Le farmaco-interazioni da evitare

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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:
- ABBOTT Italia
- NOVO Nordisk Italia
- Lilly Italia

Il problema

- Patients with type 2 diabetes mellitus are generally treated with many pharmacological compounds and are exposed to a high risk of drug-drug interactions. Indeed, **blood glucose control usually requires a combination of various glucose-lowering agents,** and the recommended global approach **to reduce overall cardiovascular risk generally implies administration of several protective compounds**, including statins, antihypertensive compounds and antiplatelet agents.

- … the growing numbers of **patients living much longer** and confronting a number of disease states and chronic conditions over the course of their lives. .. they are living with a **growing medication burden** that affects their ability to cope with their illnesses and presents healthcare providers with the challenge of balancing **the need for multiple medications with the possibilities of harmful drug–drug interactions**.

- The need to be diligent with medication review and proper prescribing is imperative to reduce healthcare costs and improve patient health.

Characteristics of Adults With Type 2 Diabetes Mellitus

Prevalence rate of comorbidity	Aged < 65 years	Aged > 65 years
Hyperlipidemia	71%	82%
Hypertension	58%	71%
Obesity	58%	40%
CAD	6%	16%
Depression	7%	5%

Am J Manag Care, 2015

Number of drugs recommended for each condition in each NICE guideline considered

Condition	Guideline No	Year published	No of drugs/drug classes recommended	
			First line	Second line
Type 2 diabetes	CG87	2009	4	19
Depression	CG90	2009	1	12
Heart failure	CG108	2010	2	9
Atrial fibrillation	CG36	2006	4	7
Dementia	CG42	2006	3	1
Secondary prevention post-MI	CG48	2007	4	13

Many guidelines recommend drug treatments, but current guidelines rarely consider drug-disease or drug-drug interactions in these recommendations

BMJ, 2015

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

Schemi di trattamento per la cura del diabete

Schema di trattamento	Percentuale rispetto al totale dei pazienti trattati con farmaci antidiabetici
Monoterapia non insulinica	45,2
Duplice terapia non insulina	19,6
Triplice non insulinica	7,0
Quadruplice (o più) non insulinica	2,9
Analogo basale + altri farmaci ma non incretine	3,1
Analogo basale + incretina	0,9
Insulina non basale + incretina	1,0
Analoghi (ma non solo basale) + farmaci non incretinici	6,4
Insulina umana con o senza altri farmaci	0,3
Analoghi variamente combinati senza altri farmaci	5,1
Analogo basale + analogo prandiale senza altri farmaci	7,5
Altre combinazioni di insuline	1,0

