Terapie antidiabetiche e tumori

Dott.ssa Gabriella Piscitelli

U.O.S. Diabetologia Territoriale e Cure croniche

Presidio dei Poliambulatori

ASST Nord Milano

Conflitto di interessi

- Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

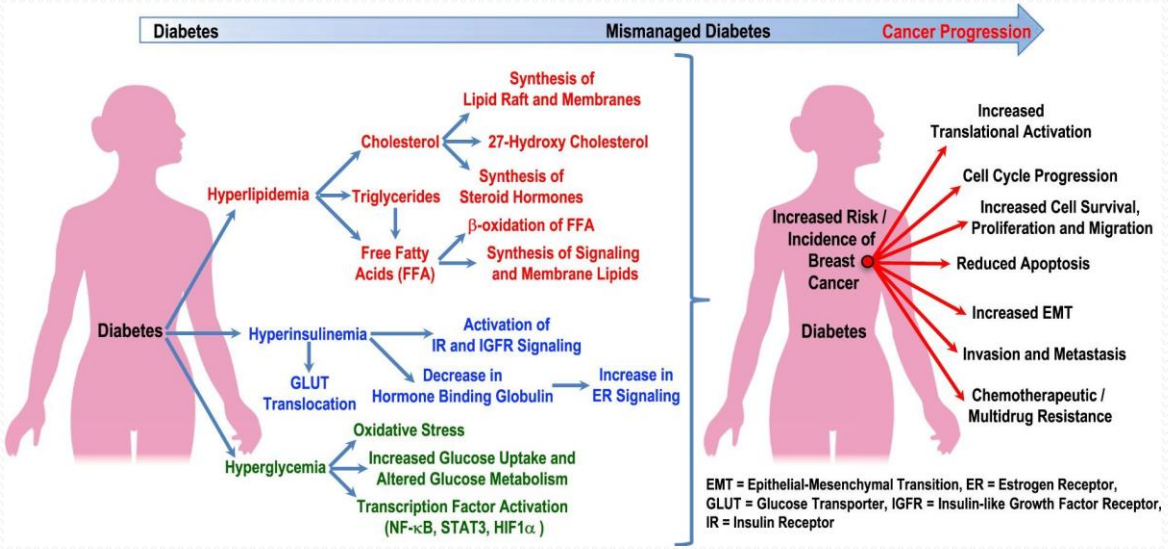
Relationship	**Company/Organization**
Consulenza Scientifica	Recordati
Partecipazione a Congressi	Boeringer Lilly

Terapie Antidiabetiche e Tumori

- Classi di terapie ipoglicemizzanti
- Evidenze cliniche sulla relazione tra farmaci antidiabetici e cancro per classe farmacologica
- Sommario e Conclusioni

Factors Linking Diabetes and Cancer

- **Biological factors**
  - Obesity
  - Hyperinsulinemia
  - Hyperglycemia
  - Hyperlipidemia
  - Inflammatory cytokines
  - Elevated estrogens
  - Elevated IGF-1
  - ↑ ROS
  - .....



