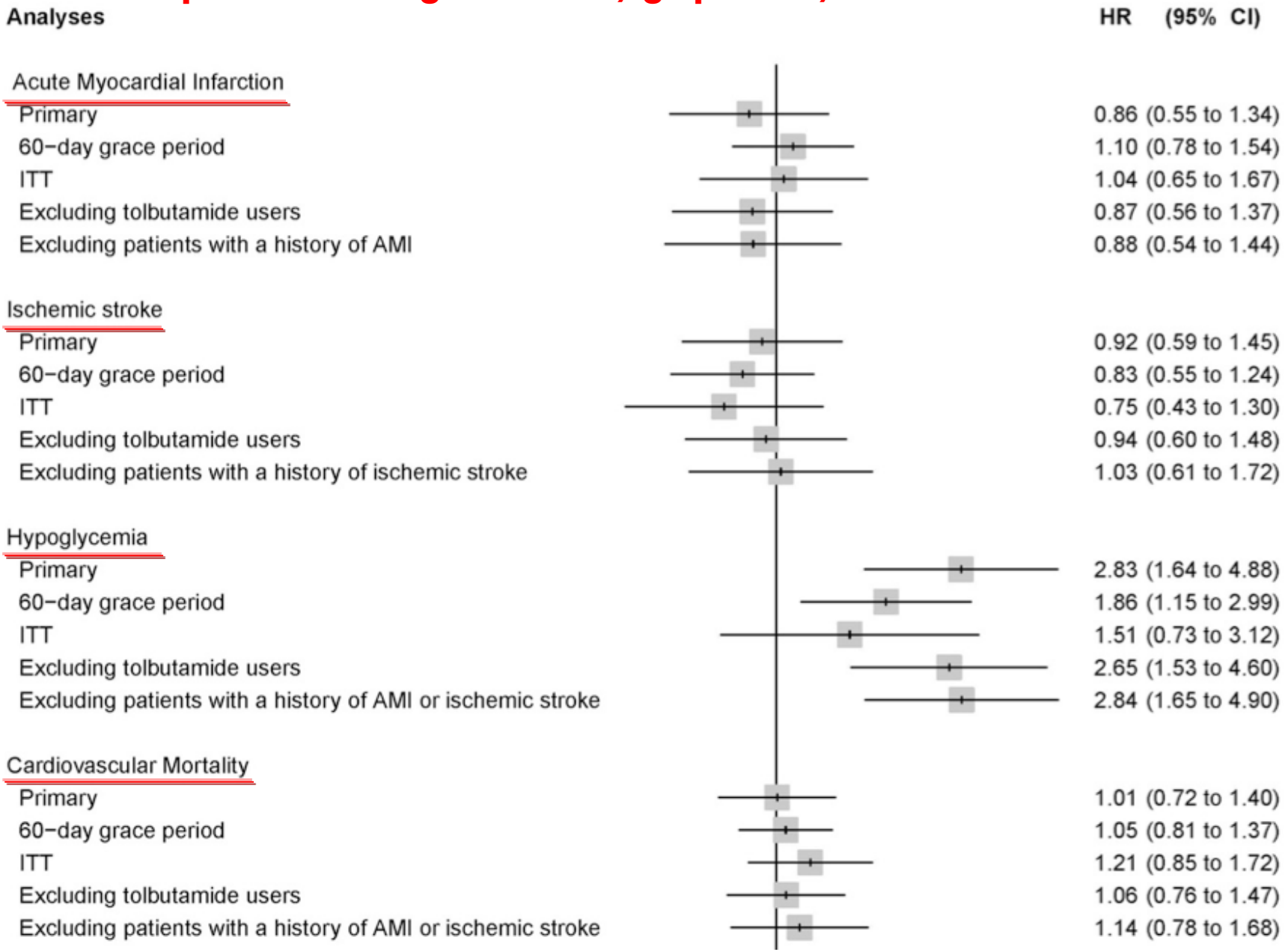
Sarcolemmal:

1. Blocked by sulfonylureas

Mitochondrial:

1. Opened by diazoxide
2. Blocked by 5-HD

HRs for all outcomes associated with glyburide and glimepiride compared with gliclazide, glipizide, and tolbutamide