Terapia non insulinica (da duplice a quadruplice) circa 30%

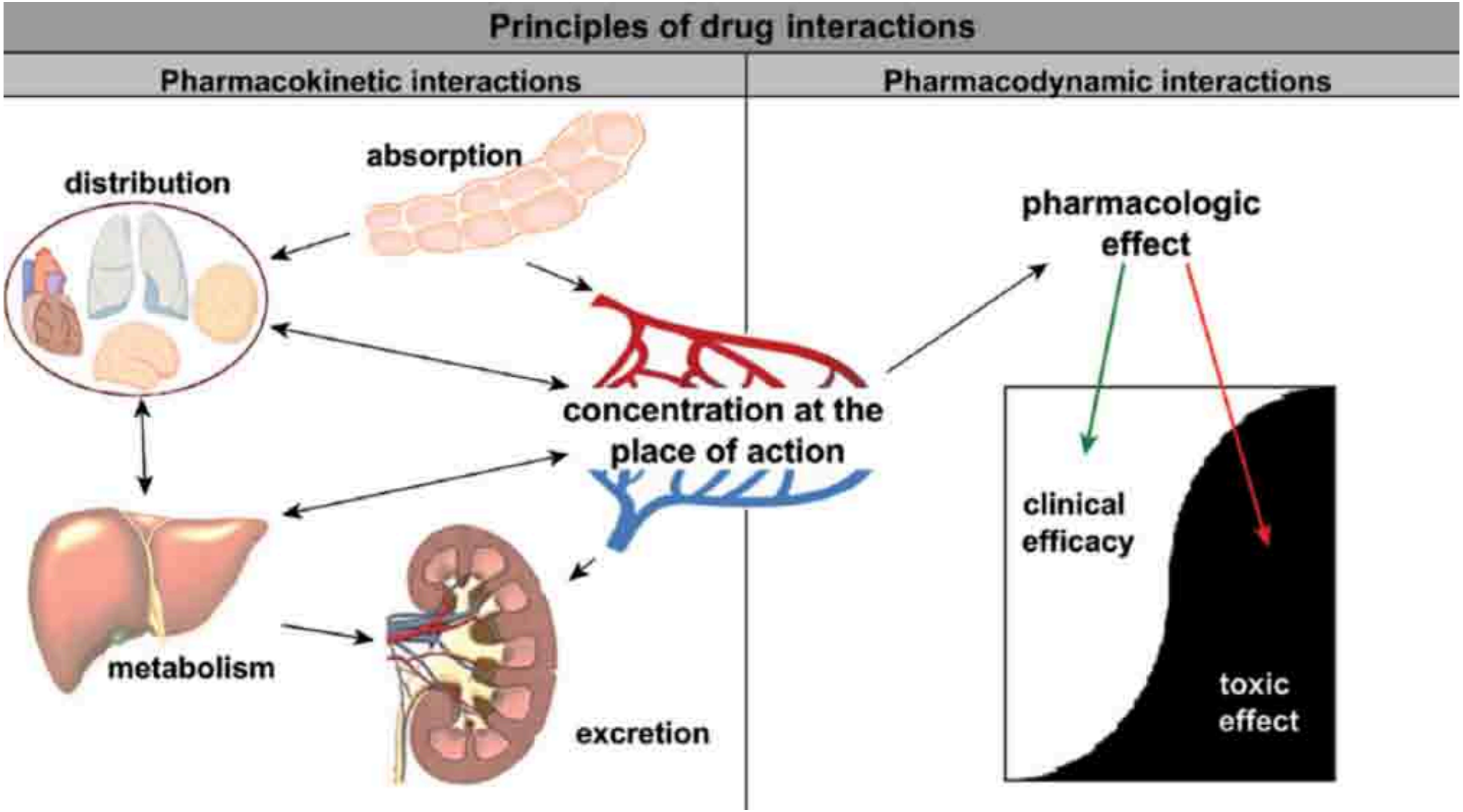
Insulina con varie modalità circa 27,5%

Osservatorio ARNO Diabete CINECA-SID - 2014

Le farmaco-interazioni da evitare

- Interazioni farmaco-dinamiche e farmaco-cinetiche
- Interazioni dei farmaci antidiabetici tra loro e con altri farmaci

Interazioni farmaco-farmaco: farmacocinetiche e farmacodinamiche



Le interazioni farmacologiche

- Nelle **interazioni farmacocinetiche** sono modificati l'assorbimento o la distribuzione o il metabolismo o l'escrezione (ADME) del farmaco.
- Nelle **interazioni farmacodinamiche** la modificazione della risposta al farmaco non è accompagnata da modificazioni dell'ADME. Un esempio molto comune è l'azione ipoglicemizzante sinergica di sulfoniluree e metformina.

- Nella pratica clinica le interazioni più preoccupanti sono di tipo farmacocinetico. Le più frequenti sono legate alle interferenze nel metabolismo del farmaco oppure alla alterazione della via escretrice (renale).

- Le interazioni da induzione enzimatica spesso sono tardive poiché la sintesi può richiedere tempo, mentre le interazioni da inibizione enzimatica sono solitamente a rapida insorgenza.

Drug Safety, 2014

Pharmacokinetic properties of different oral antidiabetics drugs

Drug	Oral bioavailability	Protein binding	Primary route of metabolism	Transporters	Main route of excretion
Metformin	55%	Very low	Not significant	OCT1-2, MATE 1-2, PMAT, P-gp	Renal (80-100%)
Glyburide	90%	98-99%	CYP2C9 + CYP3A4?	OAT2B1, P-gp, MRP1, BCRP	Renal/bile
Gliclazide	97%	95%	CYP2C9 (minor CYP2C19)		Renal
Glimepiride	100%	>99%	CYP2C9		Renal
Repaglinide	63%	>98%	CYP2C8	OATP1B1	Bile
Pioglitazone	>80%	>99%	CYP2C8		Bile/renal

TIPS, 2012

Summary of drug interactions associated with metformin therapy

Drugs affecting plasma concentration of metformin	Mechanism	Management	Clinical significance
Cimetidine (H2 antagonists)	MATE1, MATE2K inhibition	Monitor glycemia and observe patient for any adverse event; reduce dose if required	LOW
Cephalexin	MATE1, MATE2K inhibition	Monitor glycemia and observe patient for any adverse event; reduce dose or change antibiotic	UNCERTAIN

Drugs associated with risk of lactic acidosis		Management	Clinical significance
Iodinated contrast media	Contrast media-induced nephrotoxicity	**Contraindicated.** Stop metformin 48 h before contrast media administration and initiate 48 h after contrast media administration	**HIGH**

Drug Safety, 2014

Primary route of metabolism

CYP450: isoenzimi	Substrati	Induttori enzimatici	Inibitori
CYP2C9	**Sulfoniluree,** rosuvastatina , FANS, fenobarbital, fenitoina, ac. valproico, losartan, warfarin, amiodarone	Rifampicina, barbiturici, fenitoina, carbamazepina	Amiodarone, cimetidina, cotrimoxazolo
CYP3A4	**Saxagliptin, sitagliptin e linagliptin** (minimo)**, (glibenclamide?),** simvastatina, atorvastatina, SSRI, Benzodiazepine, nifedipina, felodipina, verapamil	Rifampicina, barbiturici, fenitoina, carbamazepina	Eritromicina, chetoconazolo, itraconazolo, simvastatina (dai 20 mg), fluvastatina (dai 40 mg)
CYP2C8	**Repaglinide, sitagliptin** (minimo)**, pioglitazone**	Rifampicina	Ciclosporina, gemfibrozil

Original Article | Journal of INTERNAL MEDICINE
doi: 10.1111/j.1365-2796.2010.02257.x

Potential CYP2C9-mediated drug–drug interactions in hospitalized type 2 diabetes mellitus patients treated with the sulphonylureas glibenclamide, glimepiride or glipizide

Studio retrospettivo su 84247 pazienti ricoverati in 8 anni all'Osp. Universitario di TURKU (Finlandia)

- 3257 pazienti DMT2 in terapia con SU senza concomitante trattamento con inibitori del CYP2C9
- 627 (16.1%) in terapia con SU e concomitante trattamento con inibitori del CYP2C9.