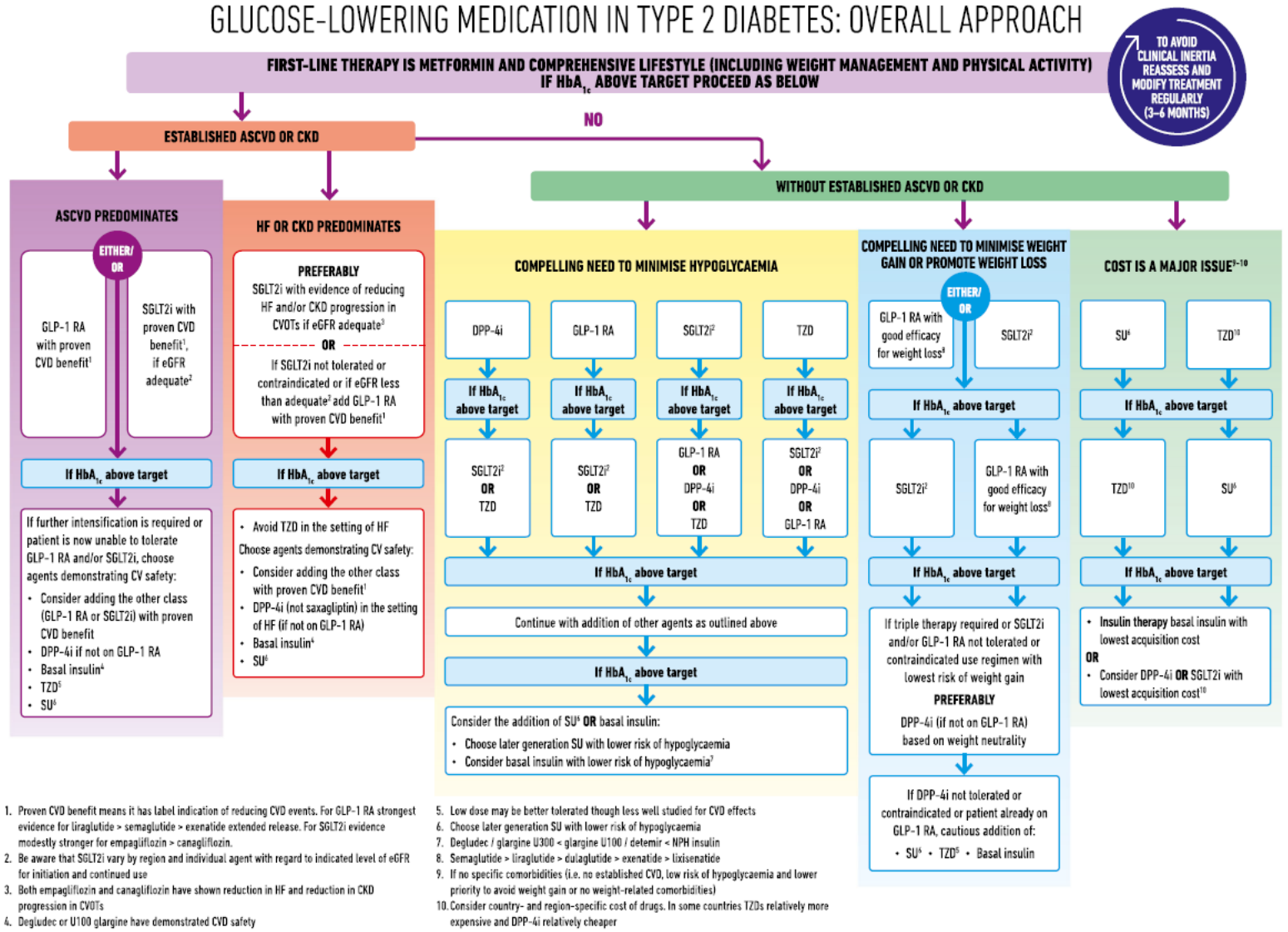
[Cancer Treatment Reviews 2018 70, 98-111]

- **Glucose-lowering agents**
  - May act as suppressors or enhancers of cancer cell growth
  - May act as initiators of cancer
  - Might interfere with anti-cancer therapies

Glucose-lowering agents

- First line: Biguanides - Metformin
- Second/Third line
  - Thiazoledinediones
  - Incretins
    - Dipeptidyl peptidase-4 inhibitors (DPP4-I)
    - Glucagon-like peptide-1 receptor agonists (GLP1-RA)
  - Sodium Glucose Trasporter 2 inhibitors (SGLT2-I)
  - α Glicosidase inhibitors
  - Sulfonylureas
  - Glinides
  - Insulin

