I farmaci per la terapia del DM2: quali solo, come gestirli, come usarli e i piani terapeutici … (cui prodest? cui nocet?)

Alberto De Micheli
ACISMOM, Genova

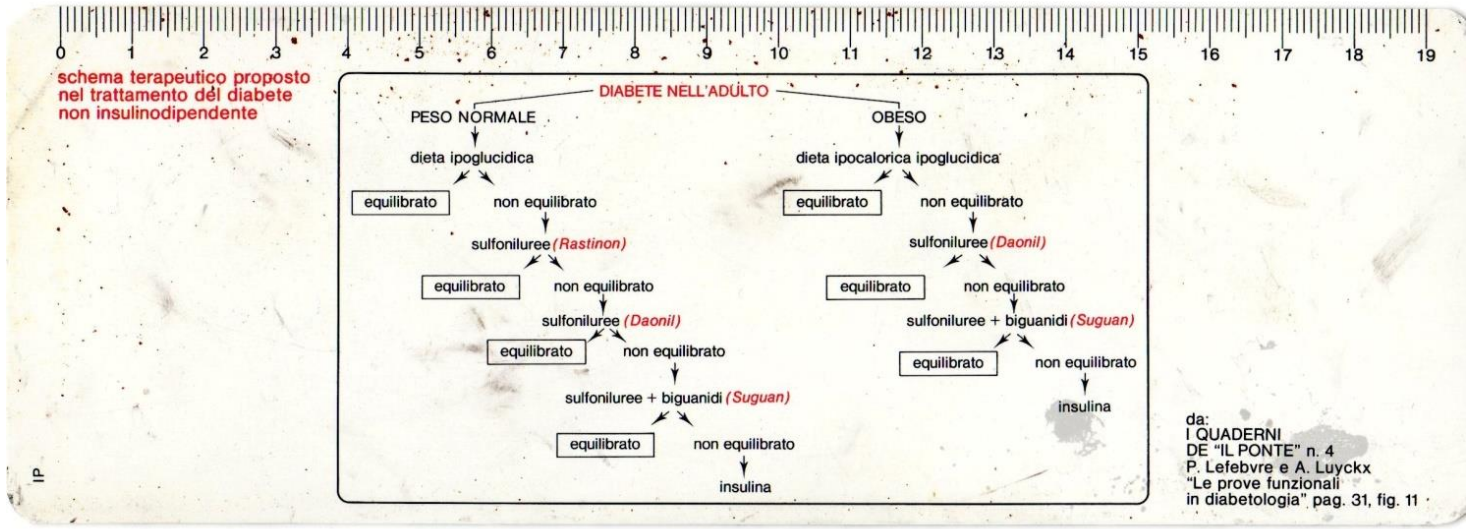
Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Novo Nordisk Italia
Johnson & Johnson

In fede
Alberto De Micheli

L'evoluzione della terapia per il diabete tipo 2

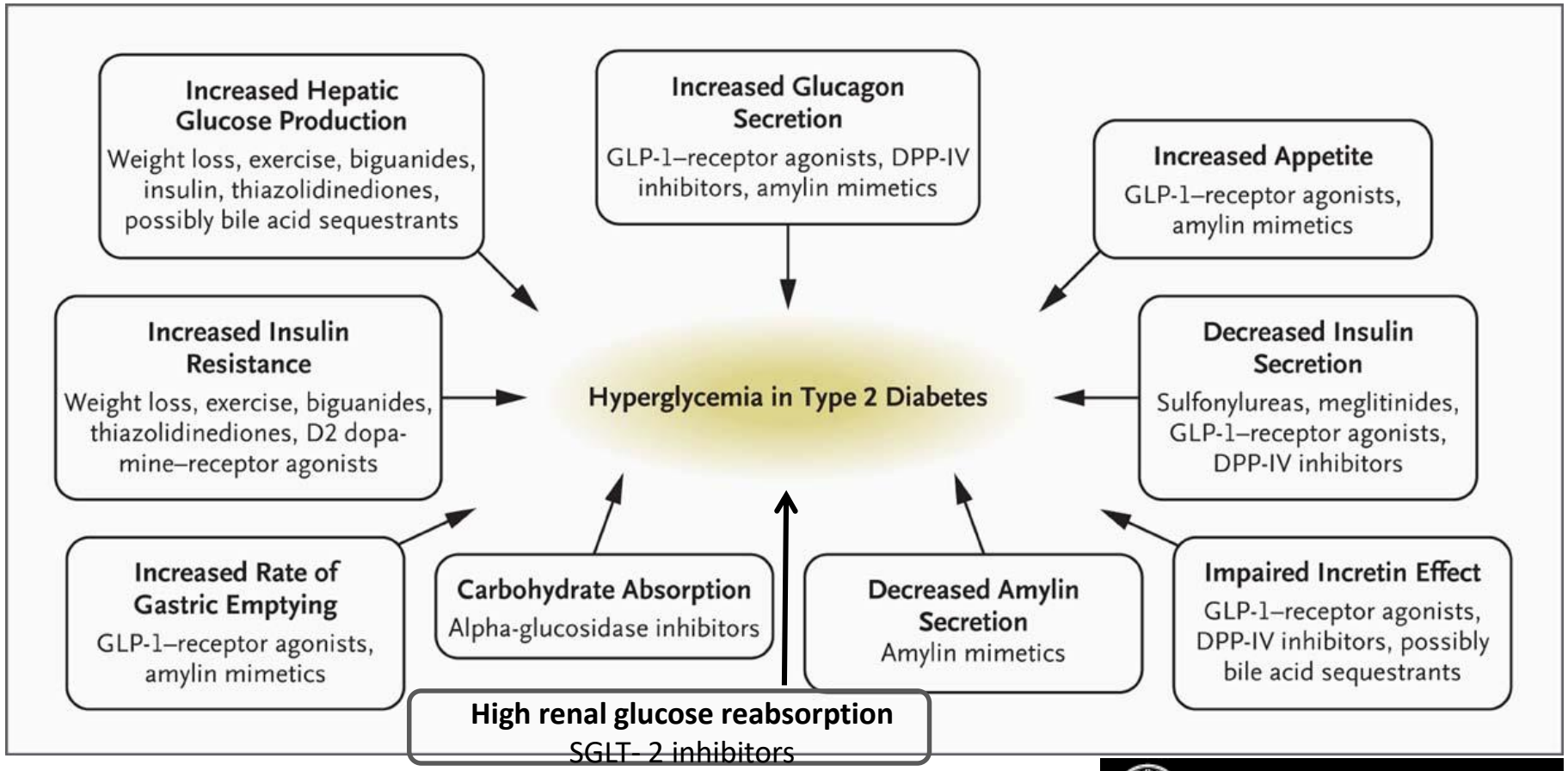
40 anni fa



Secretagoghi
Tolbutamide
Clorpropramide
Glibenclamide
Insulino sensibilizzanti
Fenformina
Metformina
Insuline
Insulina Pronta
Insulina Intermedia
Premiscelate

Pierre J. Lefebvre, Alfred Luyckx; Le prove funzionali in diabetologia, I quaderni de "Il Ponte" , 1974

Oggi: Terapia del diabete tipo 2 basata sulle alterazioni fisiopatologiche



Ismail-Beigi F. N Engl J Med 2012;366:1319-1327

The NEW ENGLAND JOURNAL of MEDICINE

L'ipoglicemizzante ideale

- Efficace nel controllare l'iperglicemia
- Efficace nel mantenere a lungo la funzionalità beta pancreatica
- Efficace nel prevenire le complicanze micro e macroangiopatiche
- Sicuro e privo di effetti collaterali:
  - ipoglicemia
  - incremento del peso
  - altri
    - mortalità
    - malattie cv
    - altre patologie
    - infezioni

Il problema

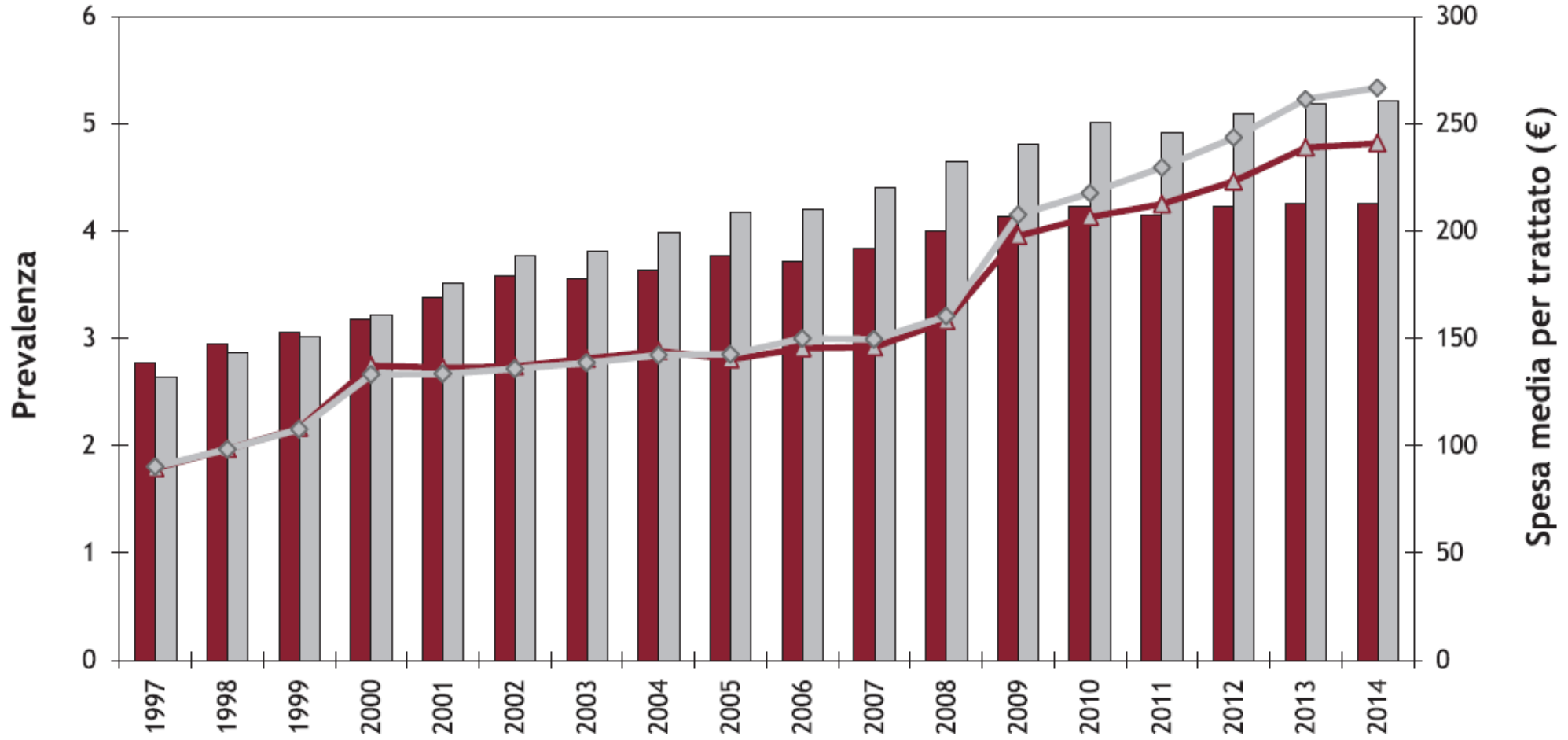
- Mechanisms for cardiovascular damage in diabetic patients:
  - hyperglycemia
  - oxidative stress
  - hypoglycemia
  - hyperinsulinemia
  - insulin resistance

- These mechanisms can be countered by the use of different glucose- lowering medications, which are therefore expected to reduce cardiovascular risk in patients with diabetes, in addition to lowering HbA1c?

Avogaro A Cardiovasc Diabetol 2016 15:111

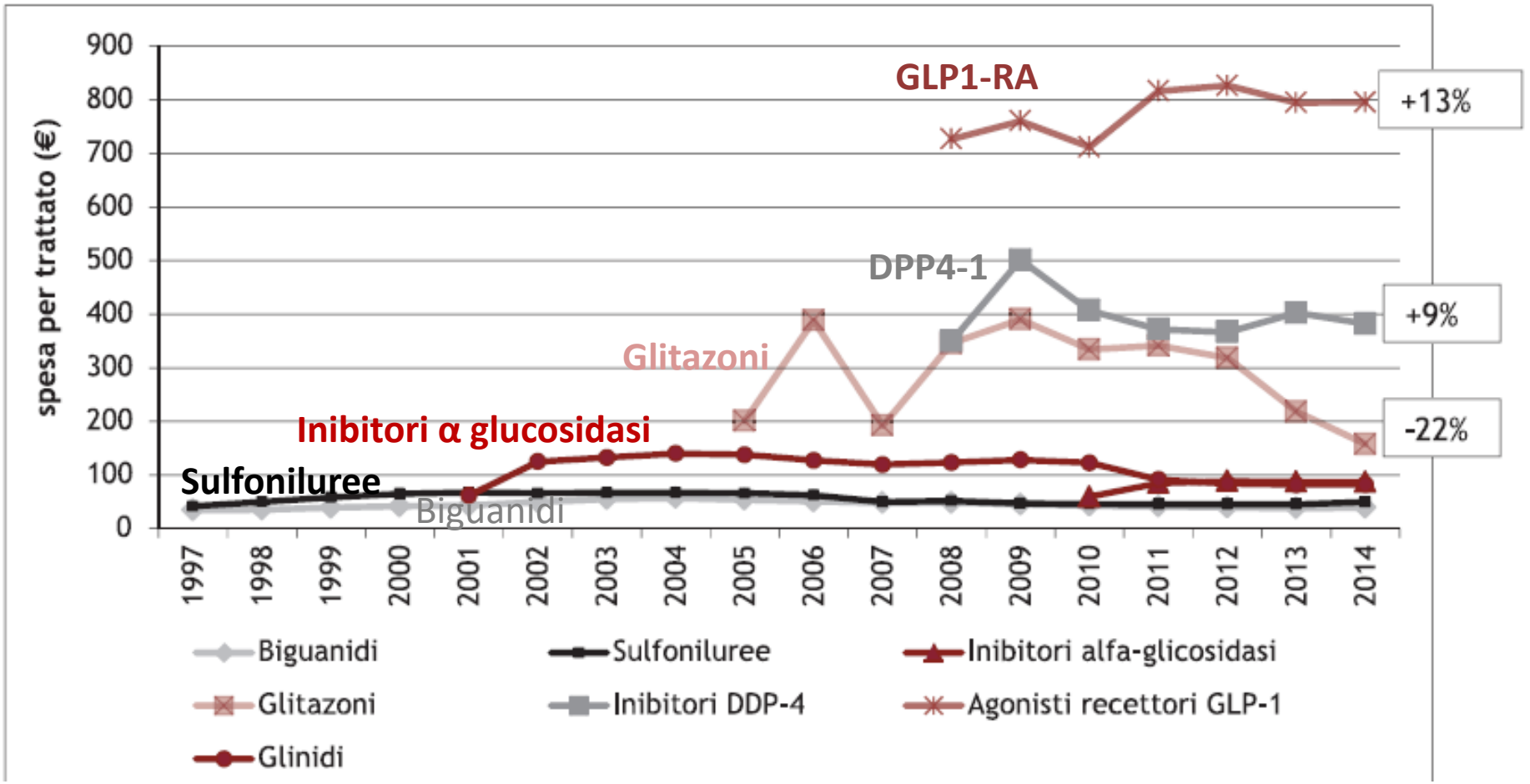
Consumi e costi in Italia

Andamento temporale (1997-2014) della prevalenza del diabete farmaco-trattato e della spesa media per trattato in funzione del sesso



Osservatorio ARNO Diabete Rapporto 2015

Spesa per trattato nel tempo con diversi framaci



Osservatorio ARNO Diabete Rapporto 2015

Pazienti trattati coi vari farmaci antidiabetici e relativa spesa

ATC	Descrizione	Trattati	% Trattati*	% spesa sul totale	Spesa media per trattato €	Spesa media pro capite €
A10B	Ipoglicemizzanti orali	396.921	86,6	48,8	129,0	93,3
A10BA	Biguanidi	278.787	60,8	10,1	38,1	19,3
A10BB	Sulfoniluree	93.870	20,5	4,2	47,2	8,1
A10BD02	Metformina e sulfoniluree	49.659	10,8	2,8	59,6	5,4
A10BD	Metformina e Inibitori DPP 4	26.814	5,8	10,0	389,7	19,0
A10BD05	Metformina e Pioglitazone	11.416	2,5	3,2	296,5	6,2
A10BD06	Glimepride e Pioglitazone	966	0,2	0,3	302,8	0,5
A10BD09	Pioglitazone e Alogliptin	73	0,0	0,0	84,0	0,0
A10BD01	Fenformina e sulfoniluree	2	0,0	0,0	5,3	0,0
A10BX02	Repaglinide	47.127	10,3	3,7	81,4	7,0
A10BX	Agonisti recettori GLP 1	7.839	1,7	5,6	749,0	10,7
A10BH	Inibitori della dipeptidilpeptidasi 4	19.902	4,3	6,4	338,4	12,3
A10BG	Pioglitazone	9.681	2,1	1,5	157,6	2,8
A10BF	Acarbosio	13.652	3,0	1,0	79,7	2,0

Osservatorio ARNO Diabete Rapporto 2015

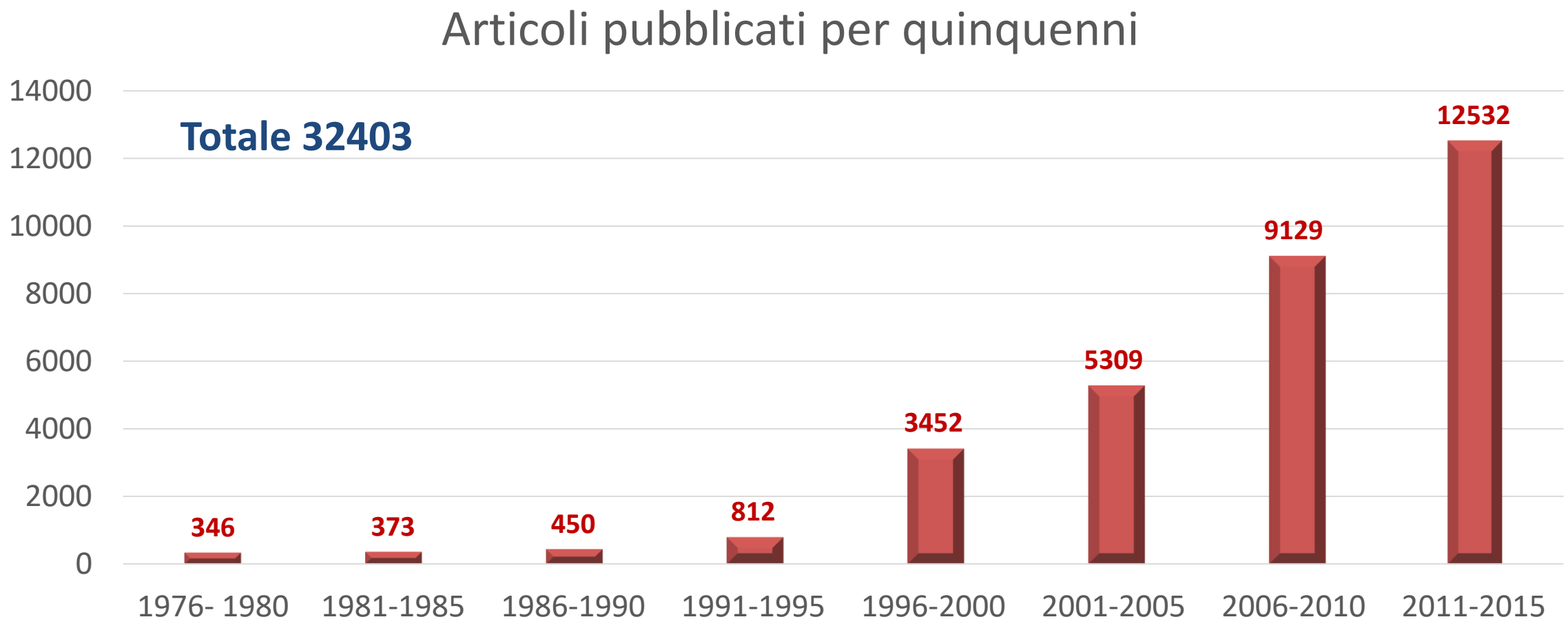
Appropriatezza dell'uso di antidiabetici nel 2016