	SUs + CYP2C9 inhibitors	Controls	
FPG media (mg/dl)	153 ± 61	164 ± 45	p< 0.05
HbA1c max (%)	8.4 ± 22	9.2 ± 2.0	p<0.001
TGO media (U/L)	56 ± 34	36 ± 61	p<0.05
GammaGT media (U/L)	137 ± 209	93 ± 172	p<0.05
Episodi di ipoglicemia (< 72 mg/dl)	**25.6%**	**17.6%**	

J Int Med, 2010

Original Article | Journal of INTERNAL MEDICINE
doi: 10.1111/j.1365-2796.2010.02257.x

Potential CYP2C9-mediated drug–drug interactions in hospitalized type 2 diabetes mellitus patients treated with the sulphonylureas glibenclamide, glimepiride or glipizide

CYP2C9 inhibitor	n.	%
Metronidazole	242	28.2
Fluconazole	98	11.4
Amiodarone	59	6.9
Miconazole	33	3.9
Sulphamethoxazole	20	2.3
Fluvoxamine	4	0.5
Trimethoprim	342	39.9
Valproate	25	2.9
Gemfibrozil	22	2.6

Original Article | Journal of INTERNAL MEDICINE
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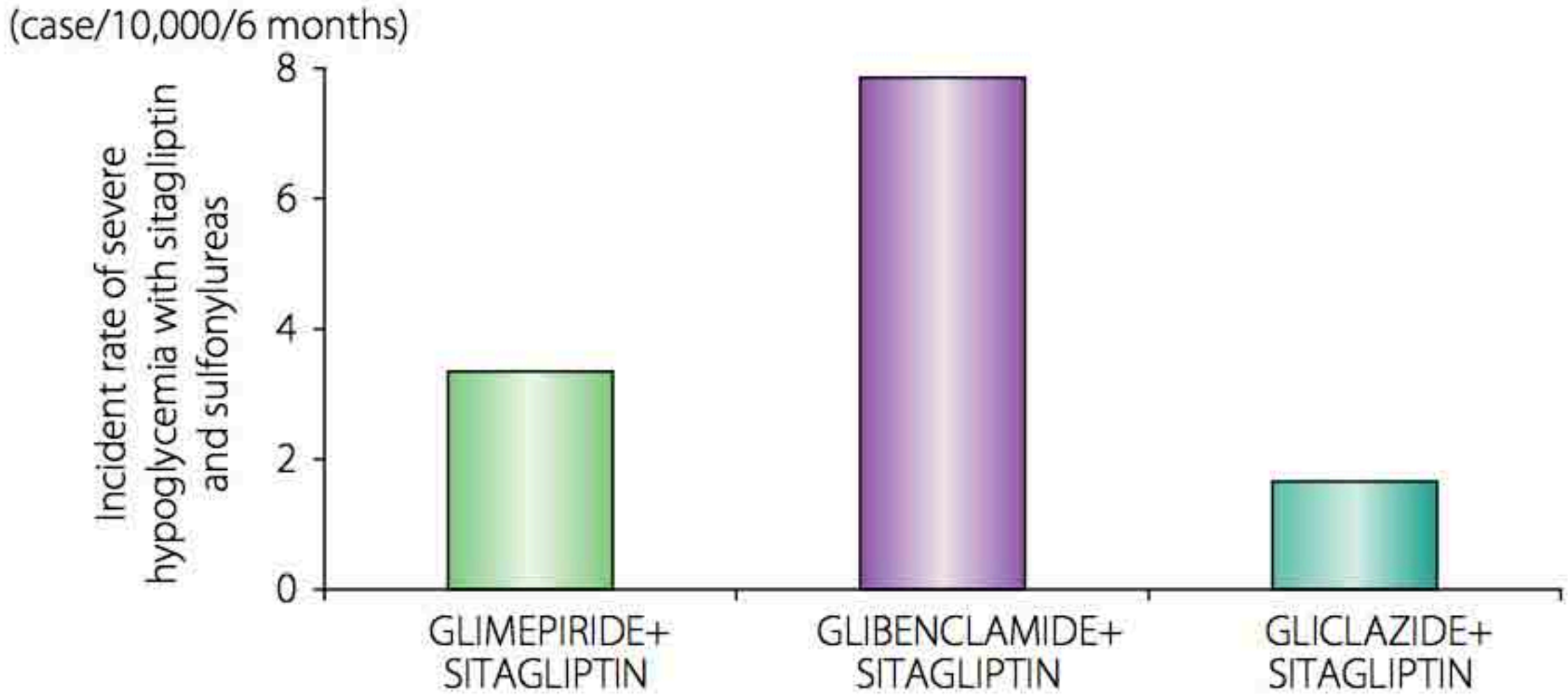
Valproate	25	2.9
Gemfibrozil	22	2.6

Substance-specific-drug-drug interactions with antidiabetic medication in clinical routine

	Medication with risk of interaction	Mechanism	Potential clinical effect	Clinical management	Clinical relevance
Sulfonylurea	Fluconazole, miconazole, fibrates, cimetidine	Inhibition of CYP2C9	Elevated risk of hypoglycemia	Dose reduction if applicable, blood glucose monitoring	Moderate
	Clarithromicin, verapamil	Inhibition of P-glicoprotein and CYP enzymes	Elevated risk of hypoglycemia	Dose reduction if applicable, blood glucose monitoring	Moderate

Ther Adv Endocrinol Metab, 2016

Dipeptidyl peptidase-4 inhibitors and sulfonylureas for type 2 diabetes: Friend or foe?



JDI, 2014

Dipeptidyl peptidase-4 inhibitors and sulfonylureas for type 2 diabetes: Friend or foe?

Recommendation

Doses of sulfonylureas are recommended to be reduced when dipeptidyl peptidase-4 inhibitors are initiated in patients on sulfonylurea, especially in the elderly and/or patients with renal insufficiency.