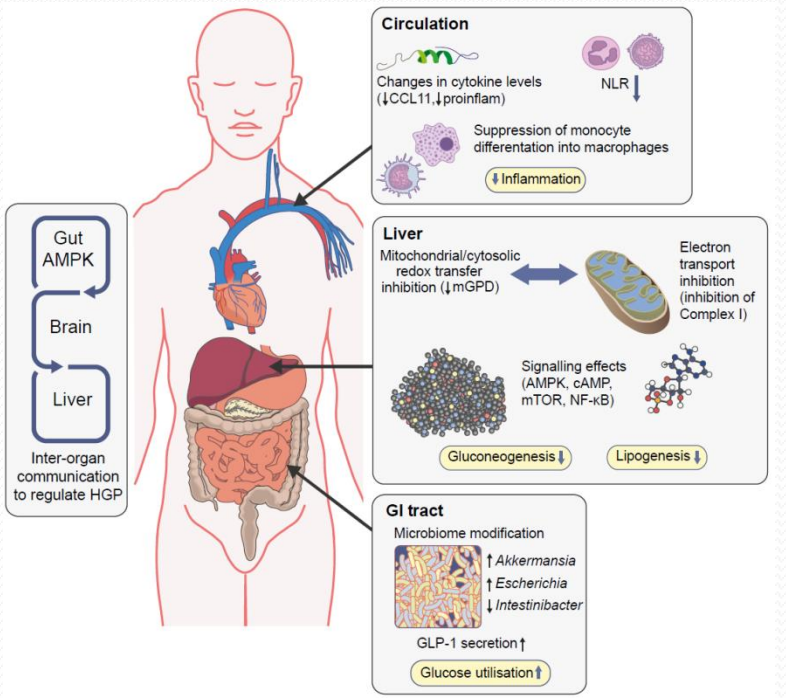
2018 Consensus Report by ADA and EASD



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Biguanides

- **Medications in class**
  - Metformin
- **MOA**
  - improves insulin sensitivity in peripheral tissues
  - inhibits hepatic glucose production
  - multiple other non-insulin-mediated mechanisms



[From: Rena AG et al. Diabetologia. 2017; 60(9): 1577–1585]

Metformin Antitumor Effect - Clinical Evidence

Year 2005

- First evidence for **reduced risk of cancer** in T2DM patients receiving metformin

  [Evans et al BMJ 330: 1304-1305, 2005]

Year 2006

- First report of **reduced cancer-associated mortality** rate in patients with cancer and DM in T2DM patients receiving metformin compared with that of sulfonylureas and insulin

  [Bowker et al Diabetes Care 29: 254-258, 2006]

Metformin Antitumor Effect - Clinical Evidence

- **Observational studies point to**
  - **A 20-40% reduction of overall cancer risk in T2DM patients when used as monotherapy** compared with other treatments **or in combination** with other glucose-lowering agents -sulphonylureas , insulin, pioglitazone, or DPP4 -I - compared to monotherapy

  [Evans JM et al. 2005; BMJ 330: 1304-1305] [Libby G et al. Diabetes Care 2009; 32:1620–1625]

  [Currie CJ et al. Diabetologia 2009; 52:1766–1777]

  - **A significant reduction of cancer-associated mortality in patients with cancer and DM treated with metformin compared to sulfonylureas and insulin**

  [Bowker et al Diabetes Care 29: 254-258, 2006] [Landman et al Diabetes Care 33: 322-326, 2010]

- **Metformin effects on tumor growth are site-specific**
  - Evidence for reduced risk for HCC CRC pancreatic cancer
  - Conflicting results for breast and prostate cancer

  [Donadon et al World J Gastroenterol 16: 3025-3032, 2010] [Donadon et al Liver Int 30: 750-758, 2010]

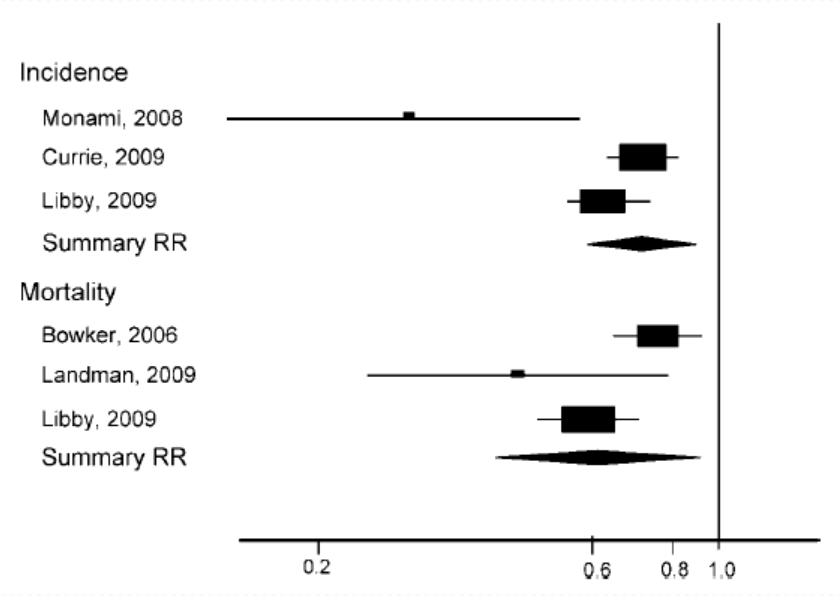
  [DeCensi et al.Cancer Prev Res 3(11): 1451–61, 2010] [Bodmer et al Diabetes Care 33:1304–1308, 2010]

  [Jonathan et al Cancer Causes Control 20:1617–1622, 2009] [Young Lee et al Nature Scientific Reports 8:9719,2018]