Indicatore	Descrizione dell'indicatore	Lug2015-Giu2016	Lug2014-Giu2015	Lug2013-Giu2014
H-DB 3.1	Percentuale di pazienti in trattamento con farmaci antidiabetici aderenti al trattamento	63,4	63,3	63,4
H-DB 3.2	Percentuale di pazienti in trattamento con DPP-IV inibitori senza i criteri previsti dalle precisazioni sulle limitazioni generali alla rimborsabilità dei DPP-IV inibitori	10,5	12,1	24,1
H-DB 3.3	Percentuale di pazienti con i criteri previsti dalle precisazioni sulle limitazioni generali alla rimborsabilità dei DPP-IV inibitori non in trattamento con DPP-IV inibitori	67,2	70,9	71,7

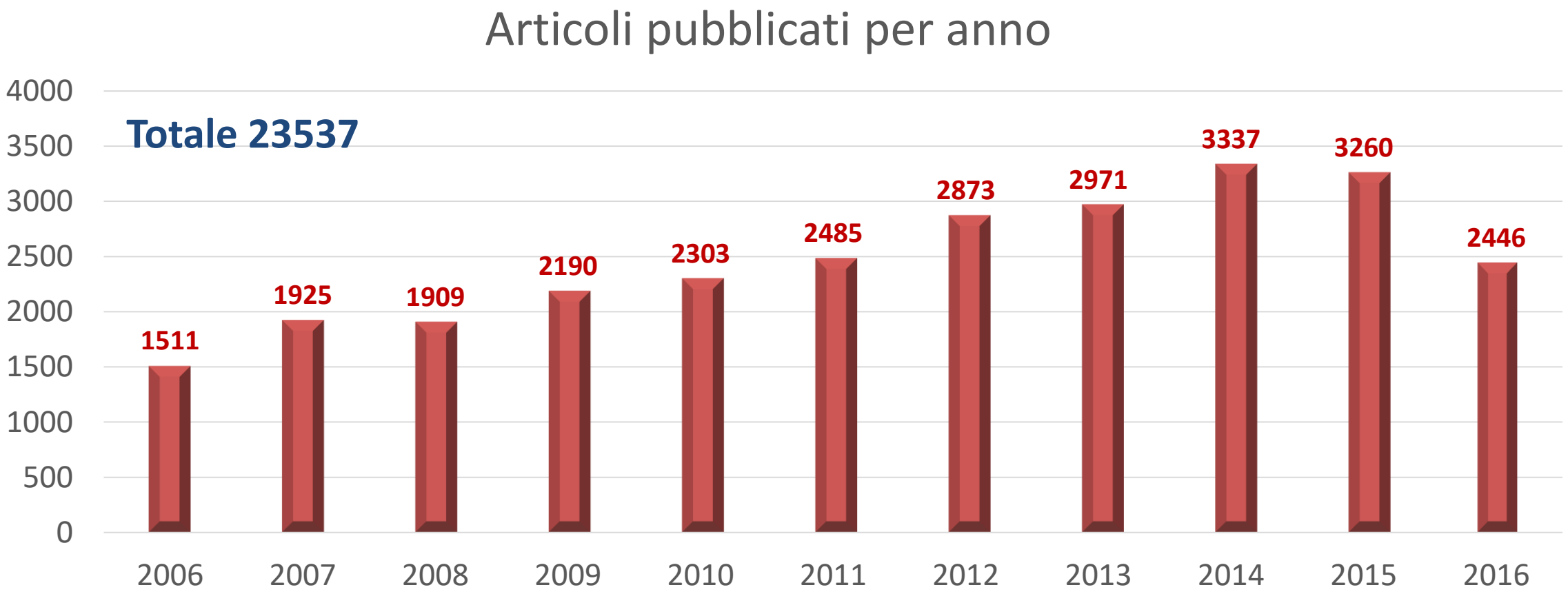
Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. RapportoNazionale Gennaio-Settembre 2016. Roma: Agenzia Italiana del Farmaco, 2017

Che cosa ci orienta nella scelta?
Le fonti di informazione

Articoli reperibili su Pub Med (Mesh Hypoglicemic Agents [Major topic] 1976-2015)

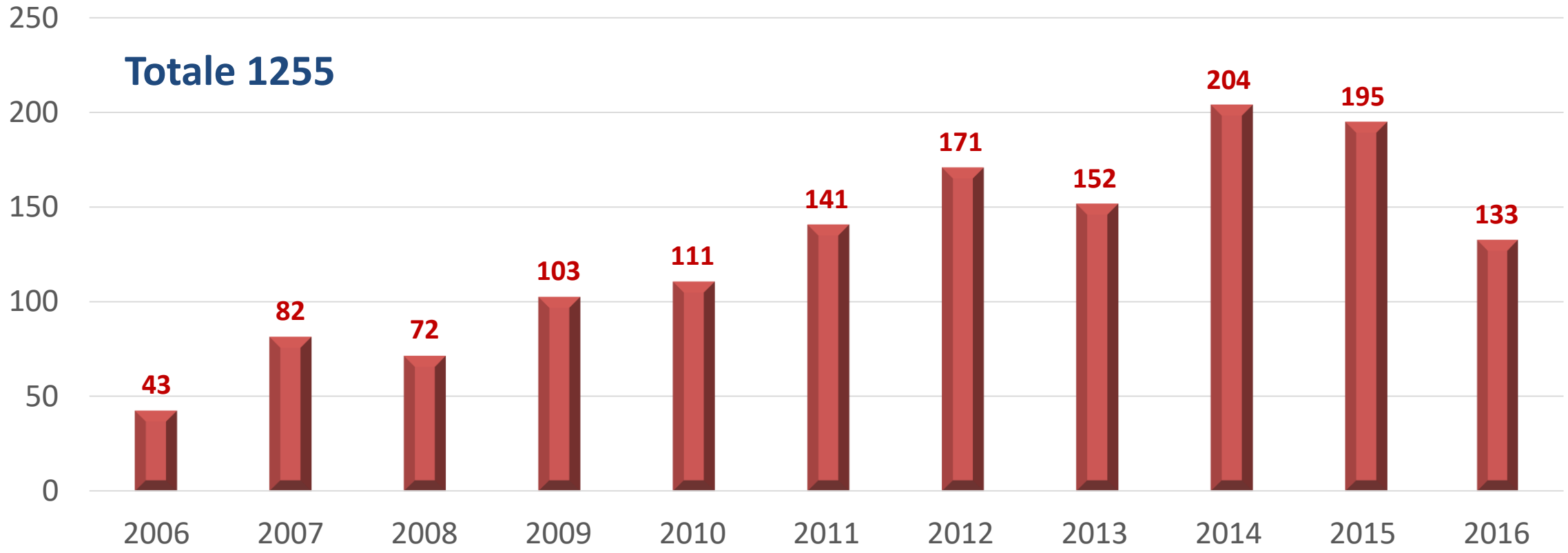


Articoli reperibili su Pub Med (Mesh Hypoglicemic Agents [Major topic] 2006- 2016)



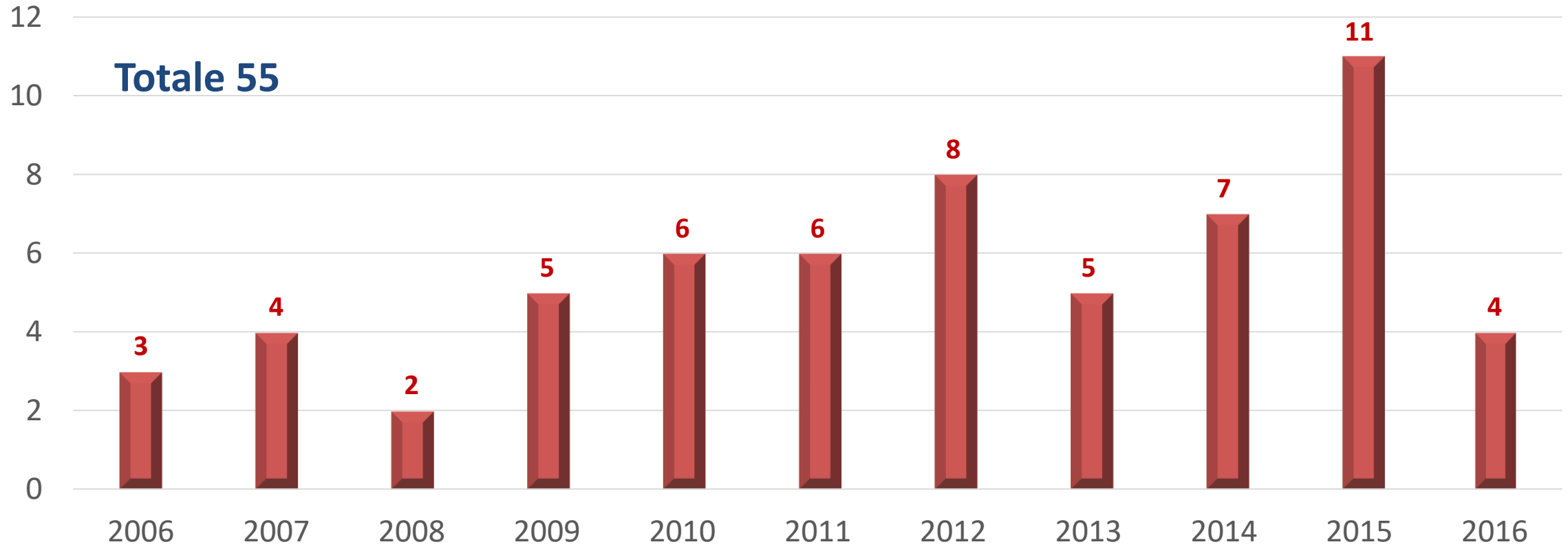
Metanalisi e revisioni sistematiche pubblicate su PubMed (Mesh Hypoglicemic Agents [Major topic] 2006- 2016)

Metanalisi e revisioni sistematiche pubblicate per anno

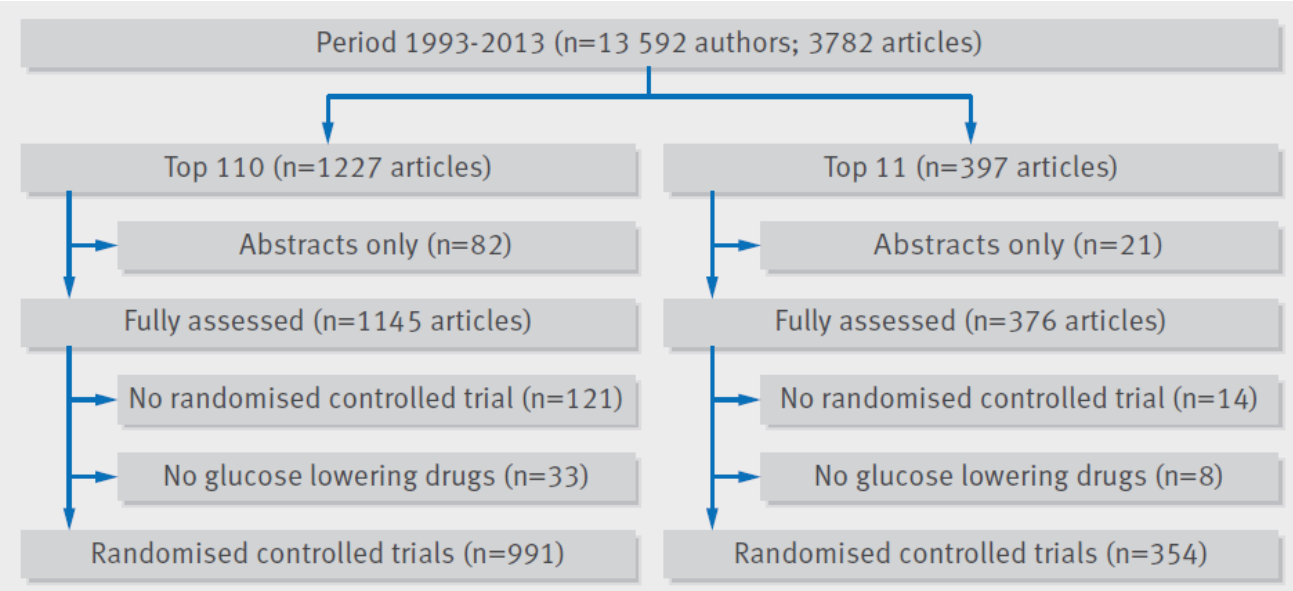


Linee guida reperibili su Pub Med (Mesh Hypoglicemic Agents [Major topic] 2006- 20156)

Linee guida pubblicate per anno



High prolific authors and supertrialist

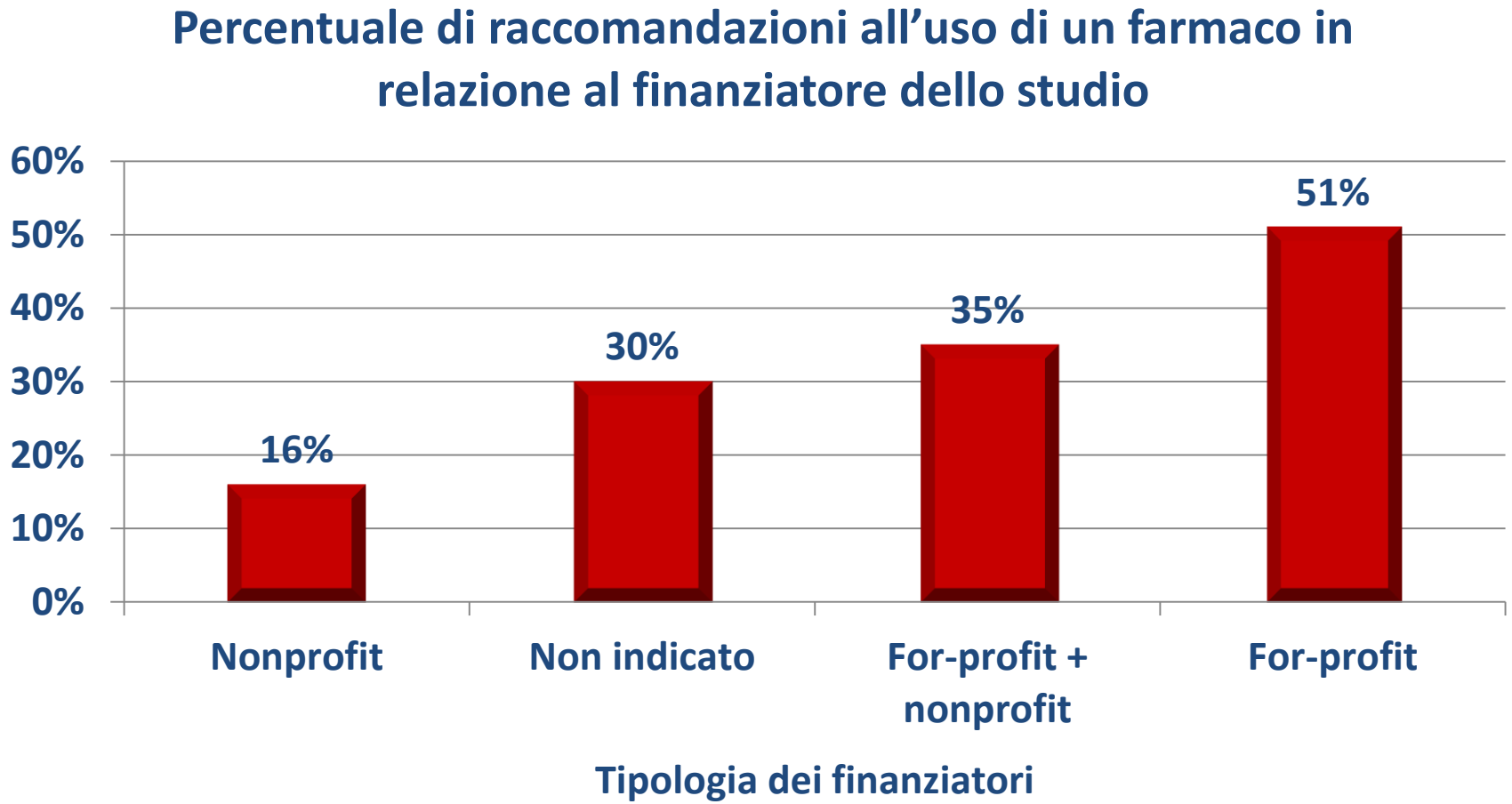


- the **top 110** authors were involved in **991 RCTs** for a **median of 20 (range 4-77)** RCTs per author;
- the **top 11** were involved in **354 RCTs** for a median of **42 (36-77) RCTs** per author since 1993

- This analysis shows that 110 highly prolific authors contributed to one third of the evidence base for glucose lowering treatment;
  - 44% were company employees and
  - 56% were academics who work closely with the pharmaceutical companies
- 11 authors, including 9 academics—here designated supertrialists— contributed 10% of the entire evidence base
- This concentration of influence adds to concerns about the independence and integrity of the evidence base for treatment for diabetes.