Glimepiride	≤ 2mg/day
Gliclazide	≤ 40mg/day
Glibenclamide	≤ 1.25mg/day

When appropriate glycemic control is not achieved after initiation of dipeptidyl peptidase-4 inhibitors, increasing the dose of sulfonylureas should be considered. When hypoglycemic episodes are confirmed, reduction of the dose of sulfonylureas should be considered.

Committee for appropriate use of incretin-related drugs (GLP-1 receptor agonists and DPP-4 inhibitors)

JDI, 2014

Interazioni farmacologiche della glibenclamide (da scheda tecnica)

Potenziamento dell'effetto ipoglicemizzante con:

acido para-aminosalicilico, anabolizzanti, azapropazone, ciclofosfamide, **chinolonici,** cloramfenicolo, derivati cumarinici, disopiramide, fenfluramina, fenilbutazone, fibrati, fluoxetina, H2-antagonisti, inibitori delle MAO, miconazolo, pentossifillina (per via parenterale ad alte dosi), ossifenbutazone, probenecid, salicilati, simpaticolitici quali beta-bloccanti e guanetidina, sulfamidici, sulfinpirazone, tetracicline …

Glimepiride (Solosa®, Amaryl®)

- Riduzione dell'azione ipoglicemizzante con estrogeni, progestinici, **diuretici tiazidici**, derivati della fenotiazina, clorpromazina, fenitoina, barbiturici, acetazolamide

- Aumento dell'az ipoglicemizzante con fenilbutazone e derivati, salicilati, cloramfenicolo, anticoagulanti cumarinici, fibrati, ACEi, allopurinolo, fluoxetina, **chinolonici**, tetracicline, fluconazolo …

Incidence of potential drug-drug interactions with antidiabetic drugs

Retrospective study on 225 type 1 and type 2 diabetic patients (Mean age 66 y).

Drug class	n	Interaction	Category	Effect
Thiazide and thiazide like diuretics	176	Metformina-HCTZ	C	Thiazide diuretics may diminish the therapeutic effect of metformin
ACE inhibitors	125	Glimepiride-ramipril	B	ACE-i may enhance the hypoglycemic effect of sulfonylureas
Antidiabetics	93	Glimepiride-sitagliptin	C	Hypoglycemic agents may enhance the adverse/ toxic effect of other hypoglycemic agents
Beta blockers	65	Glimepiride- bisoprolol	C	Beta-blockers may enhance the hypoglycemic effect of sulfonylureas
Antibiotics	9	Glimepiride-ciprofloxacin	C	Quinolone antibiotics may enhance/diminish the hypoglycemic effect of sulfonylureas

Potential interactions were identified by Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA) software which categorizes potential DDIs according to clinical significance in five types: A= no known interaction; **B= no action needed; C= monitor therapy**; D= consider therapy modification; X= avoid combination.

Interaction: A: 2 (0.9%); B 109 (48.4%); C= 182 (80.9%); D and X 0. Pharmazie, 2015

Chinoloni e glicemia

British Journal of Pharmacology (1996) 117, 372–376

Increase in insulin release from rat pancreatic islets by quinolone antibiotics

Levofloxacin-induced Hypoglycemia: A Rare but Life-threatening Side Effect of a Widely Used Antibiotic

Am J Med, 2009

Journal of Toxicology
CLINICAL TOXICOLOGY
Vol. 42, No. 3, pp. 295–297, 2004

CASE REPORT

Refractory Hypoglycemia from Ciprofloxacin and Glyburide Interaction

MAJOR ARTICLE

Risk of Severe Dysglycemia Among Diabetic Patients Receiving Levofloxacin, Ciprofloxacin, or Moxifloxacin in Taiwan

Clin Infectious Dis, 2013

SPECIAL FEATURE

Clinical Review

Drug-Induced Hypoglycemia: A Systematic Review

J Clin Endocrinol Metab, 2009

Risk of Severe Dysglycemia Among Diabetic Patients Receiving Levofloxacin, Ciprofloxacin, or Moxifloxacin in Taiwan

Antibiotic group	Adjusted OR
Hyperglycemia	
Macrolides (29565)	1.00
Cephalosporins (20317)	1.36
Moxifloxacin (4221)	2.48
Levofloxacin (11766)	1.75
Ciprofloxacin (12564)	1.87
Hypoglycemia	
Macrolides	1.00
Cephalosporins	0.94
Moxifloxacin	2.13
Levofloxacin	1.79
Ciprofloxacin	1.46

- According to the results of several in vitro and animal model studies, quinolone may cause hypoglycemia by increasing the release of insulin via a blockade of ATP-sensitive K+ channels in a dose-dependent manner.
- The biological mechanism involved in hyperglycemic response to quinolone remains unclear.

Clin Infectious Dis 2013

Drug interactions with oral antidiabetic agents: pharmacokinetic mechanisms and clinical implications

Aleksi Tornio, Mikko Niemi, Pertti J. Neuvonen and Janne T. Backman

Victim drug	Perpetrator drug (daily dose)	AUC	Cmax	Cl_{renal}	Enzyme or transporter involved
Repaglinide					
	Clarithromicin (500 mg)	+ 40%	+ 67%	NA	CYP3A4
	Cyclosporine (100 mg)	+ 144%	+ 75%	NS	CYP3A4 OATP1B1
	Gemfibrozil (1200 mg)	+ 712%	+ 140%	NA	CYP2C8 OATP1B1
	Trimethoprim (320 mg)	+ 61%	+ 41%	NA	CYP2C8
	Ketoconazolo (200 mg)	+ 15%	+ 7%	NA	CYP3A4

TIPS, 2012

Repaglinide (Novonorm®)

Interazioni possibili con **gemfibrozil, claritromicina**, itraconazolo, **ketoconazolo**, trimetoprim, **ciclosporina**, altri farmaci antidiabetici, gli inibitori delle monoaminoossidasi, i beta-bloccanti non selettivi, gli inibitori dell'enzima di conversione dell'angiotensina (**ACE-inibitori**), i salicilati, i **FANS**, l'octreotide, l'**alcool** e gli steroidi anabolizzanti.