Metformin and Cancer – Metanalysis of Epidemiologic Studies

- **Meta-analysis of 11 epidemiologic studies** (1 prospective) on a total of 4,042 cases of cancer events and 529 cancer deaths.
  - **31% reduction in overall cancer risk**: SRR 0.69; 95% CI, 0.61-0.79 P = 0.03
    - **effect increasing by each year of use**: SRR 0.28 (95% CI, 0.05-1.55) for 5 years
  - **30% reduction in cancer mortality**: SRR 0.70, 95% CI, 0.51-0.96 P = 0.14

Cancer Risk and Mortality



[DeCensi et al.Cancer Prev Res 3(11): 1451–61, 2010]

Metformin and Cancer – Metanalysis of RCTs

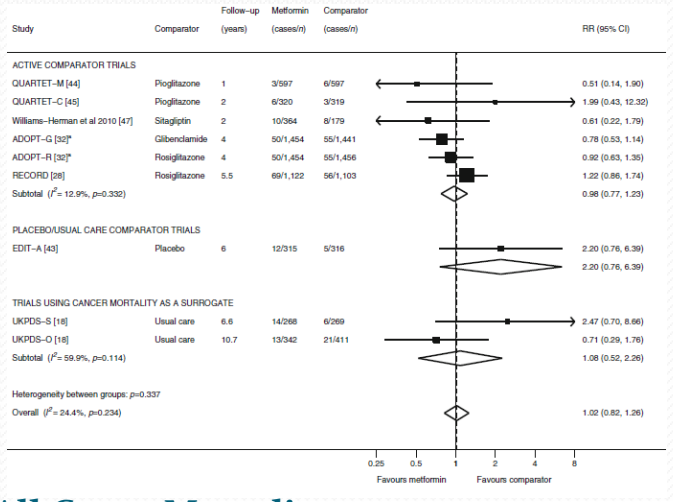
- **Meta-analysis of 11 RCTs** with 398 cancers during 51,681 person-years
  - **No significant beneficial effect on cancer risk**
  - Vs any comparator RR 1.02 , 95% CI 0.82, 1.26
  - Vs placebo/usual care RR 1.36, 95% CI 0.74, 2.49
  - Vs active comparator: RR 0.98 , 95% CI 0.77, 1.23

- **Meta-analysis of 13 RCTs** with 552 deaths during 66,447 person-years
  - **No significant beneficial effect on all cause mortality**

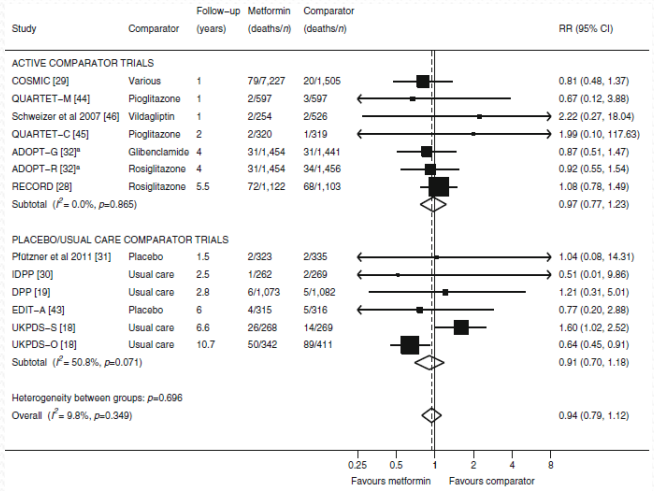
    RR 0.94, 95% CI 0.79, 1.12

[Stevens RJ et al.*Diabetologia 2012; 55: 2593–2603*]

Cancer Risk



All Cause Mortality



Metformin Antitumor Effect - Clinical Evidence

- **Evidence for improved tumor response by addition of metformin to chemotherapy is limited**
  - breast cancer/neoadjuvant setting : pCR 25% vs 8%
  - thyroid cancer/advanced setting: ↑ likelihood of complete response

  [Jiralerspong J Clin Oncol 27: 3297-3302, 2009] [Klubo-Gwiezdzinska J, J Clin Endocrinol Metab 98:3269-79, 2013]