Holleman F, BMJ 2015; 350: h2638

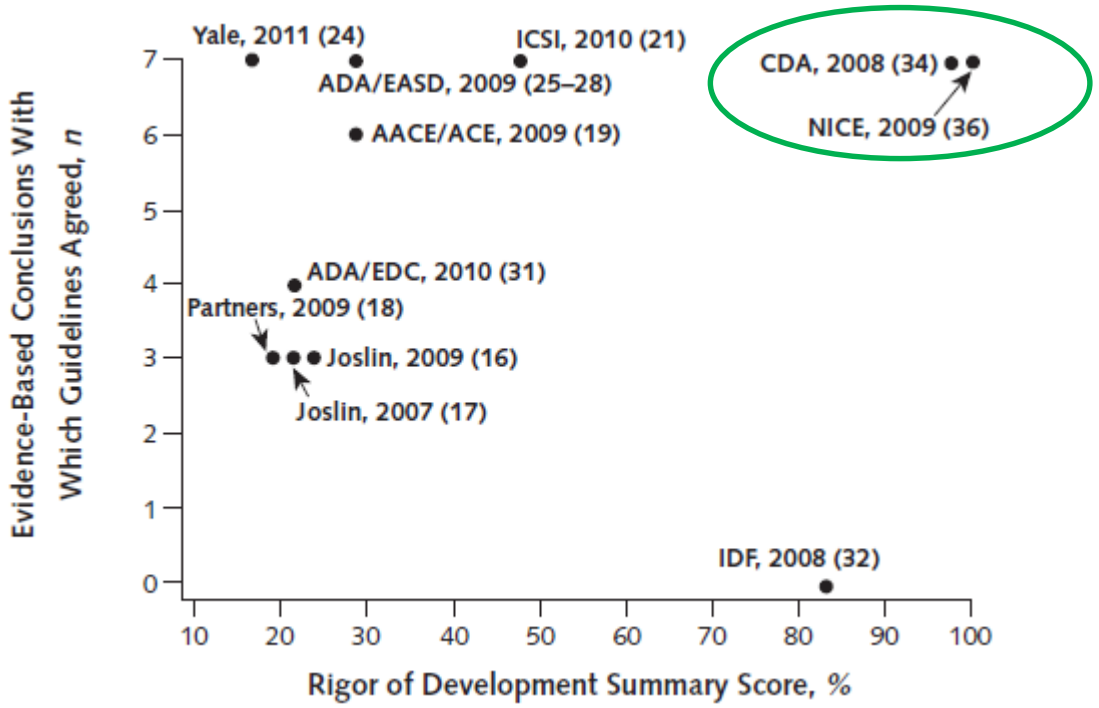
Finanziamento degli RCT e conclusioni



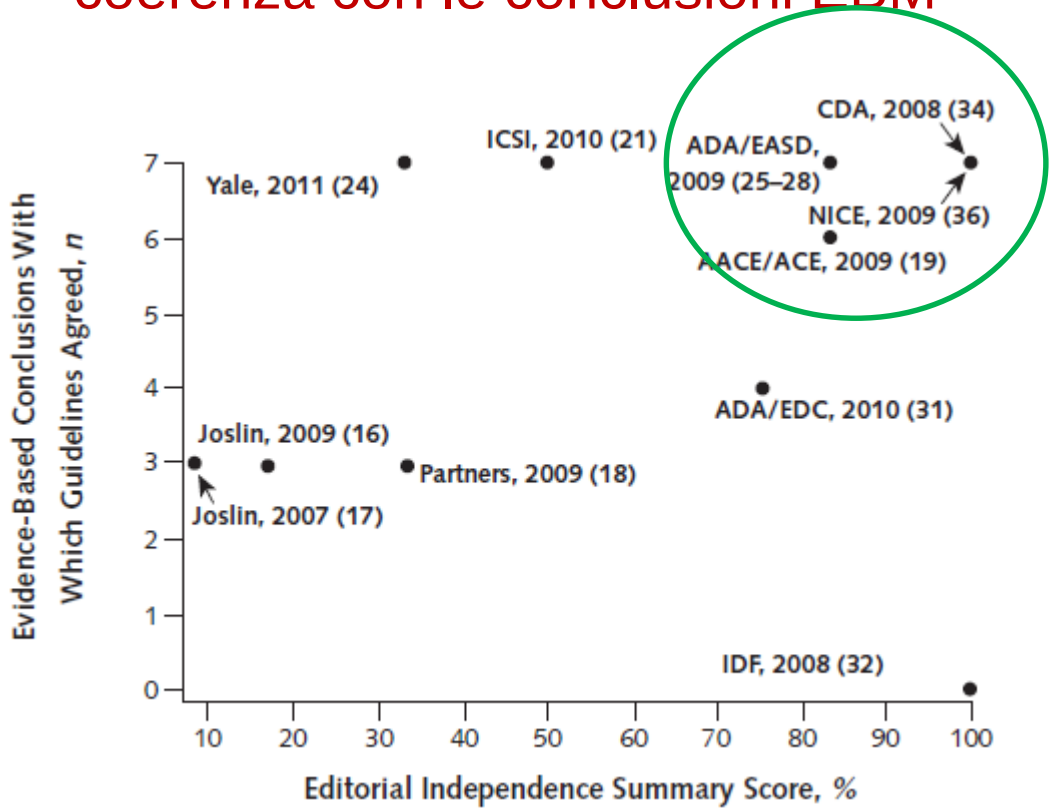
Als-Nielsen B JAMA 2003; 290: 921- 928

Relazione del rigore metodologico e dell'indipendenza editoriale con la coerenza delle LG sulla terapia antidiabetica orale con le conclusioni EBM

Relazione fra rigore metodologico e coerenza con le conclusioni EBM



Relazione fra indipendenza editoriale e coerenza con le conclusioni EBM



Bennett WL Ann Intern Med. 2012;156:27-36

Una scelta EBM

Stile di vita

Metformina

Secondo farmaco

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Linda L. Humphrey, MD, MPH; Donna E. Sweet, MD; Melissa Starkey, PhD; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the comparative effectiveness and safety of type 2 diabetes medications.

Methods: This guideline is based on a systematic evidence review evaluating literature published on this topic from 1966 through April 2010 that was identified by using MEDLINE (updated through December 2010), EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline included all-cause mortality, cardiovascular morbidity and mortality, cerebrovascular morbidity, neuropathy, nephropathy, and retinopathy. This guideline grades the evidence and recommendations by using the American College of Physicians clinical practice guidelines grading system.

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).

Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).

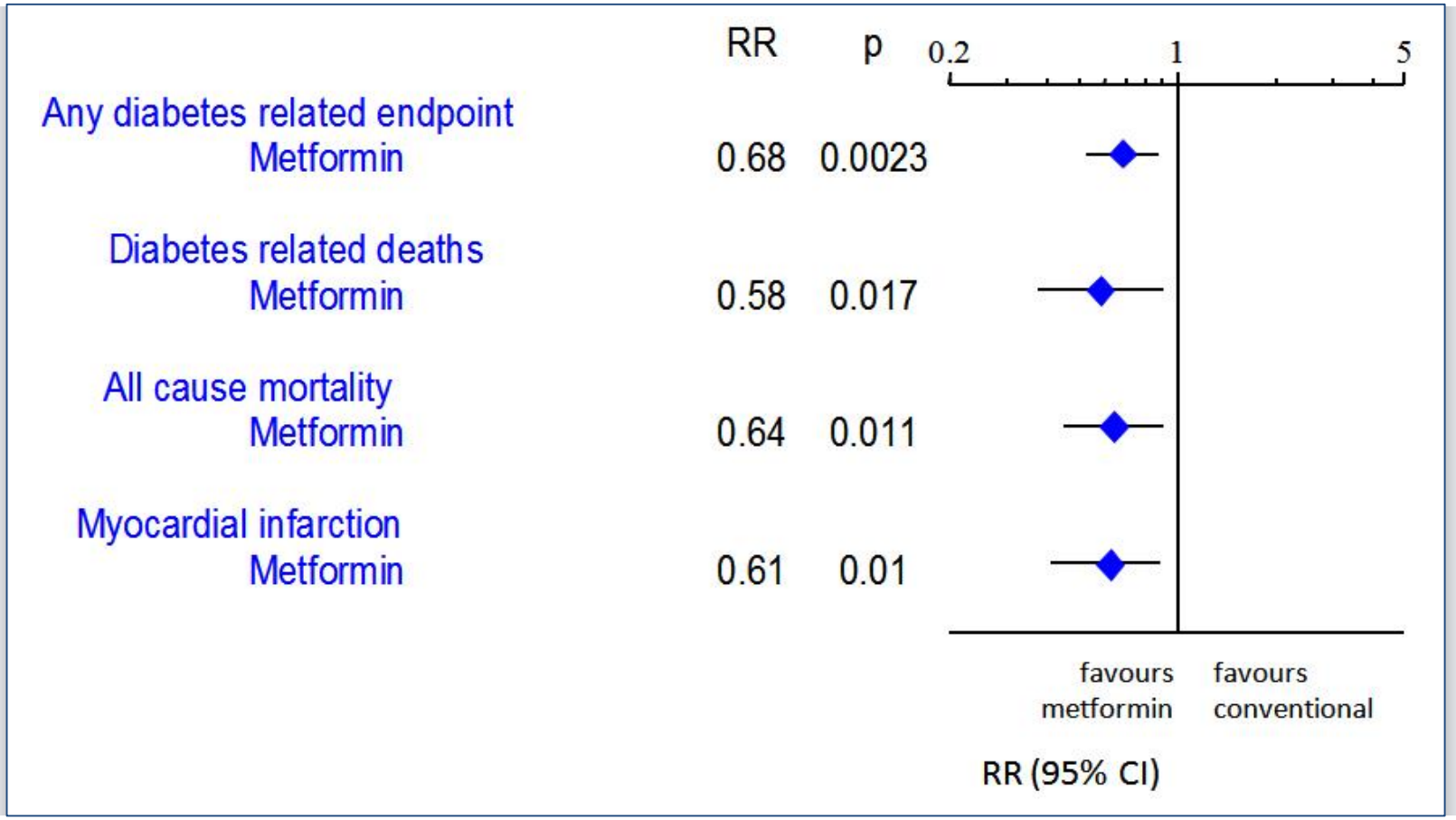
Ann Intern Med. 2012;156:218-231. www.annals.org

For author affiliations, see end of text.

Qaseem A Ann Intern Med. 2012; 156: 218- 231

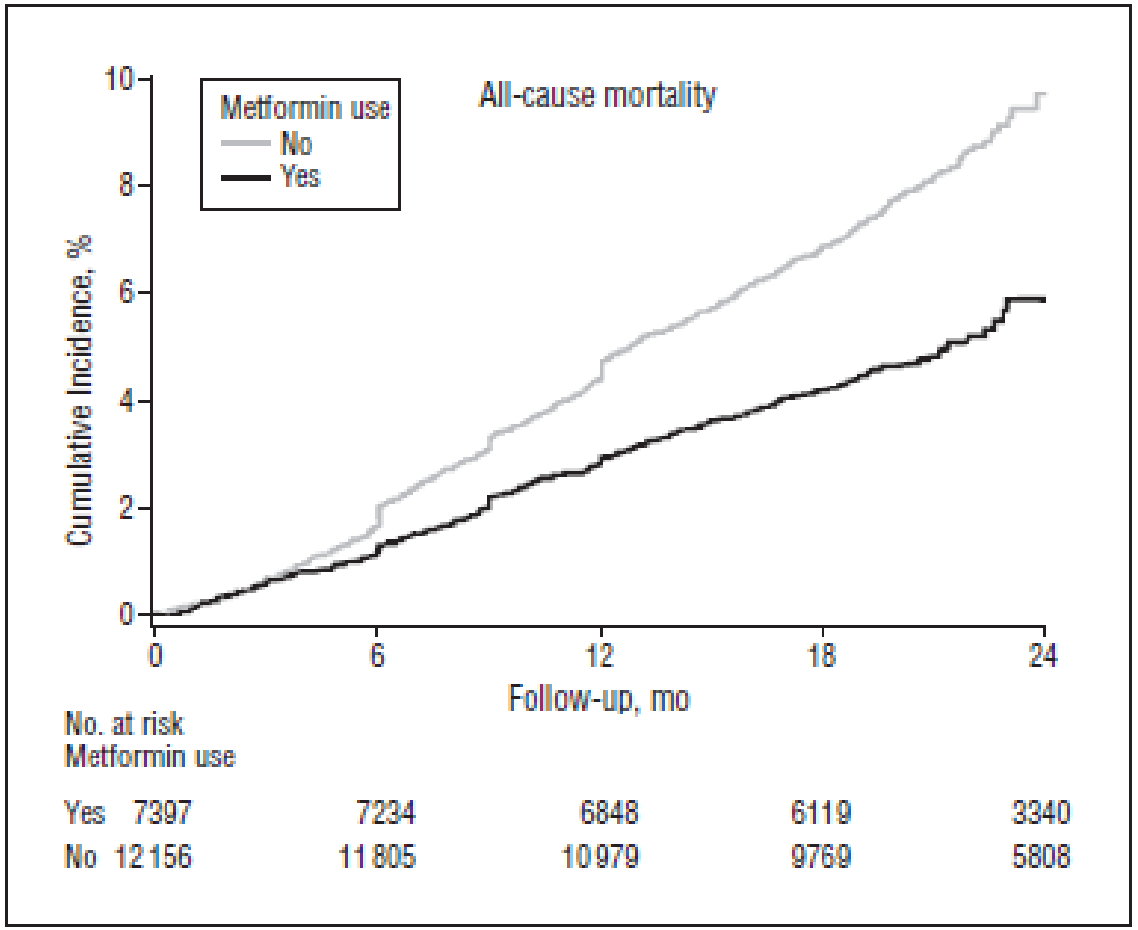
Metformina e complicanze del diabete

UKPDS: metformina vs. terapia convenzionale in pazienti in sovrappeso



UKPDS 34, Lancet 1998;352:854-65

REACH Registry: metformina e mortalità per ogni causa in prevenzione cv secondaria

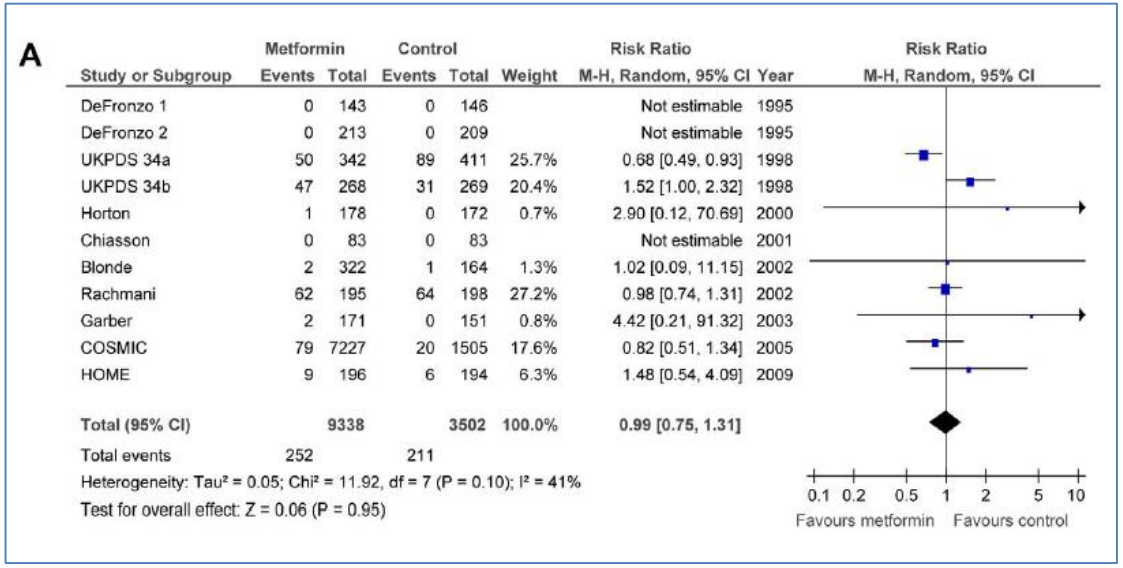


HR 0.67; 95% CI 0.59-0.75; adjusted HR 0.76; 95% CI 0.65-0.89 (*P*.001 for both, log-rank test)

Roussel Arch Intern Med. 2010;170:1892-1899

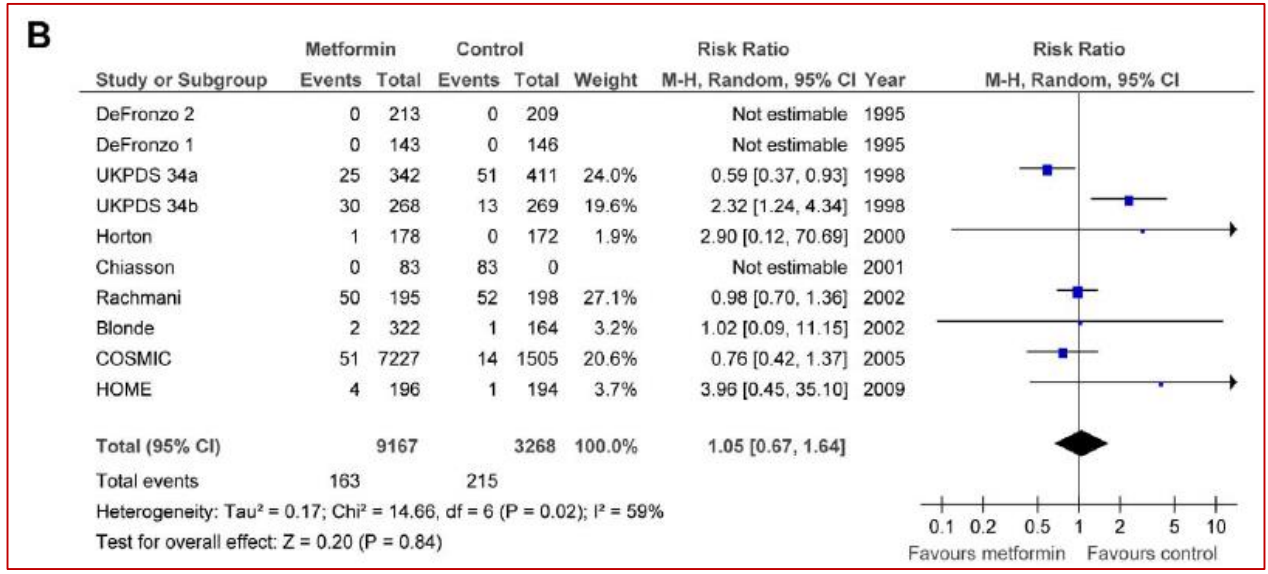
Efficacia della metformina sulla mortalità: metanalisi di RCT

Mortalità per ogni causa



RR = 0.99 (95% CI: 0.75 to 1.31),

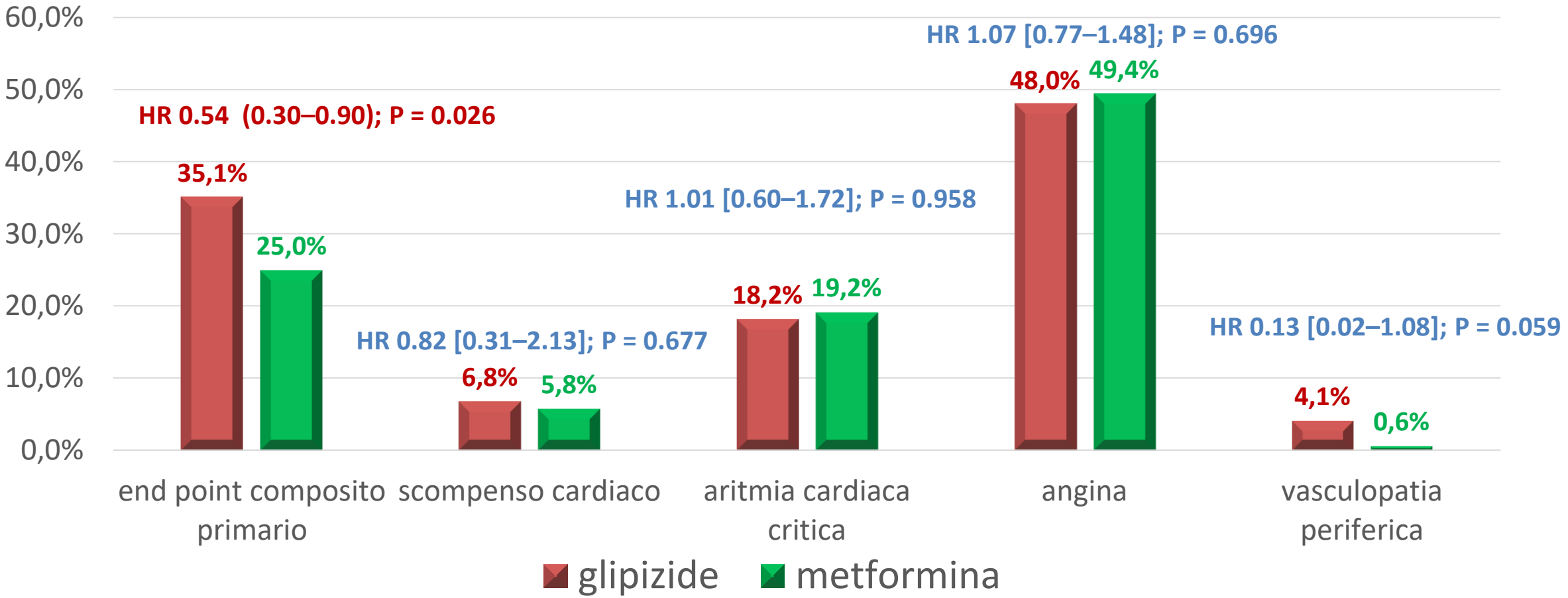
Mortalità cardiovascolare



RR = 1.05 (95% CI: 0.67 to 1.64)

Boussageon R PLoS Medicine 2012; 9: e1001204

SPREAD-DIMCAD: Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease.