Government of Canada / Gouvernement du Canada

Recalls and safety alerts

Home > Recalls & alerts

Starting date: July 31, 2015
Posting date: July 31, 2015
Type of communication: Dear Healthcare Professional Letter

Audience

Family physicians, general practitioners, nurses, nurse practitioners, pharmacists, endocrinologists and cardiovascular clinics

Key messages

- **Co-administration of repaglinide and clopidogrel (a CYP2C8 inhibitor) may lead to a significant decrease in blood glucose levels due to a drug-drug interaction.**
- **The concomitant use of repaglinide and clopidogrel is now contraindicated.**
- **The prescriber information for GLUCONORM (repaglinide) has been updated. The prescriber information for PLAVIX (clopidogrel) is currently being updated. The prescriber information for the generic products will be updated (see Products affected).**

- In a study conducted with healthy volunteers, co-administration of clopidogrel (300 mg on day 1, followed by 75 mg daily for 2 consecutive days), and repaglinide **(single dose of 0.25 mg on day 1 and day 3)** resulted in an increase in repaglinide systemic exposure by 5.1-fold and 3.9-fold on day 1 and day 3 respectively. Hypoglycemia was noted in healthy volunteers on day 1 (54 mg/dL) and on day 3 (70 mg/dL).

Drug interactions with oral antidiabetic agents: pharmacokinetic mechanisms and clinical implications

Aleksi Tornio, Mikko Niemi, Pertti J. Neuvonen and Janne T. Backman

Victim drug	Perpetrator drug (daily dose, mg)	AUC	Cmax	Cl_{renal}	Enzyme or transporter involved
Pioglitazone					
	Trimethoprim (320)	42%	NS	NA	CYP2C8
	Gemfibrozil (1200)	>200%	NS	NA	CYP2C8

TIPS, 2012

Pioglitazone: drug associated with risk of cardiovascular events

Precipitant drug	Clinical implication	Mechanism
Insulin	Edema, hypoglycemia	Unknown Possible synergistic effect
NSAIDS	Edema and heart failure	Possible synergistic effect (fluid retention)
Sulfonylureas	Hypoglycemia	Unknown

Drug safety, 2014

Substance-specific-drug-drug interactions with antidiabetic medication in clinical routine

	Medication with risk of interaction	Mechanism	Potential clinical effect	Clinical management	Clinical relevance
Sulphonylurea	Ethanol	Inhibition of gluconeogenesis	Prolonged hypoglycemia	Avoidance of increased alcohol consumption	**High**
Metformin	Iodinated contrast media	Elevated risk of contrast media induced nephropathy	Plasma values and Adverse Event augmented	Contraindicated 48 hours in advance and 48 hours after contrast media application	**High**
Pioglitazone	Insulin, NSAIDS, sulphonylurea	Unknown, potential synergistic effect	Elevated cardiovascular risk	Avoid combination if applicable, tight monitoring recommended	**High**

Ther Adv Endocrinol Metab, 2016

Pharmacokinetic properties of different oral antidiabetics drugs: DDP4-i

Drug	Oral bioavailability	Protein binding	Primary route of metabolism	Transporters	Main route of excretion
Linagliptin	30%	>80%	Minor (CYP3A4)	P-gp	Bile (90%)
Saxagliptin	50%	Very low	CYP3A4	P-gp	Renal (24% unchanged)
Sitagliptin	87%	38%	Minor (CYP3A4 + CYP2C8)	hOAT3, OATP4C1, P-gp	Renal (79% unchanged)
Vildagliptin	85%	9%	Hydrolisis, no CYPs involved	P-gp	Renal (23% unchanged)
Alogliptin	100%	20%	Minor (CYP3A4)		Renal (76%)