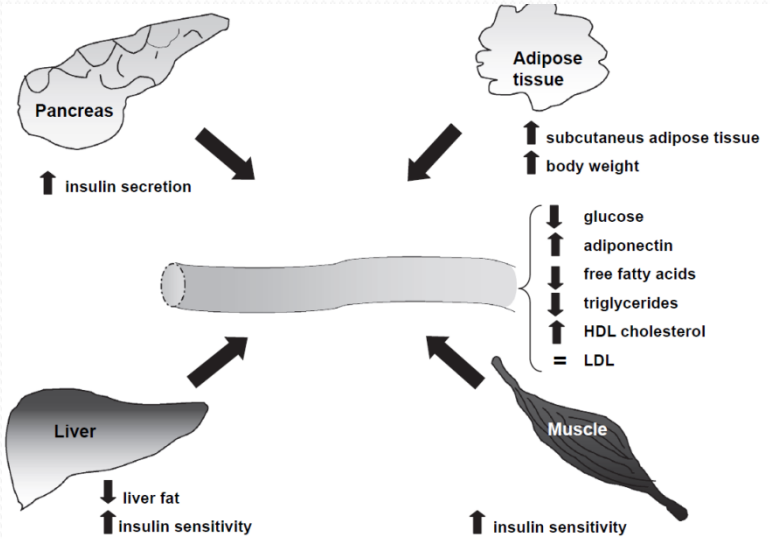
- **> 70 interventional active studies worldwide** investigating the effects of metformin on cancer-related outcomes including
  - prostate, SCLC, NSCLC, breast, colon pancreatic, endometrium, thyroid, bladder, uterus cancer, brain tumors/ metastases, HCC, H&N, NET, CLL, MM, melanoma
  - chemoprevention, adjuvant and advanced/metastatic settings

  [ClinicalTrial.gov, accessed September 16 2019]

Thiazoledinediones (TZD)

- **Medications in class**
  - Pioglitazone – [Rosiglitazone]

- **MOA**
  - ↑ binding of peroxisome proliferator–activated receptor γ (PPARγ) to its DNA response element
  - ↑ insulin sensitivity
  - ↑glucose uptake by skeletal muscle
  - ↓hepatic glucose production
  - ↑lipolysis



From Chiarelli F and Di Marzio D
Vascular Health and Risk Management 2008;4: 297–304

TZD and Cancer – Clinical Evidence

- **TZD are not reported to rise overall cancer risk in humans**

- In several studies and metanalyses **are even associated with lower overall and site-specific cancer risk** including breast, liver, CRC, brain, uterus, stomach, prostate, ear–nose–throat, kidney, lung and lymphatic malignancies

  [Bosetti C et al. Oncologist 2013; 18: 148–156] [Monami M et al. Acta Diabetol 2014; 51: 91–101]

  [Monami Diabetes Care 2008; 31: 1455–1460]

- Numerous studies and metanalysis of observational and RCTs , however, point to a **higher risk of bladder cancer** for patients treated with pioglitazone

Pioglitazone and Bladder Cancer

- **In 2005 the PROactive randomized controlled trial** - CVOT in 5238 pts FU for 34·5 mos - unexpectedly showed an **imbalance in the number of cases of bladder cancer with pioglitazone** compared with placebo

  [Dormandy JA et al Lancet 2005; 366: 1279–1289]

- **In 2011 the five year interim analysis** of an **observational study in 193,099 patients** using the Kaiser Permanente Northern California database showed
  - **Use of pioglitazone for≥ 24 months associated with increased risk of bladder cancer** (HR 1.4, 95% CI 1.03 - 2.0)

  [Lewis JD at al. Diabetes Care 2011 ;34:916-22]
  - **In final analysis with FU extended to 10 years (median 2.8 yrs)**, the use of pioglitazone was **no longer significantly associated with an increased risk of bladder cancer** (HR, 1.06; 95% CI, 0.89-1.26)

  [Lewis JD at al. JAMA 2015 ;314:265-77]

- **2013 and 2014 metanalyses of 17 observational studies and 22 RCT**
  - **Neutral effect of TZD on overall cancer risk**
  - **Excess risk of bladder cancer in pioglitazone users**

  [Bosetti C et al. Oncologist 2013; 18: 148–156] [Monami M et al. Acta Diabetol 2014; 51: 91–101]

Pioglitazone and Bladder Cancer

- **2016 UK population based study** on 145,806 patients newly treated with antidiabetic drugs, median FU 4.7 yrs
  - **Increased risk of bladder cancer with pioglitazone Vs other antidiabetic drugs** (HR 1.63, 95% CI 1.22 - 2.19)
  - Duration-response and dose-response relations