Hong J Diabetes Care 2013; 36:1304–1311

La metformina come farmaco di prima scelta

- Metformin was associated with moderately lower HbA1C levels compared with other drugs including sulfonylureas, thiazolidinediones, and DPP-4 inhibitors.
- Basal insulin and sulfonylureas were associated with greatest odds of hypoglycemia, with an absolute risk difference of 10% compared with metformin.
- DPP-4 inhibitors were associated higher odds of treatment failure and with lower risks of hypoglycemia
- Metformin was associated with small reductions in body weight relative to sulfonylurea or thiazolidinedione treatment.
- Low cost
- *Choose GLP-1 receptor agonists when weight management is a priority,*
- *Consider SGLT-2 inhibitors based on their favorable combined safety and efficacy profile (weight, HBA1c, hypoglycemia)*

Palmer SC JAMA 2016;316:313-324

Gli altri farmaci

Original Investigation

Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes

A Meta-analysis

IMPORTANCE. Numerous glucose-lowering drugs are used to treat type 2 diabetes.

OBJECTIVE. To estimate the relative efficacy and safety associated with glucose-lowering drugs including insulin.

DATA SOURCES. Cochrane Library Central Register of Controlled Trials, MEDLINE, and EMBASE databases through March 21, 2016.

STUDY SELECTION. Randomized clinical trials of 24 weeks' or longer duration.

DATA EXTRACTION AND SYNTHESIS. Random-effects network meta-analysis.

MAIN OUTCOMES AND MEASURES. The primary outcome was cardiovascular mortality. Secondary outcomes included all-cause mortality, serious adverse events, myocardial infarction, stroke, hemoglobin A_{1c} (HbA_{1C}) level, treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and body weight.

Palmer SC JAMA 2016;316:313-324

Original Investigation

Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes

A Meta-analysis

- 301 randomized clinical trials
  - In 177 trials (56 598 patients), drugs as monotherapy
  - in 109 trials (53030 patients), drugs added to metformin
  - in 29 trials (10 598 patients),drugs added to metformin and sulfonylurea therapy
- 118 094 patients
- The number of patients allocated to each treatment in trials ranged between 82 and 1562 (median, 104 [interquartile range, 46-190])

Palmer SC JAMA 2016;316:313-324

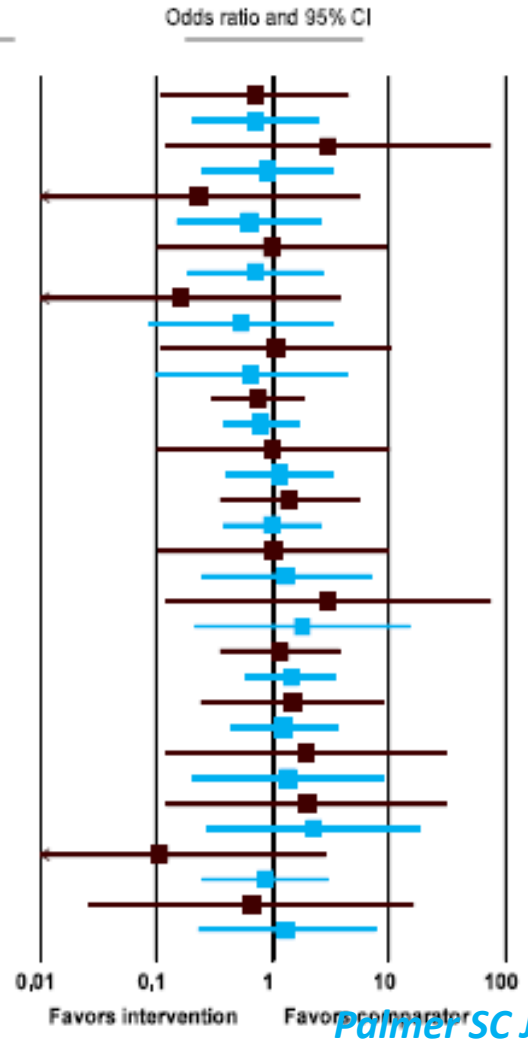
Eventi cardiovascolari

Outcome primario, mortalità CV. Farmaci in monoterapia

There were **no significant differences** in the associations between any drug class as monotherapy with odds of **cardiovascular mortality**

Direct and network treatment estimates for cardiovascular mortality - monotherapy

Drug comparison	Trials, n	Intervention n/N	Comparator n/N	Odds ratio and 95% CI
MET v PCO direct	3	2/833	1/420	0.71 0.11 4.54
MET v PCO network				0.72 0.21 2.46
SU v PCO direct	1	1/92	1/92	3,03 0,12 75,95
SU v PCO network				0.91 0.25 3.26
TZD v PCO direct	1	1/1749	0/137	0,24 0,01 5,69
TZD v PCO network				0,63 0,15 2,61
DPP-4-i v PCO direct	3	1/605	1/532	0.99 0.10 9.55
DPP-4-i v PCO network				0.72 0.19 2.71
SGLT-2-I v PCO direct	1	0/392	1/192	0.16 0.01 3.90
SGLT-2-I v PCO network				0,54 0,09 3,30
AGI v PCO direct	2	0/185	2/552	1,08 0,11 10,43
AGI v PCO network				0,66 0,10 4,37
MET v SU direct	3	9/387	11/379	0,76 0,31 1,86
MET v SU network				0,80 0,38 1,69
MET v TZD direct	2	1/132	1/135	1.02 0.10 10.03
MET v TZD network				1,15 0,40 3,31
MET v DPP-4-i direct	4	5/1148	3/823	1,40 0,36 5,45
MET v DPP-4-i network				1,00 0,38 2,65
MET v SGLT-2-I direct	2	1/409	1/422	1,03 0,11 9,94
MET v SGLT-2-I network				1,33 0,25 7,06
MET v GLITINIDE direct	1	1/178	0/179	3,03 0,12 74,81
MET v GLITINIDE network				1,81 0,22 15,04
SU v TZD direct	5	10/1931	8/1926	1.16 0.36 3.76
SU v TZD network				1,44 0,59 3,51
SU v DPP-4-i direct	1	3/212	2/210	1.49 0.25 9.03
SU v DPP-4-i network				1,26 0,44 3,58
SU v AGI direct	1	1/92	1/180	1.97 0.12 31.76
SU v AGI network				1.36 0.21 8.86
SU v GLITINIDE direct	1	1/193	1/383	1.99 0.12 31.96
SU v GLITINIDE network				2,27 0,28 18,45
TZD v DPP-4-i direct	1	0/565	1/186	0.11 0.00 2.83
TZD v DPP-4-i network				0,87 0,25 3,03
DPP-4-i v SGLT-2-I direct	1	0/135	1/270	0.66 0.03 16.33
DPP-4-i v SGLT-2-I network				1,33 0,23 7,67



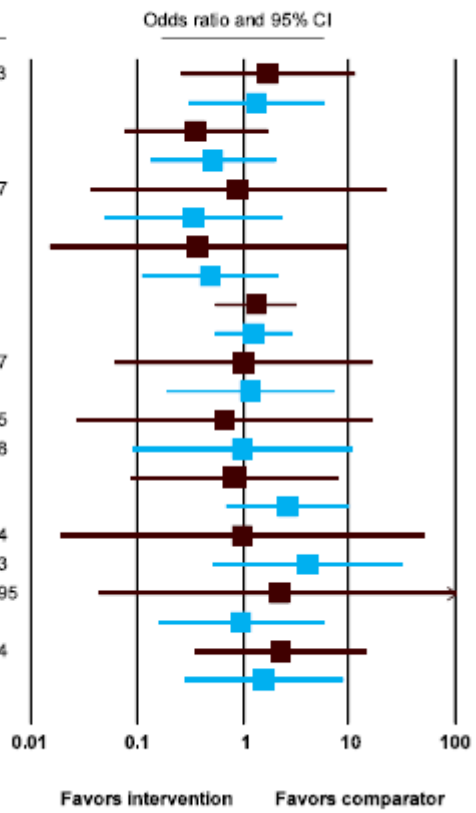
Palmer SC JAMA 2016;316:313-324

Outcome primario: mortalità CV. Farmaci aggiunti.

Farmaci aggiunti a metformina

Direct and network treatment estimates for cardiovascular mortality – dual therapy

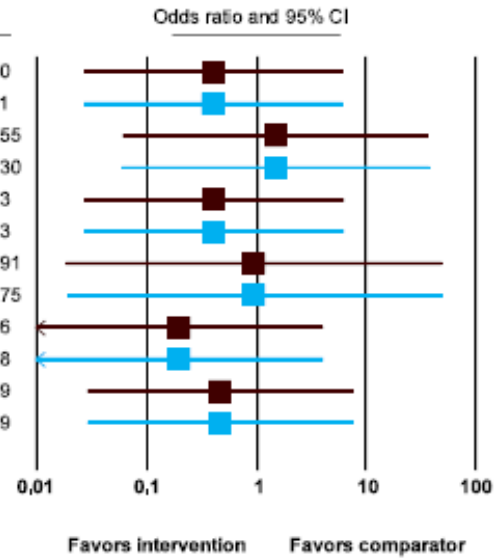
Drug comparison	Trials, n	Intervention n/N	Comparator n/N	Odds ratio and 95% CI		
TZD v PCO direct	3	3/624	0/253	1,70	0,26	11,13
TZD v PCO network				1,31	0,30	5,69
DPP-4-i v PCO direct	5	1/1655	2/683	0,35	0,07	1,64
DPP-4-i v PCO network				0,51	0,13	1,96
GLP-1RA v PCO direct	1	1/606	0/177	0,88	0,04	21,57
GLP-1RA v PCO network				0,33	0,05	2,25
SU v TZD direct	1	0/185	1/204	0,37	0,01	8,98
SU v TZD network				0,48	0,11	2,09
SU v DPP-4-i direct	6	10/4335	10/5219	1,32	0,55	3,15
SU v DPP-4-i network				1,24	0,55	2,79
SU v SGLT-2-I direct	1	1/408	1/406	1,00	0,06	15,97
SU v SGLT-2-I network				1,16	0,19	7,09
SU v GLITNIDE direct	1	0/187	1/374	0,66	0,03	16,35
SU v GLITNIDE network				0,97	0,09	10,38
TZD v DPP-4-i direct	2	1/552	1/423	0,82	0,08	7,87
TZD v DPP-4-i network				2,59	0,68	9,87
TZD v GLP-1RA direct	1	1/165	1/160	0,97	0,02	49,34
TZD v GLP-1RA network				4,00	0,52	30,63
DPP-4-i v SGLT-2-I direct	1	1/128	1/277	2,16	0,04	108,95
DPP-4-i v SGLT-2-I network				0,94	0,16	5,57
DPP-4-i v GLP-1RA direct	3	2/700	1/1205	2,24	0,35	14,24
DPP-4-i v GLP-1RA network				1,54	0,28	8,49



Farmaci aggiunti a metformina+ sulfonilurea

Direct and network treatment estimates for cardiovascular mortality – triple therapy

Drug comparison	Trials, n	Intervention n/N	Comparator n/N	Odds ratio and 95% CI		
TZD v PCO direct	1	1/277	1/115	0,42	0,03	6,20
TZD v PCO network				0,41	0,03	6,11
SGLT-2-I v PCO direct	1	1/444	0/225	1,53	0,06	37,55
SGLT-2-I v PCO network				1,53	0,06	38,30
GLP-1RA v PCO direct	1	1/277	1/115	0,42	0,03	6,33
GLP-1RA v PCO network				0,42	0,03	6,33
TZD v GLP-1RA direct	1	1/277	1/271	0,98	0,02	49,91
TZD v GLP-1RA network				0,98	0,02	48,75
DPP-4-i v SGLT-2-I direct	1	0/378	2/378	0,20	0,01	4,06
DPP-4-i v SGLT-2-I network				0,20	0,01	4,08
GLP-1RA v BASAL direct	1	1/545	1/262	0,48	0,03	7,69
GLP-1RA v BASAL network				0,48	0,03	7,69

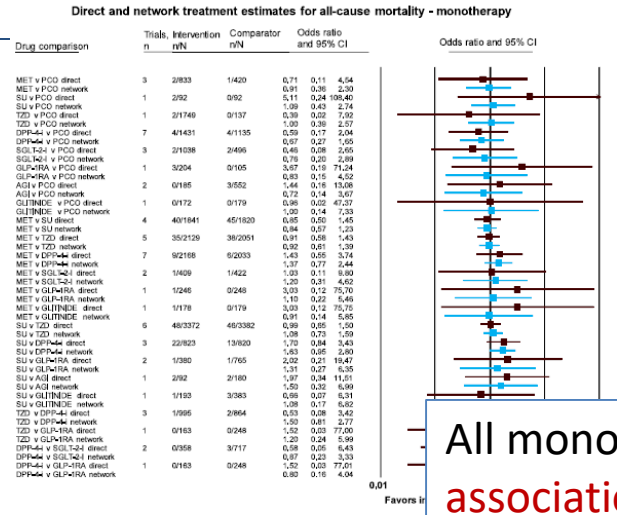


There was **no significant association** between any drug class and odds of **cardiovascular mortality**

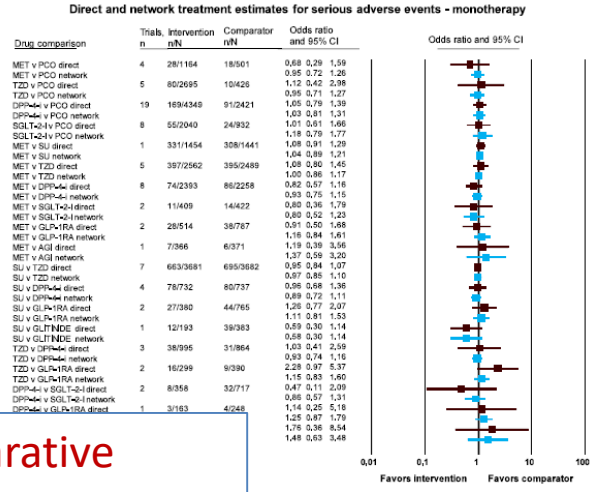
Palmer SC JAMA 2016;316:313-324

Mortalità per ogni causa, eventi avversi, IMA, ictus. Farmaci in monoterapia.