TIPS, 2012

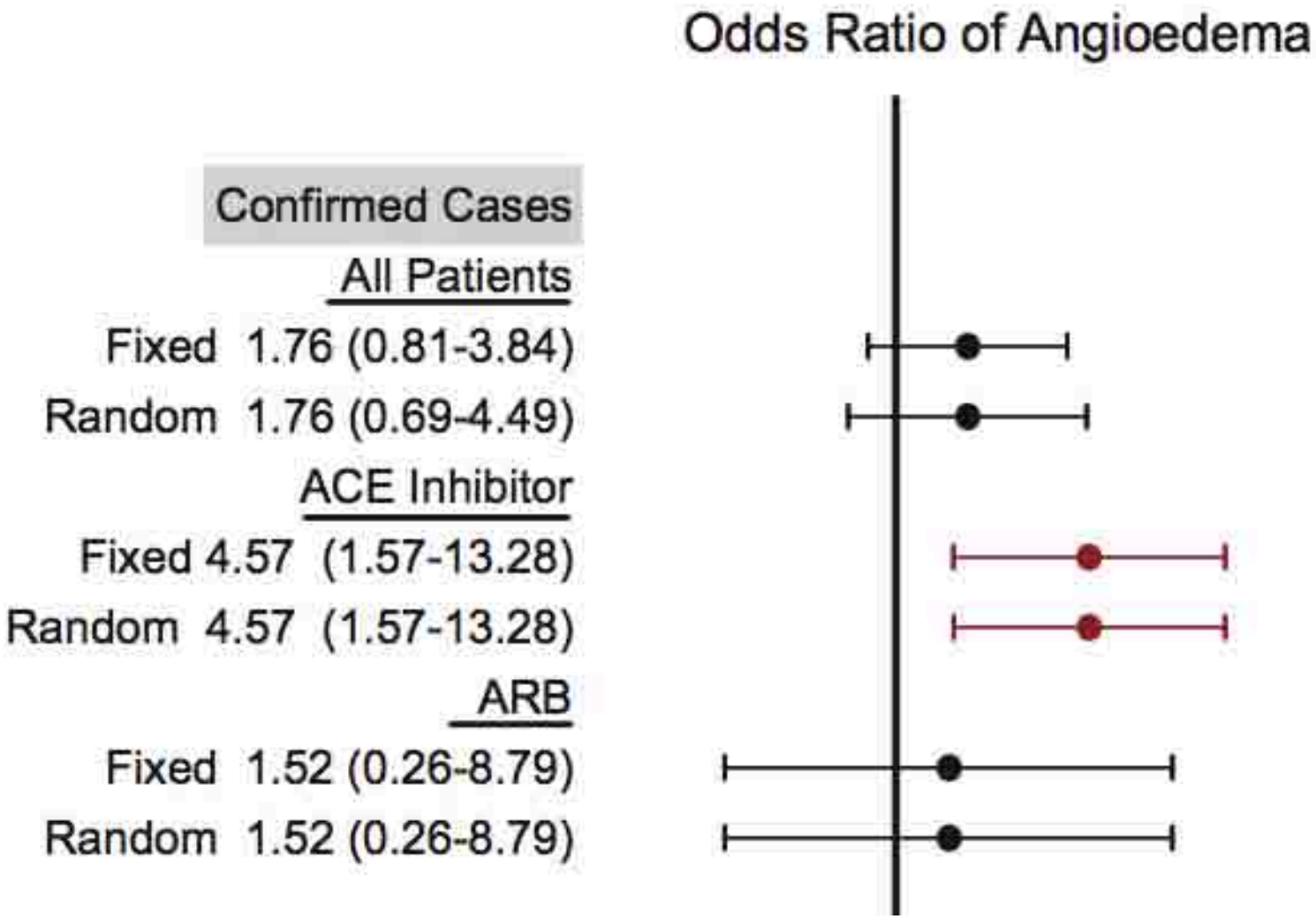
Substance-specific-drug-drug interactions with antidiabetic medication in clinical routine

	Medication with risk of interaction	Mechanism	Potential clinical effect	Clinical management	Clinical relevance
DPP4-inhibitors	Ketoconazole, diltiazem, clarithromicin	Inhibition of CYP3A4 **(clinically relevant in case of saxagliptin)**	Augmented Plasma values and Adverse Event Rate	Tight blood glucose monitoring and AE monitoring recommended	Moderate
	Rifampicin	Induction of CYP3A4 and P-glycoprotein **(clinically relevant in case of saxagliptin)**	Reduced efficacy, elevated blood glucose	Dose increase if applicable, blood glucose monitoring	Moderate

Ther Adv Endocrinol Metab, 2016

Dipeptidyl Peptidase-IV Inhibitor Use Associated With Increased Risk of ACE Inhibitor-Associated Angioedema