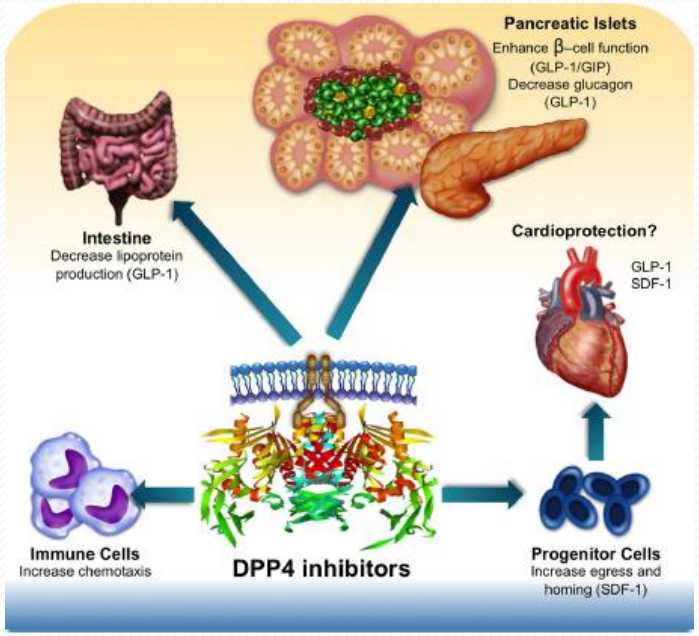
  [Tuccori M et al. BMJ 2016;352:i1541]
- **2018 Medicare database study** in pts initiating treatment with pioglitazone (N = 38 700), DPP-4s (N = 82 552) or sulfonylureas (N = 126 104) between 2007-2014
  - **Increased risk of bladder cancer with pioglitazone Vs DPP4-I (HR 1.57, 95%CI 1.23-2.00) and sulfonylureas (HR 1.32, 95%CI 1.02-1.70)**
  - Risk emerging within the first 2 years of treatment, attenuated after discontinuing

  [Garry EM Diabetes Obes Metab. 2018;20:129–140]
- **FDA PI** recommends not to use pioglitazone in patients with active bladder cancer and use with caution in patients with a prior history of bladder cancer
- **EMA SPC** contraindicates use in patients with current bladder cancer or a history of bladder cancer

Dipeptidyl peptidase IV Inhibitors (DPP4-I)

- **Medications in Class**
  - Sitagliptin - Alogliptin - Linagliptin -Vildagliptin - Saxagliptin

- **MOA**
  - Enhance levels of endogenously secreted glucagon-like peptide-1 (GLP-1) by inhibiting its degradation by the DPP4 enzyme
    - Glucose dependent ↑ insulin secretion
    - Glucose dependent ↓ glucagon secretion
    - Produce multiple biological actions in peripheral tissues



[Mulvihill EE &Drucker DJ Endocr Rev, 2014; 35:992–1019]

DPP4-I and Cancer – Clinical Evidence

- **A 2011 review of the 2004-2009 FDA Adverse Event Reporting System** suggested a potential **increased risk of acute pancreatitis, pancreatic, and thyroid cancer with use of incretin-based drugs** Vs other therapies
  - OR for pancreatitis 6.74 with sitaglitin ($p= 2 \times 10^{-16}$)
  - OR for pancreatic cancer 2.72 with sitaglitin (p=0.008)
  - OR for thyroid cancer 1.48 with sitaglitin (p=0.65)

[Elashof M et al. Gastroenterology 141:150–156, 2011]

- **In 2014 FDA and EMA independent reviews** of all clinical and preclinical data **did not confirm a possible causative relationship**

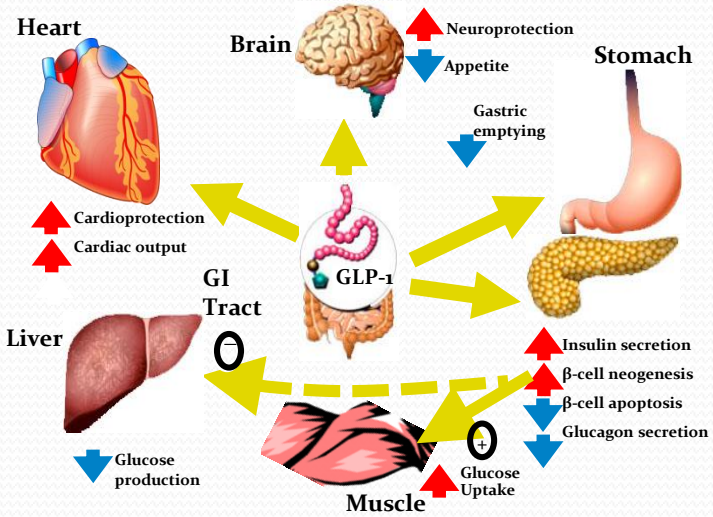
[Egan AG at al. NEJM2014; 370: 794–797]