Diabetes Care Publish Ahead of Print, published online September 1, 2017

Metformin vs other OHAs

Aggregate Endpoint	*p*
Any diabetes related endpoint	**0.0034**
Diabetes related deaths	**0.11**
All cause mortality	**0.021**
Myocardial infarction	**0.12**
Stroke	**0.032**
Peripheral vascular disease	**0.62**
Microvascular	**0.39**

UKPDS 34, Lancet 1998; 352: 854-65

Riduzione del rischio cardiovascolare indiretta e diretta della metformina

Obiettivo	Indiretta (dipendente dalla riduzione della glicemia) MET vs CONV	Diretta (indipendente dalla riduzione della glicemia) MET vs INT
Ogni evento legato al diabete	**↓ 32%; p=0,002**	**↓ 25%; p=0,003**
Morti legate al diabete	**↓ 42%; p=0,017**	p=NS
Mortalità per tutte le cause	**↓ 36%; p=0,011**	**↓ 28%; p=0,021**
Infarto del miocardio	**↓ 39%; p=0,01**	p=NS
Ictus cerebrale	p=NS	**↓ 56%; p=0,032**
Arteriopatia periferica	p=NS	p=NS

UKPDS 34, Lancet 1998; 352: 854-65

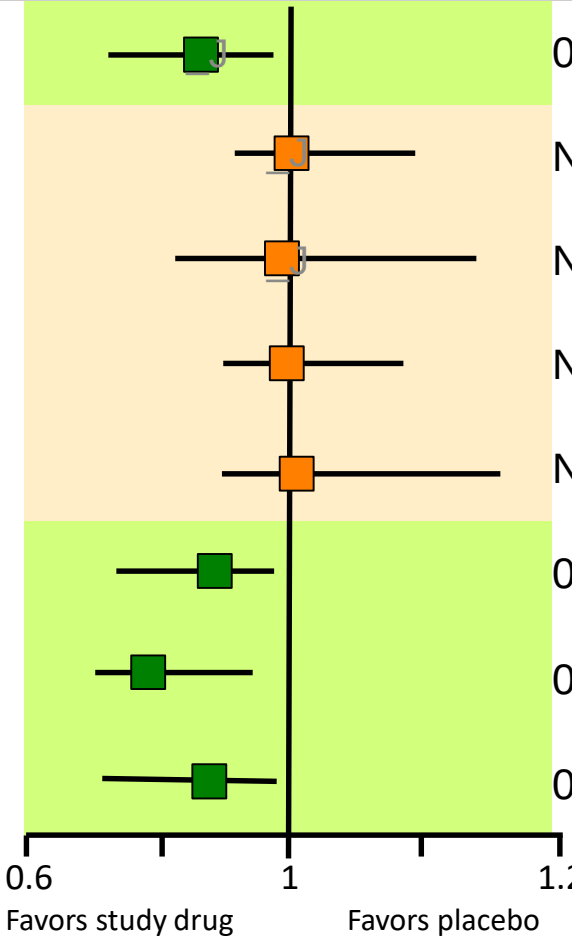
In cardiopathic type 2 diabetic patients…

- Metformin remains first-line therapeutic agent for its potential cardioprotective action 

- Pioglitazone is not recommended for possibly causing heart failure
- Sulfonylureas should be avoided because of their negative effect on the heart and hypoglycemic burden

CVOT (3 MACE)

Study	Glucose-lowering drug	HR	95% CI	*P*-value
PROACTIVE	Pioglitazone	0.84	0.72-0.98	0.027
SAVOR	Saxagliptin	1.00	0.89-1.12	NS
EXAMINE	Alogliptin	0.96	0.80-1.15	NS
TECOS	Sitagliptin	0.99	0.89-1.10	NS
ELIXA	Lixisenatide	1.02	0.89-1.17	NS
LEADER	Liraglutide	0.87	0.78-0.97	0.010
SUSTAIN-6	Semaglutide	0.74	0.58-0.95	0.020
EMPA-REG	Empagliflozin	0.86	0.74-0.99	0.038



*CV mortality, non-fatal MI, non-fatal stroke