Nancy J. Brown, Stuart Byiers, David Carr, Mario Maldonado, Barbara Ann Warner



Hypertension, 2009

Angiotensin-Converting Enzyme and Dipeptidyl Peptidase IV Inhibitors

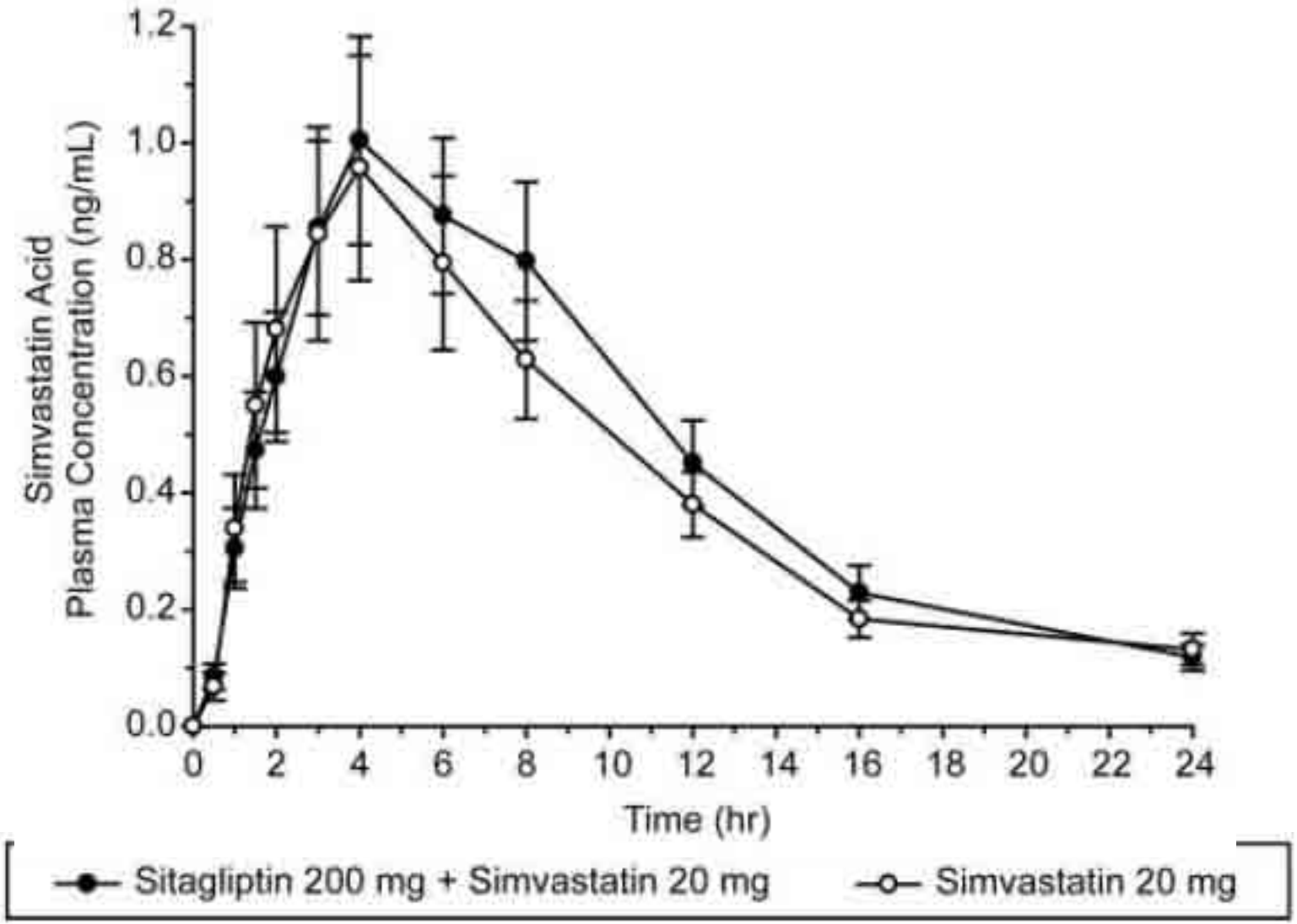
An Increased Risk of Angioedema

Eric Grouzmann, Françoise Livio, Thierry Buclin

- No data are yet available regarding DPPIV other than vildagliptin.
- Blacks have a 4-fold higher basal risk than whites to develop angioedema under ACE inhibition but is unclear whether additional DPPIV inhibition may further increase this risk.
- A similar question applies to women who are at higher risk than men to suffer from angioedema induced by ACE inhibition.
- About one third of the patients enrolled in vildagliptin phase III trials received ACE inhibition concomitantly.
- Substituting ACE inhibitors with angiotensin II-receptor blockers in diabetic patients receiving a gliptin may represent a prudent alternative to minimize such a risk.

Hypertension, 2009

Effect of Sitagliptin on the Pharmacokinetics of Simvastatin



J Clin Pharmacol, 2009

GLP-1 analogs

- The pharmacokinetic properties of these drugs indicate a low potential for DDIs.
- GLP-1 analogs have been successfully studied as add-on therapies to metformin, sulfonylureas, and thiazolidinediones.
- Liraglutide has also been successfully studied in combination therapies with atorvastatin, digoxin, griseofulvin, lisinopril, ethinylestradiol, and levonorgestrel
- Exenatide decreased the rate of absorption of paracetamol but the extent of absorption remains unaffected. Similar results were also observed when liraglutide was co-administered with paracetamol. The underlying mechanism is a delay in gastric emptying time by GLP-1 analogs.
- **Up to now, no clinically relevant drug-drug interactions have been described.**

Drug Safety, 2014; Ther Adv Endocrinol Metab, 2016

Pharmacokinetic properties of different oral antidiabetics drugs: SGLT2-i

Drug	Oral bioavailability	Protein binding	Primary route of metabolism	Transporters	Main route of excretion
Dapagliflozin	78%	91%	Glucuronidation		Mainly urine
Canagliflozin	65%	99%	Glucuronidation		Mainly feces
Empagliflozin	78%	86%	Glucuronidation	OAT	Feces and urine

TIPS, 2012

FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

(5-15-2015) From March 2013 (approval of the first drug in the class) through June 6, 2014, … identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis reported with the sodium-glucose cotransporter-2 (SGLT2) inhibitors.

The median time to onset of symptoms following initiation of drug therapy was 2 weeks (range 1 to 175 days). **DKA case presentations were atypical** in that glucose levels were only mildly elevated at less than 200 mg/dL in some reports, while patients with type 1 diabetes who have DKA typically have glucose levels greater than 250 mg/dL.

Potential DKA-triggering factors that were identified in some cases included acute illness or recent significant changes such as infection, urosepsis, trauma, reduced caloric or fluid intake, and reduced insulin dose.

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors

Julio Rosenstock[1] and Ele Ferrannini[2]