Mortalità per ogni causa

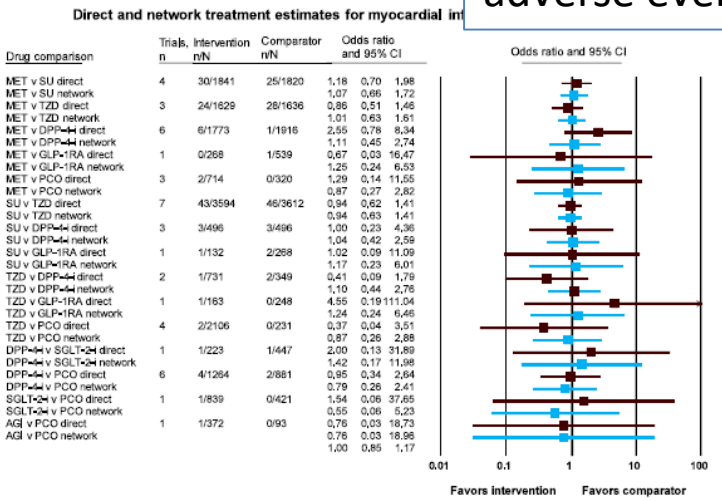


Eventi avversi seri

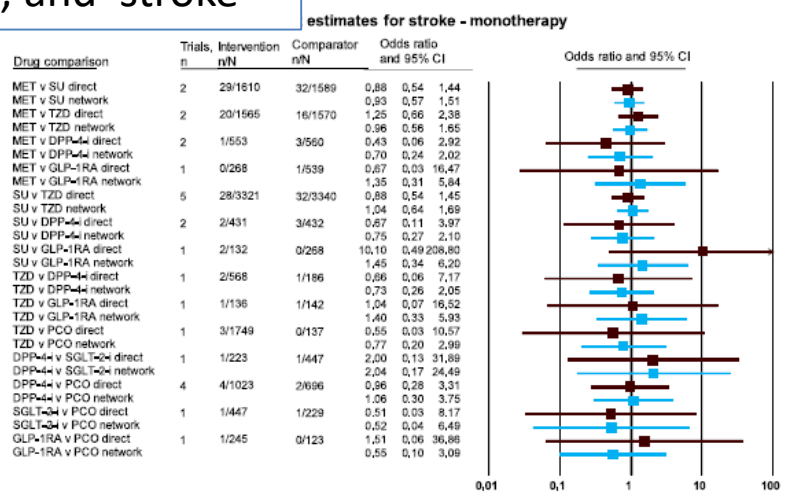


All monotherapies had uncertain comparative associations with all-cause mortality, serious adverse events, myocardial infarction, and stroke

IMA



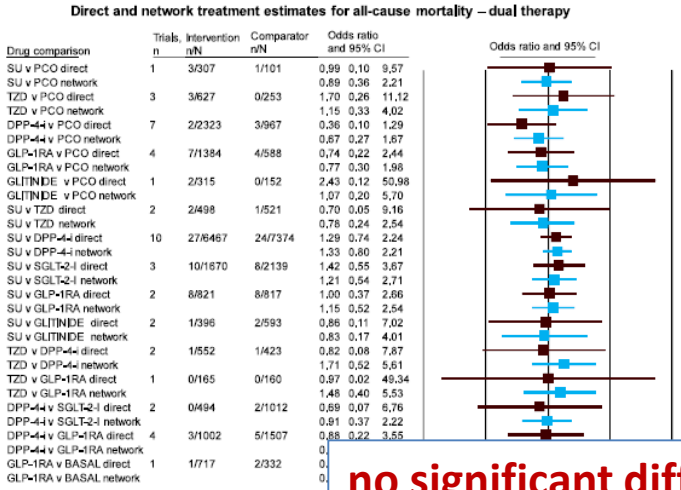
Ictus



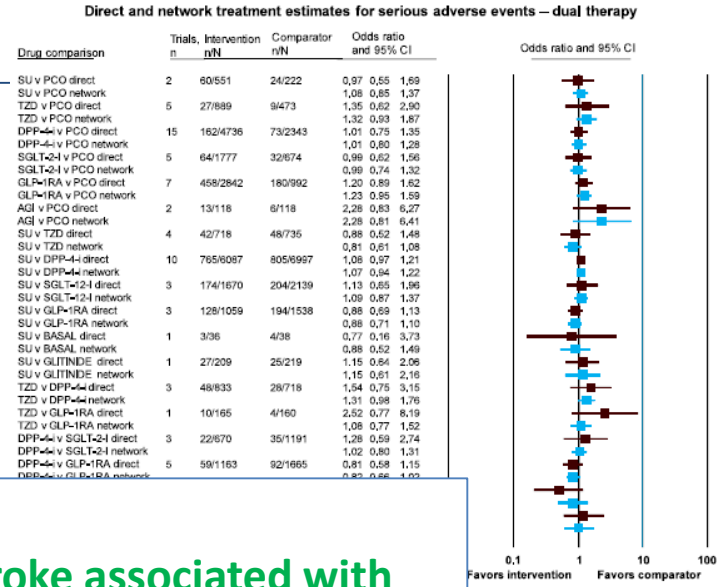
Palmer SC JAMA 2016;316:313-324

Mortalità per ogni causa, eventi avversi, IMA, ictus. Farmaci aggiunti a metformina

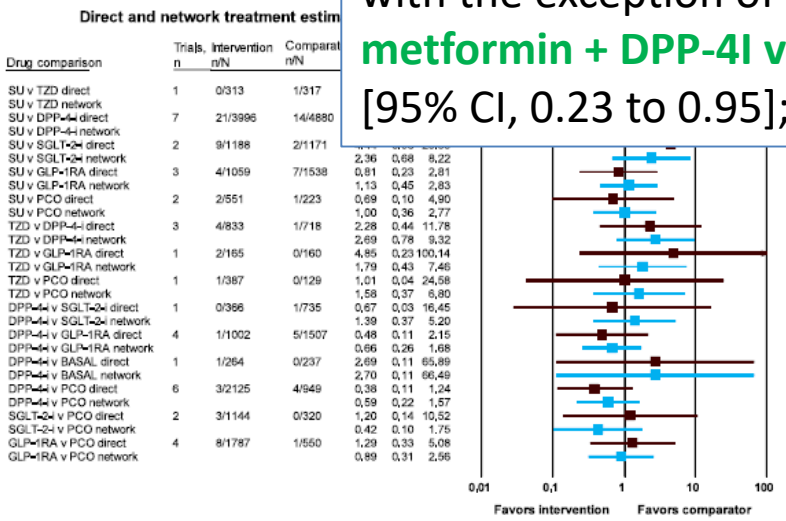
Mortalità per ogni causa



Eventi avversi seri



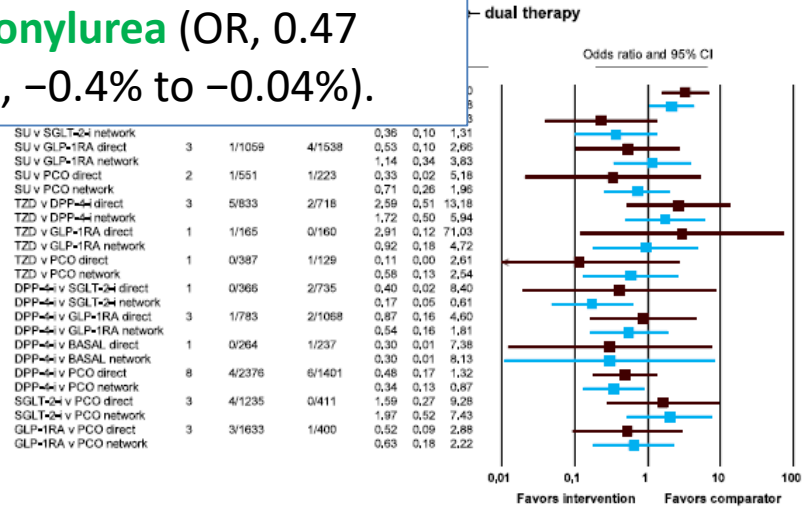
IMA



no significant differences

with the exception of a **lower odds of stroke associated with metformin + DPP-4I vs metformin + sulfonylurea** (OR, 0.47 [95% CI, 0.23 to 0.95]; RD, −0.2% [95% CI, −0.4% to −0.04%).

Ictus



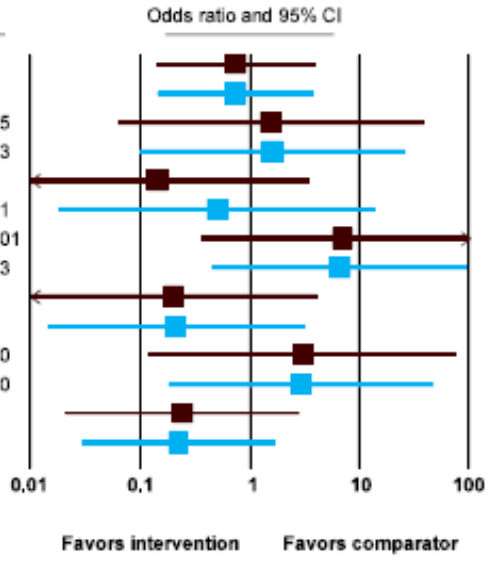
Palmer SC JAMA 2016;316:313-324

Mortalità per ogni causa, eventi avversi.
Farmaci aggiunti a metformina+ sulfonilurea

Mortalità per ogni causa

Direct and network treatment estimates for all-cause mortality – triple therapy

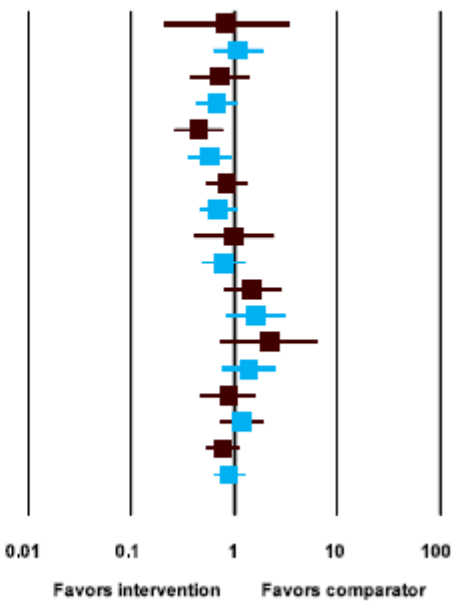
Drug comparison	Trials, n	Intervention n/N	Comparator n/N	Odds ratio and 95% CI		
TZD v PCO direct	2	3/458	2/299	0,74	0,14	3,83
TZD v PCO network				0,73	0,14	3,75
SGLT-2-I v PCO direct	1	1/444	0/225	1,53	0,06	37,55
SGLT-2-I v PCO network				1,58	0,10	24,93
GLP-1RA v PCO direct	1	0/271	1/115	0,14	0,01	3,39
GLP-1RA v PCO network				0,50	0,02	13,51
TZD v GLP-1RA direct	1	3/277	0/271	6,92	0,36	134,01
TZD v GLP-1RA nework				6,53	0,45	94,63
DPP4-i v SGLT-2-I direct	1	0/378	2/378	0,20	0,01	4,06
DPP-4-i v SGLT-2-I network				0,21	0,01	3,04
DPP-4-i v GLP-1RA direct	1	1/326	0/324	2,99	0,12	74,10
DPP-4-i v GLP-1RA network				2,89	0,18	46,00
GLP-1RA v BASAL direct	1	1/545	2/262	0,24	0,02	2,76
GLP-1RA v BASAL network				0,22	0,03	1,62



Eventi avversi seri

Direct and network treatment estimates for serious adverse events – triple therapy

Drug comparison	Trials, n	Intervention n/N	Comparator n/N	Odds ratio and 95% CI		
TZD v PCO direct	2	28/458	15/299	0,83	0,21	3,29
TZD v PCO network				1,07	0,62	1,85
DPP-4-i v PCO direct	2	28/921	17/391	0,70	0,37	1,36
DPP-4-i v PCO network				0,67	0,43	1,04
SGLT-2-I v PCO direct	3	28/866	33/490	0,45	0,26	0,77
SGLT-2-I v PCO network				0,57	0,36	0,90
GLP-1RA v PCO direct	3	53/987	30/476	0,84	0,52	1,33
GLP-1RA v PCO network				0,69	0,46	1,03
BASAL v PCO direct	1	16/232	8/114	0,98	0,41	2,36
BASAL v PCO network				0,78	0,48	1,27
TZD v GLP-1RA direct	1	25/277	17/271	1,48	0,78	2,81
TZD v GLP-1RA network				1,61	0,83	3,12
TZD v BASAL direct	1	11/112	5/104	2,16	0,72	6,43
TZD v BASAL network				1,37	0,78	2,42
DPP-4-i v SGLT-2-I direct	1	21/378	24/378	0,87	0,47	1,59
DPP-4-i v SGLT-2-I network				1,17	0,72	1,90
GLP-1RA v BASAL direct	3	77/1058	59/762	0,77	0,53	1,11
GLP-1RA v BASAL network				0,88	0,63	1,23



There was no evidence of significantly different associations with all-cause mortality or serious adverse events between any of the drug classes given as triple therapy.

Insufficient observations were available to generate evidence networks for myocardial infarction or stroke.

Palmer SC JAMA 2016;316:313-324

Ipoglicemia

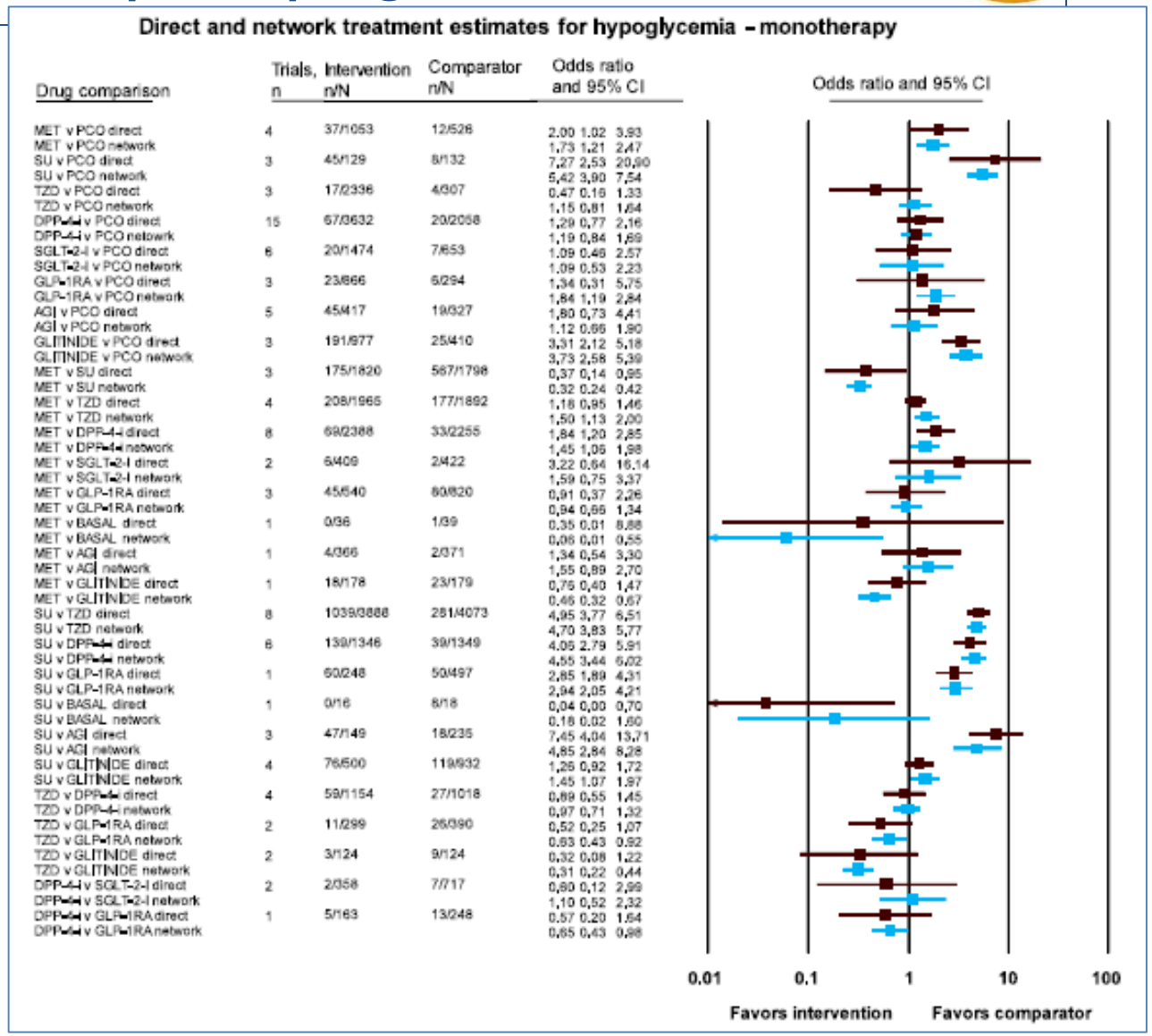
Farmaci in monoterapia: ipoglicemia

Higher hypoglycemia risk

- **Basal insulin** (OR, 17.9 [95%CI, 1.97 to 162];RD, 10%[95% CI, 0.08% to 20%])
- **Sulfonylurea** (OR, 3.13 [95% CI, 2.39 to 4.12]; RD, 10% [95% CI, 7% to 13%])

Lower risk of hypoglycemia than metformin

- **Placebo** (OR, 0.58 [95%CI, 0.40 to 0.83]; RD, −3% [95%CI, −5%to −0.2%),
- **Thiazolidinediones** (OR,0.67 [95%CI, 0.50 to 0.88]; RD, −4% [95% CI, −7% to −1%]),
- **DPP-4 inhibitors** (OR,0.69 [95%CI,0.50 to0.94;RD, −1%[95%CI, −4% to 1%])



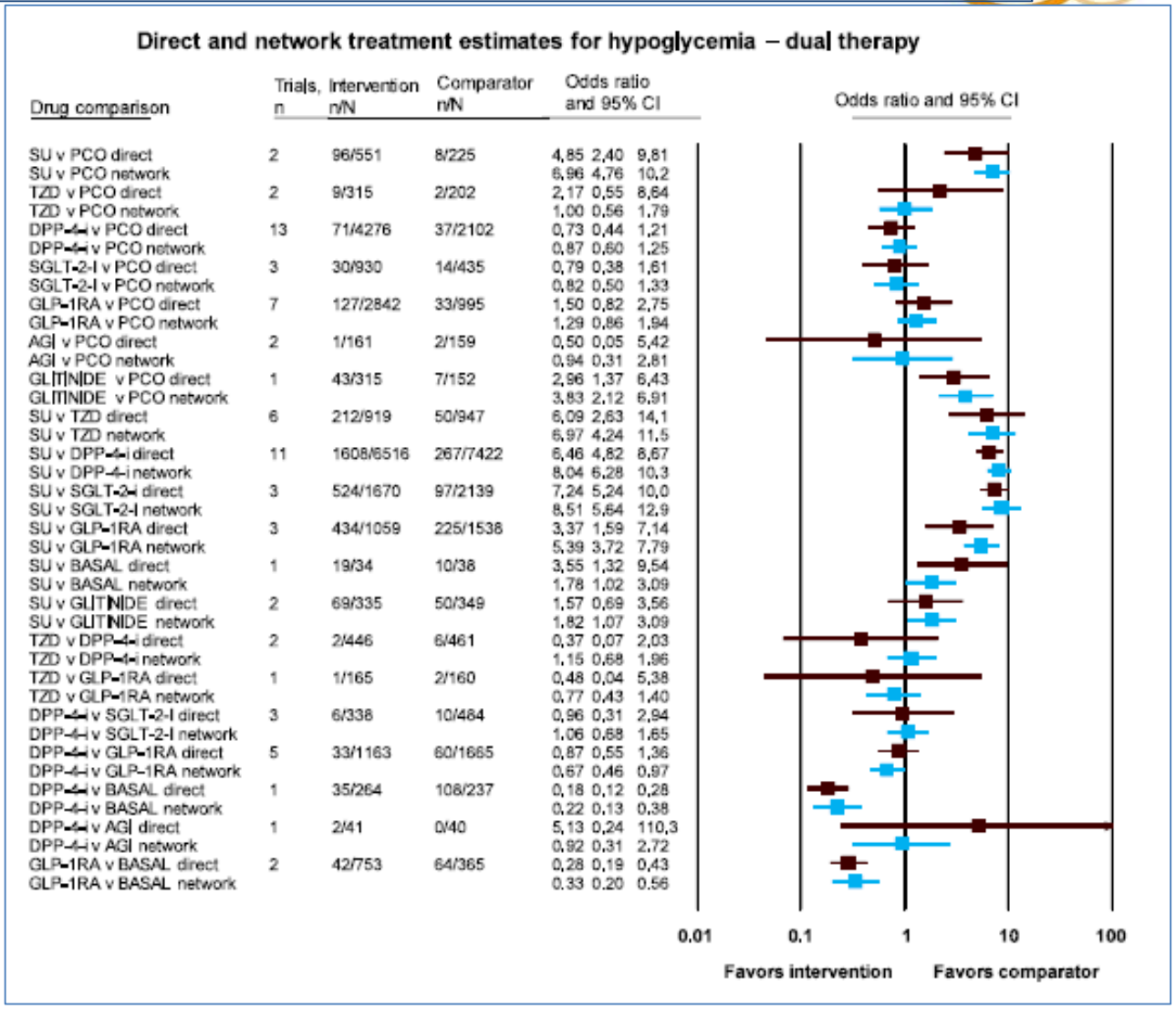
Palmer SC JAMA 2016;316:313-324

Farmaci aggiunti a metformina: ipoglicemia

All dual-therapy classes were associated with lower odds of hypoglycemia than metformin + sulfonylurea dual therapy

with mean odds of hypoglycemia ranging from
0.56 (95%CI, 0.32 to 0.98; RD, −4% [95% CI, −12% to 5%]) for **metformin + basal insulin** to