DPP4-I and Cancer - Clinical Evidence

- **Placebo-controlled CVOT including overall > 40,000 T2DM pts do not point an increased risk of site-specific cancer in DPP-4 users :**
  - **Incidence of any tumor not increased with any DPP4-I**
  - Protective effect of saxagliptin against colon cancer (HR 0.51, 95% CI = 0.27–0.92,p = 0.026)
  - Pancreatic ca incidence with linagliptin : 0.3% Vs 0.1 within placebo controlled CARMELINA study (0.5% Vs 0.8% within glimepiride-controlled CAROLINA study - 6033 pts, median FU 6.3 yrs)
  - Breast cancer incidence in vildagliptin pooled safety analysis 0.4 versus 0.2/100 SYEs versus all comparators
- **Meta-analyses of RCTs/observational studies** including thousands of T2DM patients indicate:
  - **No statistically significant association between the risk of cancers overall and any of the individual DPP4-I**
  - Statistically significant reduction of the risk of breast cancer from the pooled analysis of observational studies evaluating breast cancer (HR= 0.76, 95% CI 0.60-0.96)
- **Medicare database study** in **T2DM pts with CRC** (n=11,657) **or lung cancer** (n=15,201):
  - **OS advantage Vs reference group (pts not receiving DPP4-I nor metformin)** : HR 0.89; 95% CI: 0.82-0.97, P = 0.007
  - OS advantage more pronounced with DPP4-I + metformin
- **Retrospective series (limited sample sizes):**
  - **No statistically significant increase in new-onset cancer Vs metformin** in T2DM pts: 2.8% Vs 3.9% (HR=1.08, 95% CI=0.58–2.03, P=0.81)
  - **Significant improvement in PFS Vs metformin + sulfonylurea in T2DM pts with advanced colon or airway cancer** (HR=0.42, 95% CI: 0.21-0.84, P=0.014)

GLP1-receptor agonists

- Medications in class
  - GLP1 analogs resistant to DPP-4 degradation
  - Shorter acting: Exenatide - Lixisenatide
  - Longer acting: Dulaglutide - Exenatide LAR - Liraglutide – Semaglutide- (Albiglutide)
- MOA
  - Glucose dependent ↑ insulin secretion
  - Glucose dependent ↓ glucagon secretion
  - ↑ Satiety
  - β-cell-preserving effect



[From: Drucker DJ. *Cell Metab*. 2006;3:153-165]

GLP1-RA and Thyroid Cancer

- GLP1-RA cause thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice.
- The human relevance of GLP1-RA -induced rodent thyroid C-cell tumors has not been determined
- Notwithstanding, GLP1-RAs come with a black box warning from the FDA, which prohibits the use of these drugs in patients with personal of family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN 2)
- No such restriction is reported on the EMA SPC

GLP1-RA and Cancer – Clinical Evidence

- **A 2011 review of the 2004-2009 FDA Adverse Event Reporting System** suggested a potential **increased risk of acute pancreatitis, pancreatic, and thyroid cancer with use of incretin-based drugs** Vs other therapies
  - OR for pancreatitis with exenatide 10.68 ($p= 2 \times 10^{-16}$)
  - OR for pancreatic cancer 2.72 with exenatide 2.95 (p= 4 x 10-5)
  - OR for thyroid cancer 1.48 with exenatide 4.73 (p= 4 x 10-3)

[Elashof M et al. Gastroenterology 141:150–156, 2011]

- **In 2014 FDA and EMA independent reviews** of all clinical and preclinical data **did not confirm a possible causative relationship**

[Egan AG at al. NEJM2014; **370**: 794–797]