Diabetes Care 2015;38:1638–1642 | DOI: 10.2337/dc15-1380

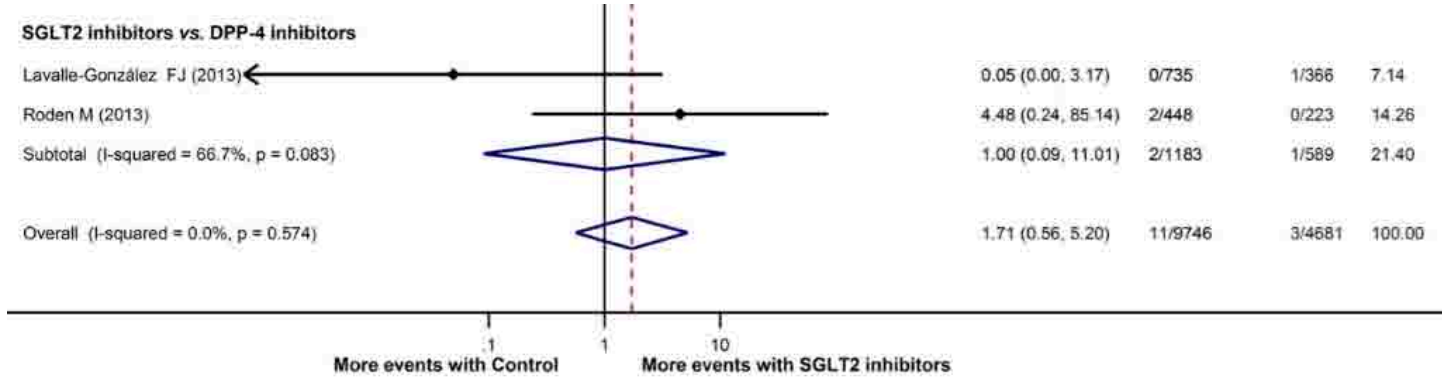
Estimated incidence rates

(it is estimated that the exposure to these medicines is over half a million patient-years):

- **0,5 e 0,8 per 1000 patient/years with canagliflozin**
- **< 0,1% with dapagliflozin and empagliflozin**

Effect of Sodium–Glucose Cotransporter 2 Inhibitors on Diabetic Ketoacidosis Among Patients With Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials

DOI: 10.2337/dc16-0885



Given the current evidence from RCT data, we found that **SGLT2 inhibitors were not significantly associated with an increased risk of DKA** among patients with T2D.

Diabetes Care, 2016

Gli SGLT2 inibitori non presentano rilevanti interazioni farmacologiche. Poiché possono aumentare il rischio di deplezione di volume, l'uso in associazione a diuretici dell'ansa non è raccomandato.

Potential Hypoxic Renal Injury in Patients With Diabetes on SGLT2 Inhibitors: Caution Regarding Concomitant Use of NSAIDs and Iodinated Contrast Media

The introduction of SGLT2 in the management of diabetes may further aggravate medullary hypoxia … conceivably reflecting enhanced solute delivery to distal nephron segments, increasing medullary transport workload and oxygen consumption.

We propose avoidance of the concomitant administration of agents that lead to iatrogenic hypoxic medullary injury: avoidance of NSAIDs in patients on SGLT2 inhibitors and cessation of SGLT2 inhibitors prior to radiocontrast studies.

Diabetes Care Publish Ahead of Print, published online January 27, 2017

Is there still a role for spontaneous reporting of adverse drug reactions?

Source	1999	2004
Pharmacist	2103 (37%)	3011 (29.4%)
Physician	1876 (25.5%)	2667 (26.2%)
Consumer or patient	1010 (14.9%)	1928 (18.8%)
Nurse	443 (6.2%)	873 (8.5%)
…	…	…
Total	5688	10238

… the US Food and Drug Administration received an average of 82 reports annually about adverse reactions related to digoxin, in a 7-year period there were over 200 000 admissions to hospital due to adverse reactions to that drug.

CMAJ, 2006

Le farmaco-interazioni da evitare

Key points

- Lactic acidosis is the main adverse event of concern associated with metformin therapy; however, the incidence of this adverse event is low. Any drug that deteriorates renal status of the patient or competes for renal excretion of metformin is likely to alter drug concentrations in the body, which may change pharmacologic response or cause adverse events.

- Hypoglycemia is the main adverse event associated with sulfonylureas. Any drug that alters cytochrome P450 2C9 isozyme levels in the body is likely to modify the concentration of drug in the circulation, which may increase or decrease pharmacologic response and result in adverse events.

Pharmacotherapy of Type 2 Diabetes Mellitus: An Update on Drug–Drug Interactions, (Drug Dafety, 2014)

Le farmaco-interazioni da evitare

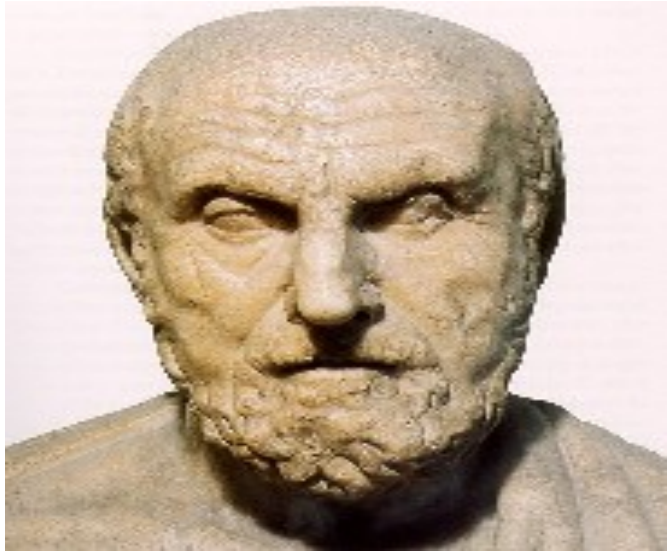
Key points

- Edema and exacerbation/precipitation of heart failure are the main adverse events associated with thiazolidinedione use. Non-steroidal anti-inflammatory drugs, insulin, nitrates, and sulfonylureas are likely to have an adverse effect.

- Generally, drug interaction potential of incretin mimetics and sodium glucose co-transporter 2 inhibitors is low, which makes these drugs a suitable choice in managing type 2 diabetes mellitus and associated complications. However, the long-term safety of these agents is not known.

Pharmacotherapy of Type 2 Diabetes Mellitus: An Update on Drug–Drug Interactions, (Drug Dafety, 2014)

Strong Commitment in Medical Care



Primum non nocere

(Hippocrates; IV-V century B.C.)

Grazie per l'attenzione