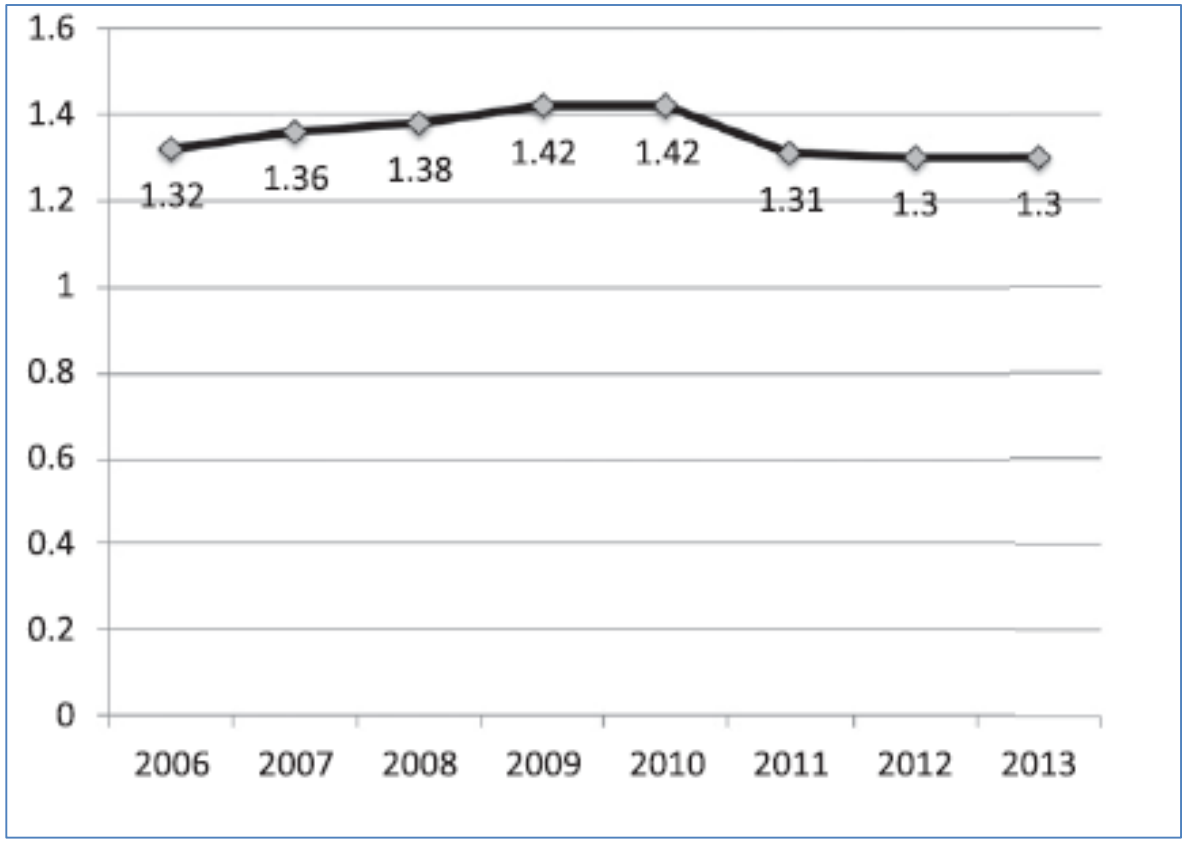
0.12 (95%CI,0.08to0.18;RD,−22%[95% CI, −27% to −18%]) for **metformin + SGLT-2 inhibitor**, which Was rank ed as the best option to avoid hypoglycemia



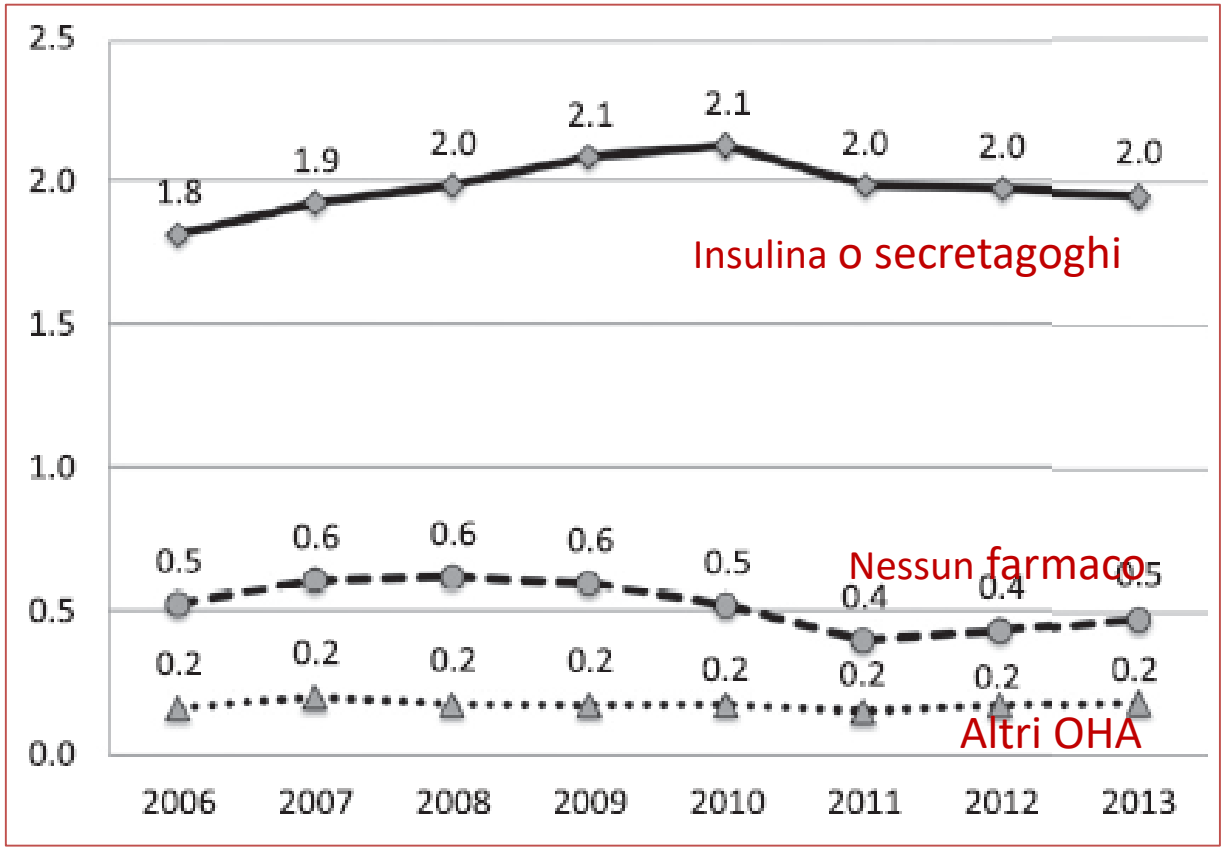
Palmer SC JAMA 2016;316:313-324

Tassi di ipoglicemie severe con accesso in PS, osservazione breve o ricovero: 2006- 2013

Ogni farmaco ipoglicemizzante



Ipoglicemizzanti specifici



Tasso per 100 persone- anno

Lipska KJ Diabetes Care Publish Ahead of Print, published online September 22, 2016

Peso corporeo

Farmaci in monoterapia: peso corporeo

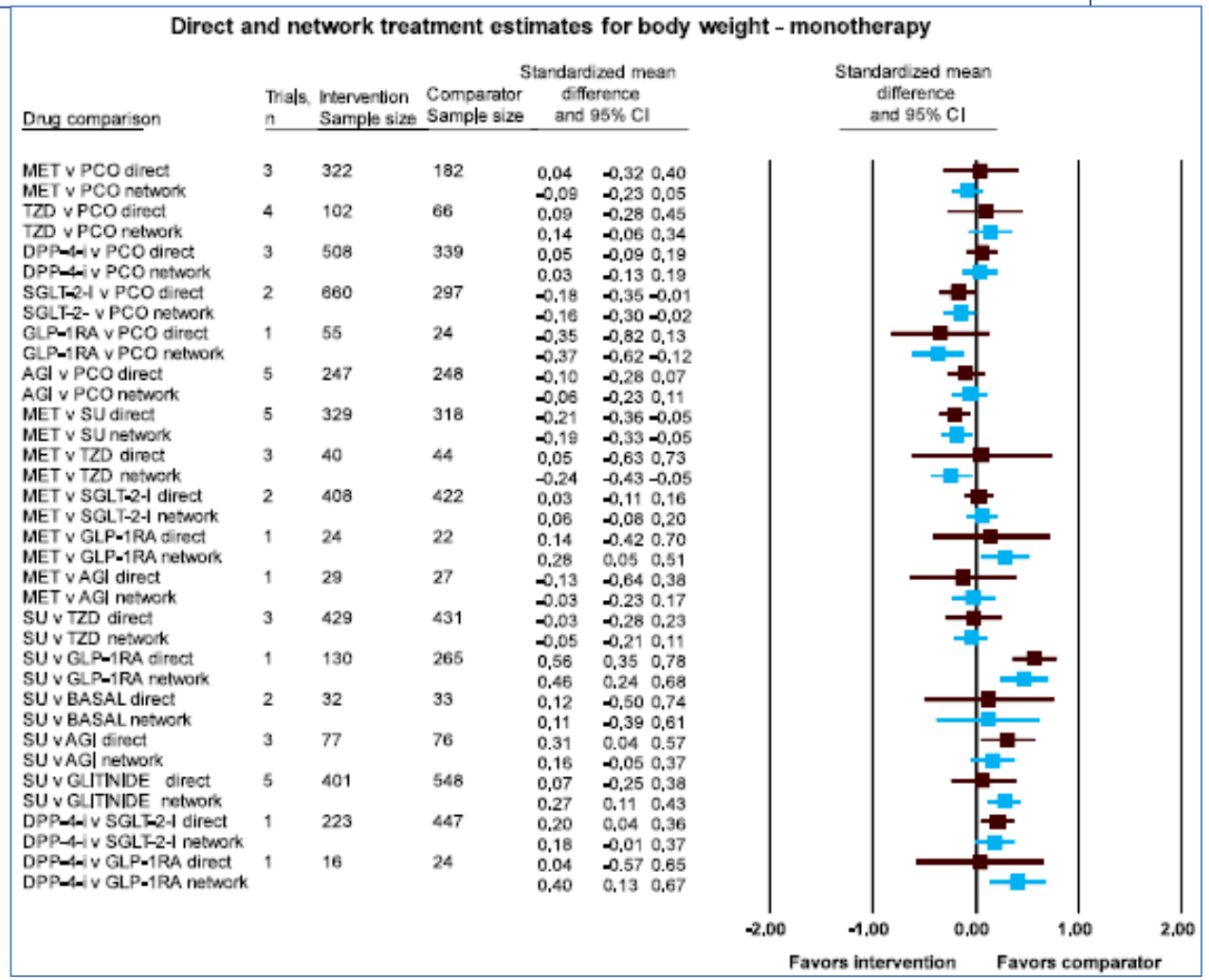
Compared with metformin,

Lower body weight

GLP-1 receptor agonist (SMD, −0.28 [95% CI, −0.52 to −0.04])

Higher body weight.

- **Sulfonylurea** (SMD,0.19 [95%CI,0.04to0.33])
- **Thiazolidinedione** (SMD, 0.24[95%CI,0.04to0.43])



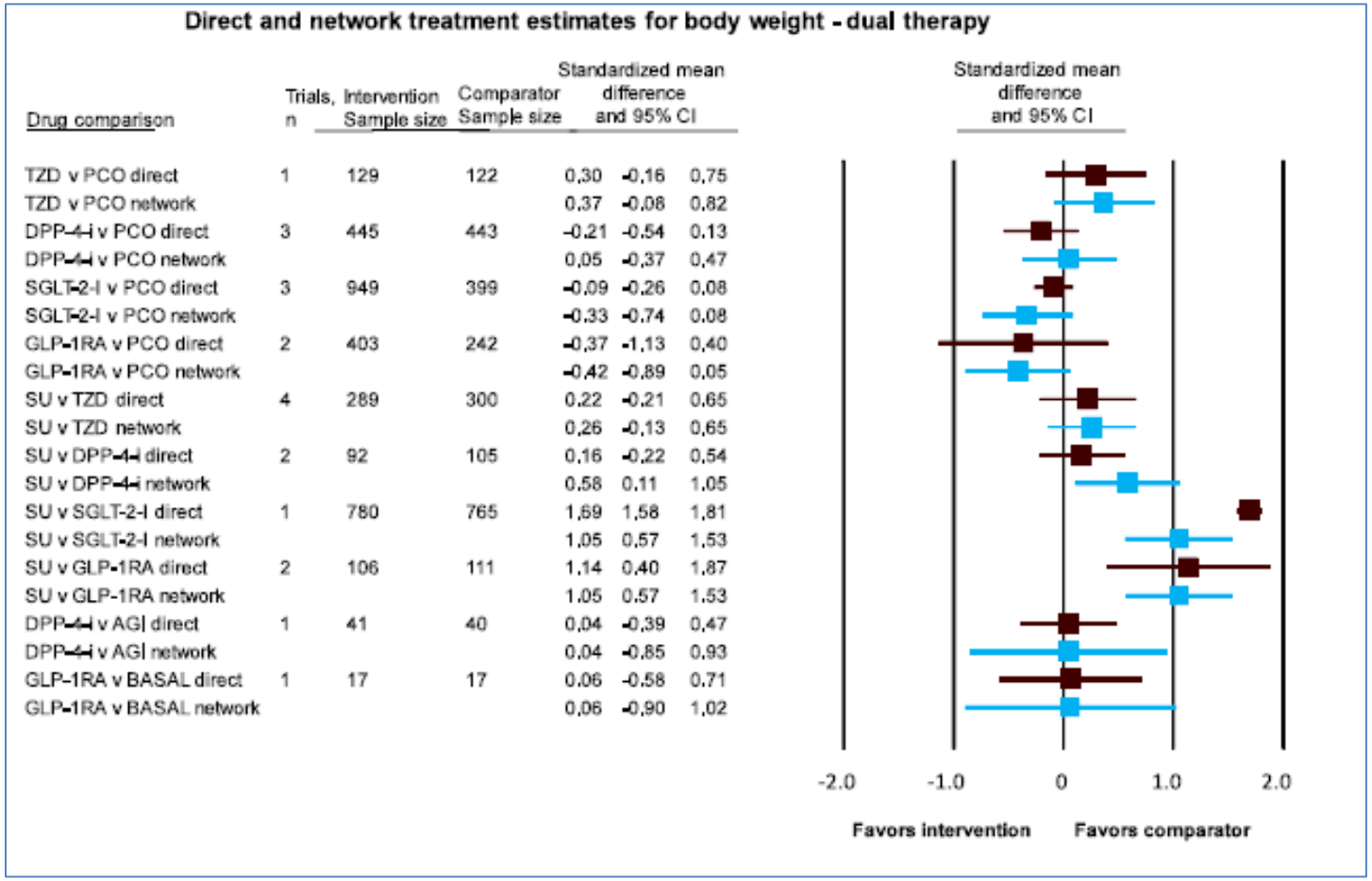
Palmer SC JAMA 2016;316:313-324

Farmaci aggiunti a metformina: peso corporeo

Metformin+sulfonylurea dual therapy was ranked worst for bodyweight.

Compared with metformin + sulfonylurea treatment,

- **metformin + DPP-4inhibitor** (SMD,**−0.58** [95%CI,−1.06 to −0.11]),
- **metformin + SGLT-2 inhibitor** (SMD, **−0.96** [95%CI, −1.46 to−0.47]),
- **metformin + GLP-1 receptor agonist** (SMD, **−1.05** [95% CI, −1.54 to −0.57]) were associated with significantly lower **body weight** at the end of treatment.



Palmer SC JAMA 2016;316:313-324

Sintesi sugli endpoint solidi

- No evidence of differences in the associations between glucose-lowering drugs alone or in combination with odds of
  - cardiovascular mortality
  - all-cause mortality
  - serious adverse events
  - myocardial infarction
  - stroke

- Considerable uncertainty about the association of drug treatment with cardiovascular mortality existed within trial evidence, largely because of few events in most available studies.

Palmer SC JAMA 2016;316:313-324

Aggiunta di farmaci alla metformina

- Sulfonylurea therapy least preferred
- SGLT-2 inhibitors to
  - avoid hypoglycemia
  - minimize treatment failure
- SGLT-2 inhibitors or GLP-1 receptor agonists
  - for those for whom weight gain is a higher priority

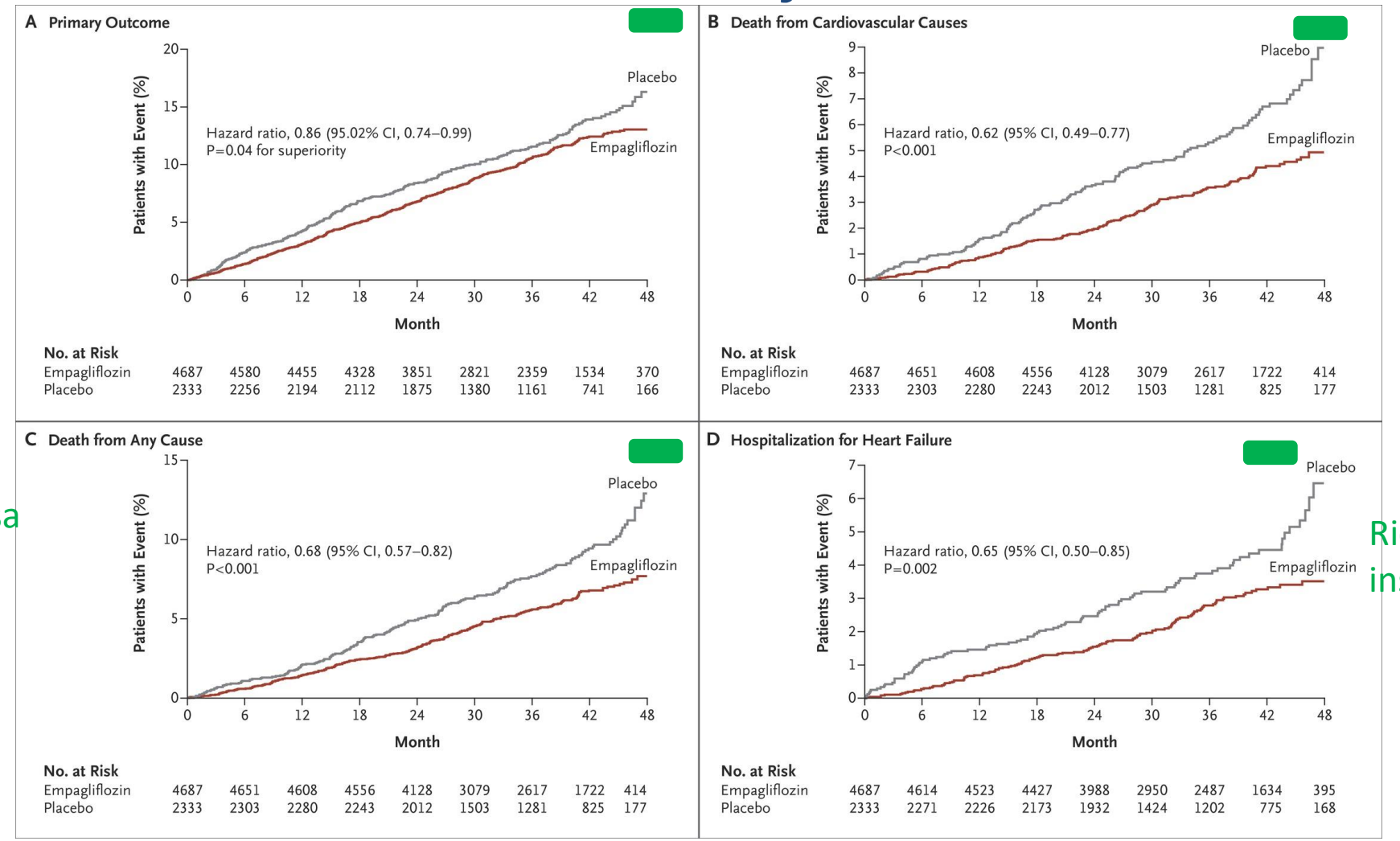
Palmer SC JAMA 2016;316:313-324

Gli studi che hanno dimostrato efficacia in prevenzione cv secondaria

EMPA-REG OUTCOME: Cardiovascular Outcomes and Death from Any Cause

Outcome primario:
Morte cv,
IMA non fatale,
ictus non fatale

Morte per ogni causa



Morte CV

Ricovero per insufficienza cardiaca

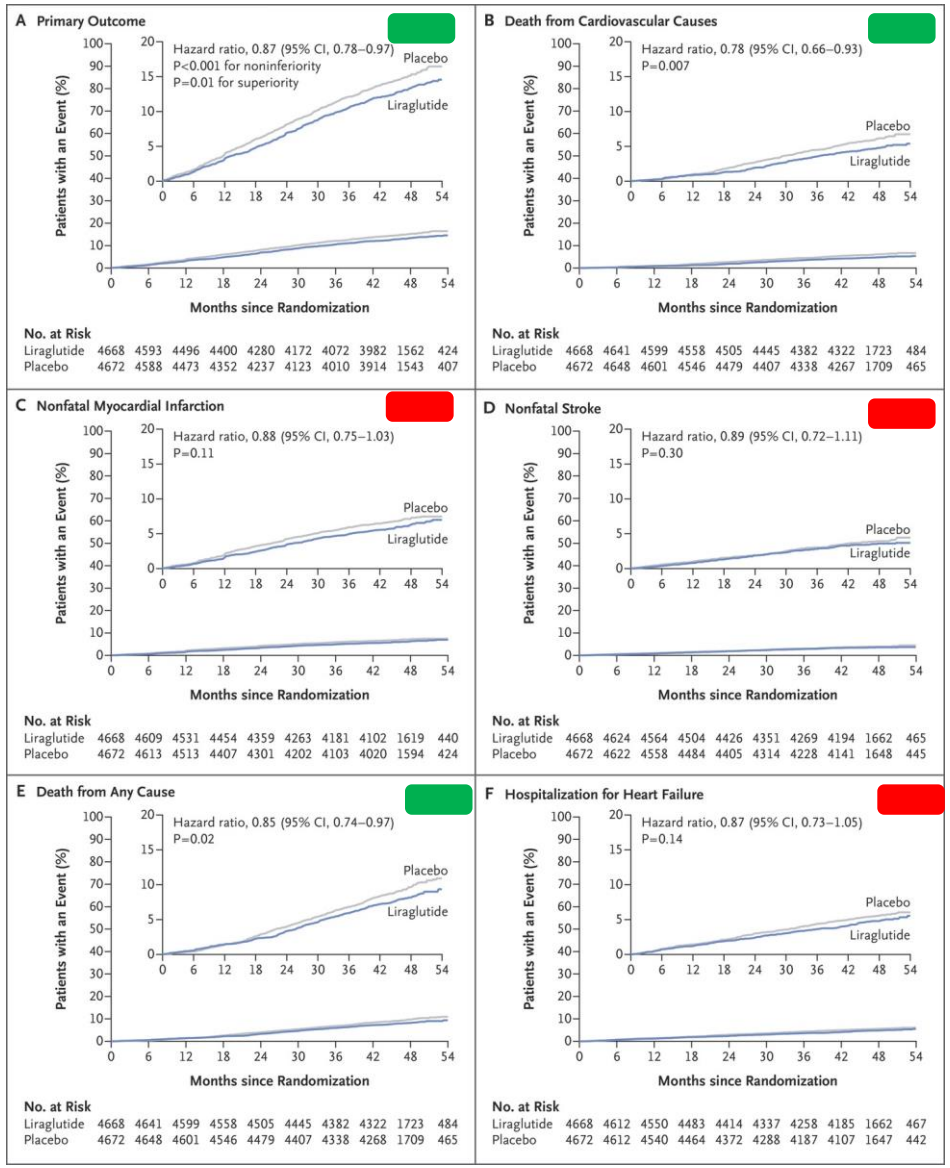
Zinman B et al. N Engl J Med 2015;373:2117-2128

LEADER Primary and Exploratory Outcomes.

Outcome primario:
Morte cv,
IMA non fatale,
ictus non fatale

IMA non fatale

Morte per ogni causa



Morte CV

Ictus non fatale

Ricovero per insufficienza cardiaca

The NEW ENGLAND JOURNAL of MEDICINE

Marso SP et al. N Engl J Med 2016;375:311-322

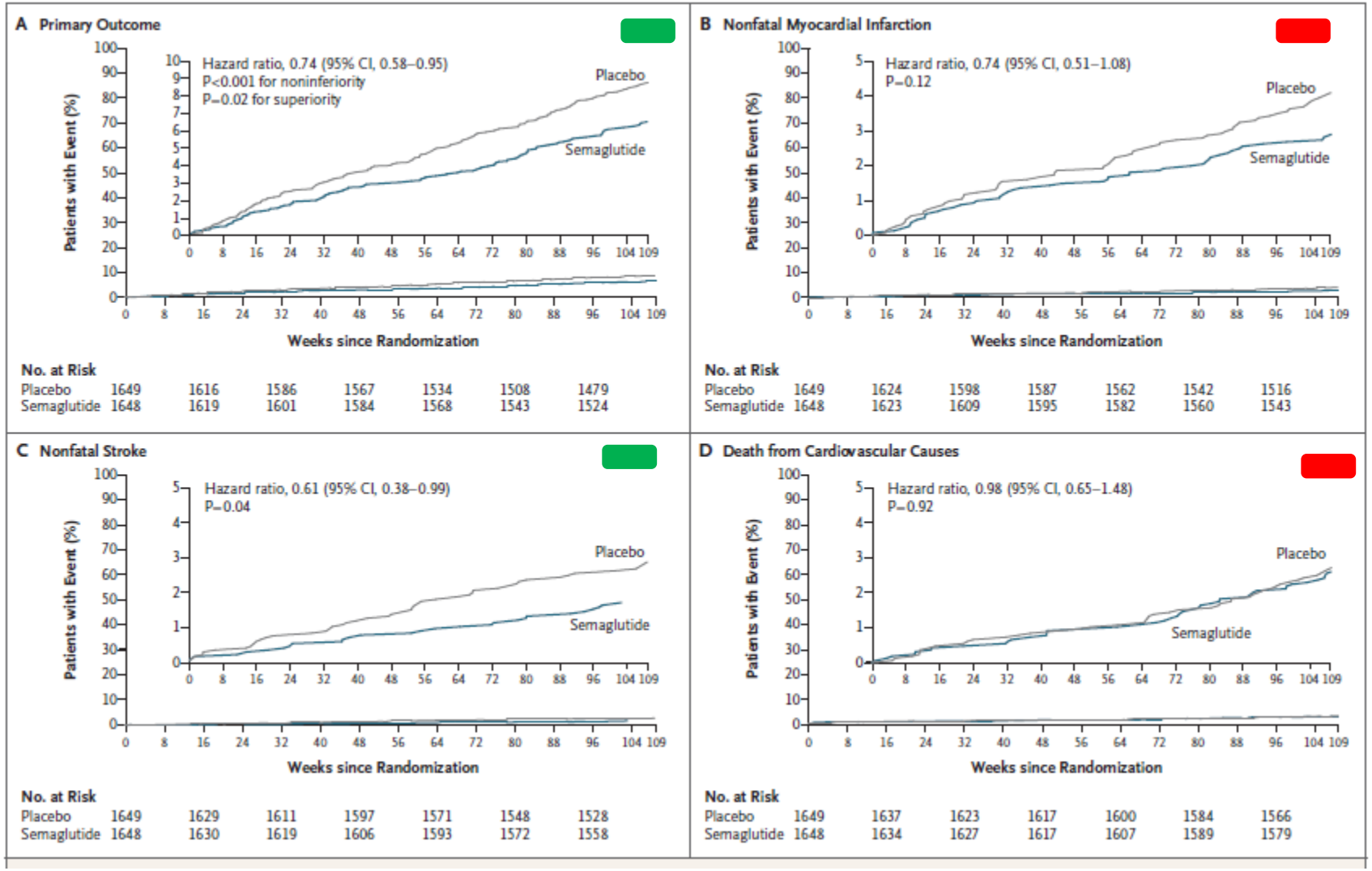
SUSTAIN-6 Semaglutide and Cardiovascular Outcomes

Outcome primario:
Morte cv,
IMA non fatale,
ictus non fatale

Ictus non fatale

IMA non fatale

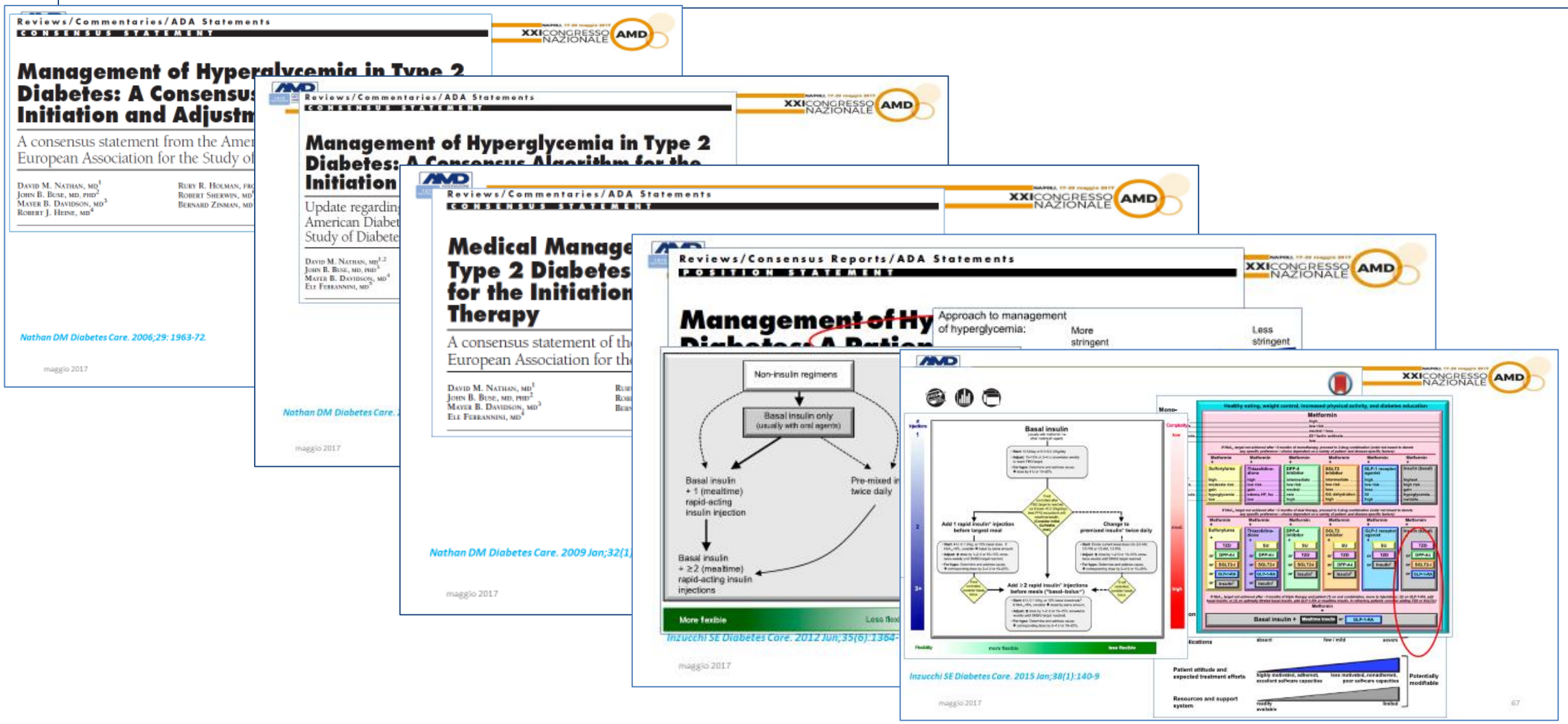
Morte per cause CV



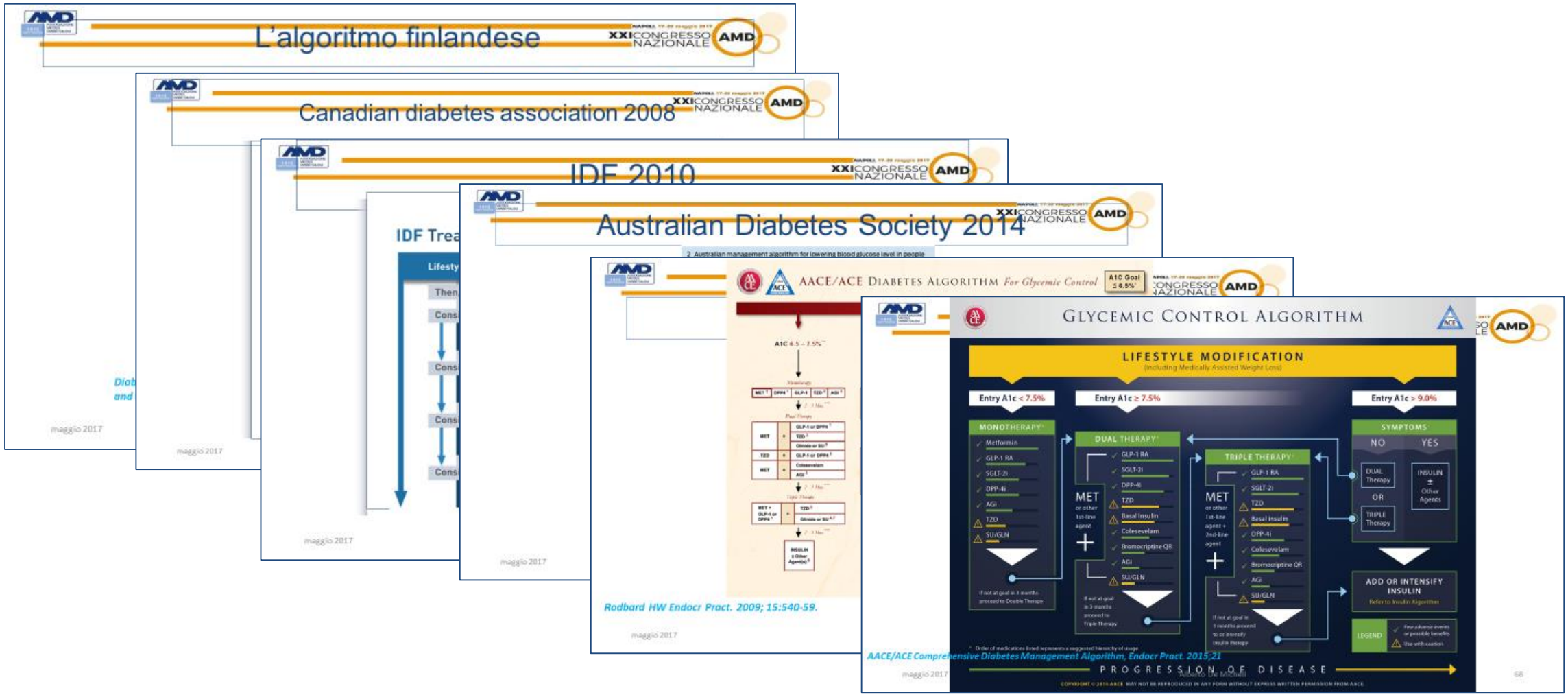
Marso SP published on September 16,2016, at NEJM.org. DOI: 10.1056/NEJMoa1607141

L'era degli algoritmi

ADA, EASD


Reviews/Commentaries/ADA Statements
CONSENSUS STATEMENT
Management of Hyperglycemia in Type 2 Diabetes: A Consensus
Initiation and Adjustm
A consensus statement from the Amer
European Association for the Study of
Nathan DM Diabetes Care. 2006;29: 1963-72.
Reviews/Commentaries/ADA Statements
CONSENSUS STATEMENT
Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation
Update regardin
American Diabet
Study of Diabete
Nathan DM Diabetes Care.
Reviews/Commentaries/ADA Statements
CONSENSUS STATEMENT
Medical Manage
Type 2 Diabetes
for the Initiation
Therapy
A consensus statement of th
European Association for th
Nathan DM Diabetes Care. 2009 Jan;32(1)
Reviews/Consensus Reports/ADA Statements
POSITION STATEMENT
Management of Hy
Approach to management of hyperglycemia:
More stringent
Less stringent
Non-insulin regimens
Basal insulin only (usually with oral agents)
Basal insulin + 1 (mealtime) rapid-acting insulin injection
Pre-mixed twice daily
Basal insulin + ≥2 (mealtime) rapid-acting insulin injections
More flexible
Inzucchi SE Diabetes Care. 2012 Jun;35(6):1364-
Basal insulin
Add 1 rapid insulin* injection before largest meal
Change to premixed insulin* twice daily
Add ≥2 rapid insulin* injections before meals ("basal-bolus")
Inzucchi SE Diabetes Care. 2015 Jan;38(1):140-9
Metformin
Basal insulin +
Patient attitude and expected treatment effects
Resources and support system
Potentially modifiable
maggio 2017

Altre associazioni internazionali



Algoritmi italiani

Perché gli algoritmi?

Il problema

- I farmaci sono sempre più costosi
  - Tecnologie sofisticate
  - Sperimentazioni complesse
  - Requisiti di registrazione rigorosi
  - Grandi investimenti
  - Grandi guadagni

L'ipotesi di soluzione: step therapy

- Iniziare con farmaco economico
  - Certificazione di inadeguato beneficio
  - Certificazione di effetti collaterali
- Aggiungere o sostituire con farmaco più costoso

Fischer MA, JAMA 2017; 17: 801-802

Pro e contro degli algoritmi

Pro

- Algoritmi fondati su EBM
- Migliorano la qualità della cura

Contro

- Poche prove
- Scarsa attenzione alle prove
- Enfasi sui costi piuttosto che sui risultati

Fischer MA, JAMA 2017; 17: 801-802

I limiti della step therapy

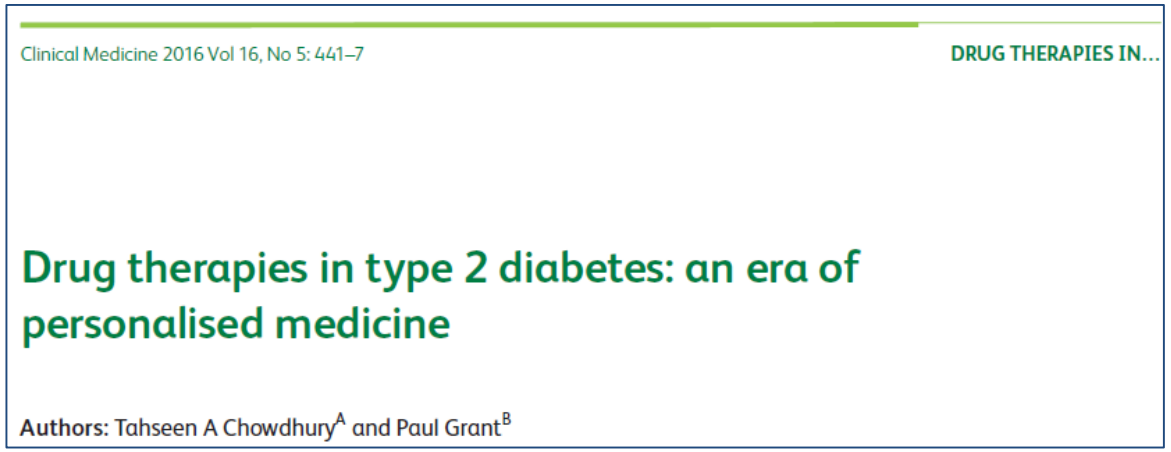
Idiosincrasie

Pz NON a target per controllo glicemico

Proseguire e rinforzare l'intervento sullo stile di vita
+
metformina
Controllo a 3 mesi

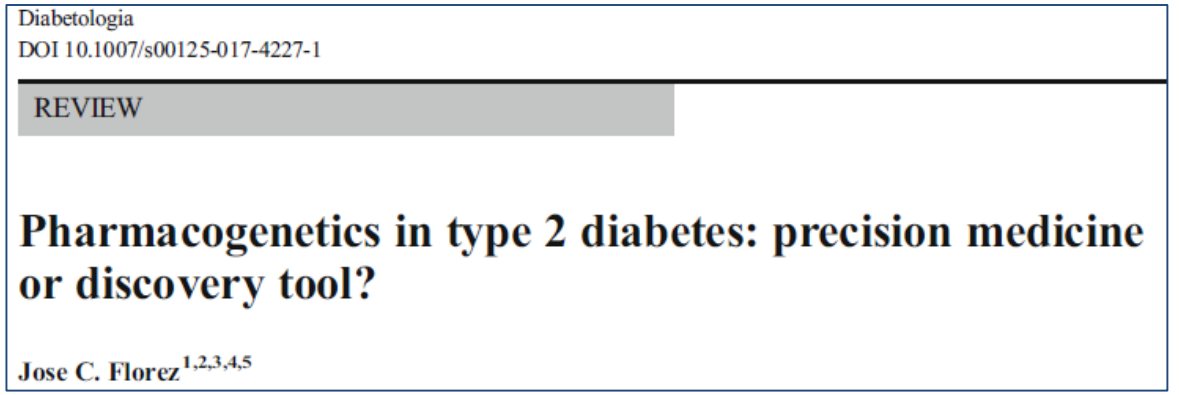
Paziente intollerante/con controindicazione a metformina dopo verifica della tolleranza anche alla metformina a rilascio prolungato

Medicina di precisione


Clinical Medicine 2016 Vol 16, No 5: 441–7 DRUG THERAPIES IN...

Drug therapies in type 2 diabetes: an era of personalised medicine

Authors: Tahseen A Chowdhury[A] and Paul Grant[B]


Diabetologia
DOI 10.1007/s00125-017-4227-1

REVIEW

Pharmacogenetics in type 2 diabetes: precision medicine or discovery tool?

Jose C. Florez[1,2,3,4,5]

Fischer MA, JAMA 2017; 17: 801-802

I contendenti

Industria farmaceutica

- Spinta per l'utilizzo di nuovi farmaci costosi:
  - Medici prescrittori
  - Pazienti
  - Mezzi diversi

Pagatori

- Budget limitati
- End points solidi
- Rapporto costo/ efficacia

Gruppi di difesa dei pazienti

- Singoli pazienti non possono avere farmaci per loro indispensabili

E' possibile risolvere queste problematiche con interventi legislativi?

Fischer MA, JAMA 2017; 17: 801-802

Le motivazioni della step therapy

- Non sempre le linee guida sono seguite
- Molte scelte terapeutiche sono inutilmente costose

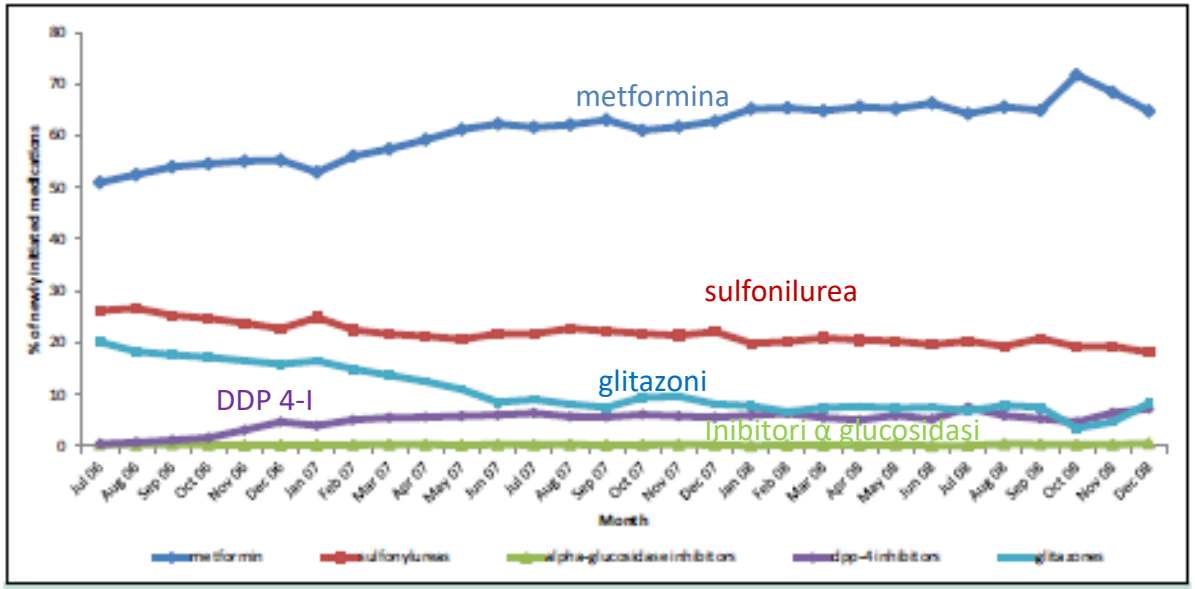


Figure 2 Temporal trends in medication initiation by therapeutic class, July 2006 to December 2008.

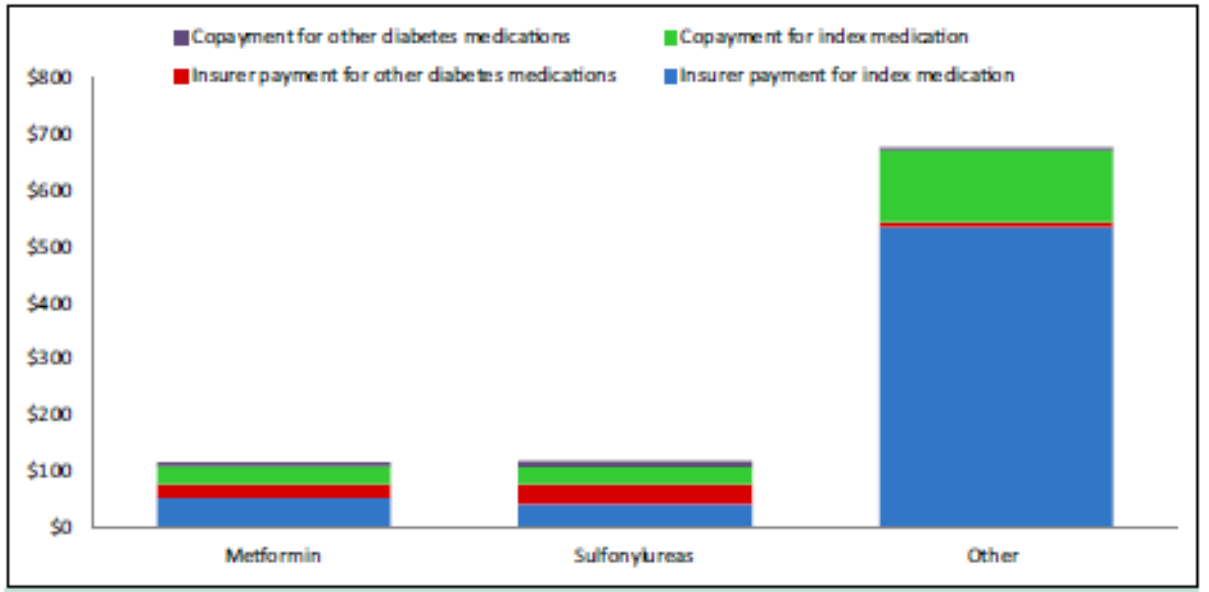


Figure 4 Total patient and insurer spending during 6 months after initiation stratified by class of medication on which patients were started.

Fischer MA, JAMA 2017; 17: 801-802
Desai NR, The American Journal of Medicine (2012) 125, 302.e1-302.e7

Implementazione della step therapy

- Agente preferito nell'ambito di una classe terapeutica (equivalente vs. brand nella stessa classe)
- Farmaci di classi diverse con meccanismi di azione simili (pari efficacia dimostrata EBM)
- Sequenza di farmaci diversi per una specifica patologia (necessità di studi di efficacia comparativa)

Fischer MA, JAMA 2017; 17: 801-802

Aspetti problematici della step therapy

Algoritmo ottimale

- Disegnato con intelligenza
- Attuato con intelligenza
- Fondato sulla EBM
- Con ragionevoli previsioni di eccezioni

- Prescrizione razionale
- Controllo dei costi
- Cure efficaci basate sui dati

Algoritmo nocivo

- Non basato su prove
- Attuato con rigidità

- Inefficacia e rischio nei singoli pazienti

Fischer MA, JAMA 2017; 17: 801-802

Conclusioni

Piani terapeutici: limitazione alla rimborsabilità

Incretine

1. Fallimento terapeutico, livelli di HbA1c ≥7.5% (58 mmol/mol)6, alla dose massima tollerata della terapia ipoglicemizzante corrente e dopo adeguata e documentata modifica dello stile di vita (dieta e attività fisica);
2. HbA1c ≤8.5% (69 mmol/mol), cioè un livello dal quale sia ragionevole raggiungere il target desiderato con l'aggiunta del nuovo farmaco,
3. Rischio di ipoglicemie severe o comunque condizionanti le attività quotidiane che sconsigli l'utilizzo di altre classi di ipoglicemizzanti. Conseguentemente la rimborsabilità dell'associazione con sulfoniluree è limitata esclusivamente ai casi di controindicazione o intolleranza alla metformina.

- *Consigliabile un target glicemico meno stringente1,2,7, il livello di HbA1c di cui al punto (2) può estendersi al 9% (75 mmol/mol).*
- *La prescrizione in monoterapia di sitagliptin, vildagliptin, saxagliptin, linagliptin è rimborsata limitatamente ai pazienti con insufficienza renale cronica moderata-severa (il principio attivo alogliptin non è indicato in monoterapia); l*
- *La rimborsabilità in associazione a insulina è limitata ai casi indicati nel piano terapeutico e alla sola insulina basale.*

AIFA Piano terapeutico per l'utilizzo appropriato dei farmaci "incretino-mimetici" nel diabete tipo 2

Inibitori SGLT-2

1. In monoterapia, nei pazienti intolleranti alla metformina nei quali l'utilizzo di un diverso ipoglicemizzante risulti controindicato o non appropriato.
2. In associazione a metformina (duplice terapia), nei casi in cui l'utilizzo di un diverso ipoglicemizzante risulti controindicato o non appropriato.
3. In associazione a insulina, con o senza metformina.

AIFA Piano terapeutico per l'utilizzo appropriato dei farmaci inibitori del co-trasportatore sodio-glucosio 2 (sglt-2) nel diabete tipo 2

Un algoritmo terapeutico può essere stabilito per legge?

- La step therapy è un modello di appropriatezza
- Efficacia e risparmio in prospettiva per gli stessi pazienti (cittadini- utenti)
- Le sfumature cliniche ed economiche che guidano una prescrizione ottimale sono molteplici
- Sistema troppo complesso per essere normato rigidamente, con poche regole

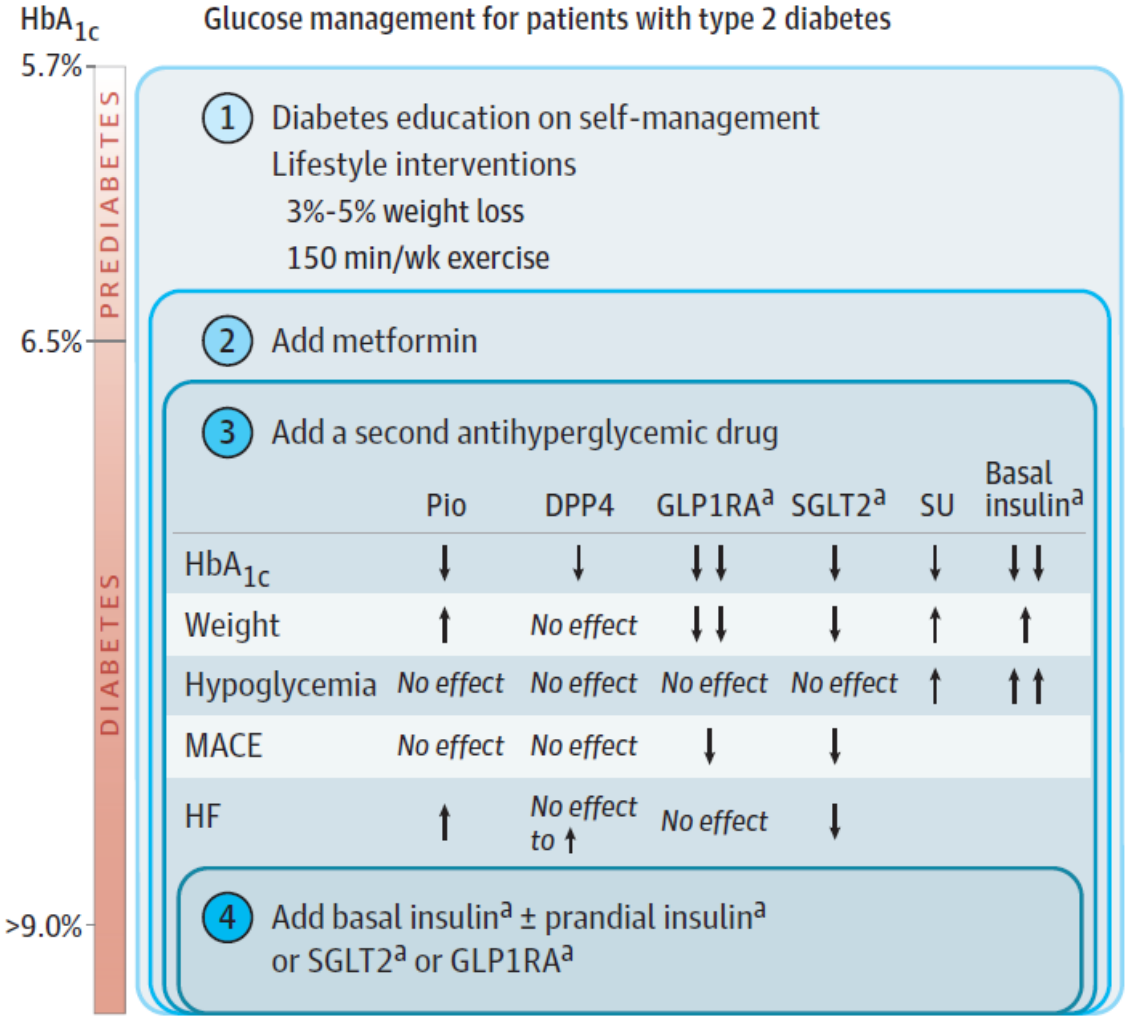
Fischer MA, JAMA 2017; 17: 801-802

Che cosa si può fare?

- Uso di EBM «vera», contrapposta a pressioni commerciali su medici, pazienti e legislatori
- Educazione dei medici alla conoscenza dei farmaci e all'appropriatezza, non sottomissione a regole rigide stabilite da altri
- Controllo dell'aderenza alla terapia, per evidenziare l'inefficacia reale
- Visione della terapia nella prospettiva della salute globale, attuale e futura
- Criteri chiari per la rimborsabilità dei farmaci
- Processi di autorizzazione automatizzati e semplici
- Richieste di eccezioni automatizzate e semplici

Fischer MA, JAMA 2017; 17: 801-802

Uno schema semplice



	Pio	DPP4	GLP1RA[a]	SGLT2[a]	SU	Basal insulin[a]
HbA_{1c}	↓	↓	↓↓	↓	↓	↓↓
Weight	↑	*No effect*	↓↓	↓	↑	↑
Hypoglycemia	*No effect*	*No effect*	*No effect*	*No effect*	↑	↑↑
MACE	*No effect*	*No effect*	↓	↓		
HF	↑	*No effect to* ↑	*No effect*	↓		

Reusch JEB, JAMA. 2017;317:1015-1016

Cui prodest? Cui nocet?

Cui prodest?

- Cultura
- Pensiero critico
- Appropriatezza
- Utilizzo razionale delle risorse
- Sensibilizzazione del paziente al valore (anche economico) delle cure che riceve

Cui nocet?

- Carico burocratico
- Rapporto medico/ paziente

Annals of Internal Medicine — POSITION PAPER

Putting Patients First by Reducing Administrative Tasks in Health Care: A Position Paper of the American College of Physicians

Excessive administrative tasks have serious adverse consequences for physicians and their patients. Stakeholders must work together to address the administrative burdens that fail to put patients first.

Erickson SM, Ann Intern Med. 2017; 166: 659-661

Grazie per l'attenzione