GLP1-RA and Cancer - Clinical Evidence

- **Placebo-controlled CVOT and metanalyses of RCTs including > 50,000 T2DM pts do not point to an increased risk of any or site-specific cancer in GLP-1 users** :
  - Incidence of any tumor not increased with any GLP1-RA
  - Incidence of thyroid carcinoma was low (<1%) and did not differ between the GLP1- RA and placebo groups
  - Risk of pancreatic cancer not significantly increased overall and with any GLP1-RA (overall RR 1.03, 95% CI 0.67-1.58, P = 0.897)
  - Signal of a possible increased risk for any thyroid cancer (incidence 0.16% Vs 0.07%, RR 2.41, 95%CI 0.85-6.85, P=0.069) but not for medullary thyroid ca (2/ 7344 pts Vs 1/7372 pts with placebo) with exenatide LAR.
  - Signal of a possible increased risk of pancreatic cancer with liraglutide (incidence 0.3% Vs 01%, RR 2.61, 95%CI 0.93-7.32, P=0.069)

[Marso SP et al. N Engl J Med 2016; 375:311-322] [Holman RR et al. N Engl J Med 2017; 377:1228-1239]
[Pinto LC et al. Nature Scientific Reports 9: 2375, 2018] [Cao C et al. Endocrine Published on line 16 August 2019]
[SL Kristensen et al. Lancet Diabetes Endocrinol 2019]

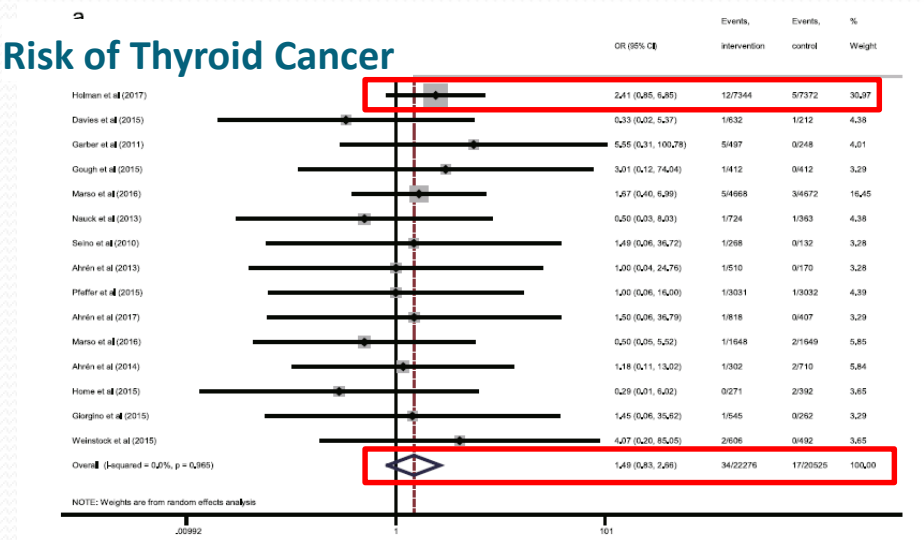
GLP1-RA and Cancer – Metanalysis of RCT

- In trials reporting at least one case of thyroid cancer (n = 15)
  - **overall risk of thyroid cancer was not different between GLP1-RAs and comparators**
    (OR 1.49,95% CI 0.83–2.66 P= 0.18)

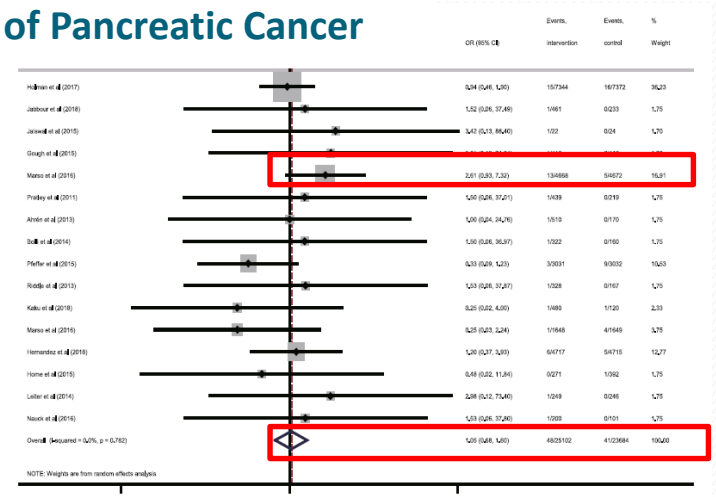
- In trials reporting at least one case of pancreatic cancer (n = 16)
  - **overall risk of pancreatic cancer was not different between GLP1 - RAs and comparators**
    (OR 1.05, 95% CI 0.68–1.60 P= 0.89)

[Cao C et al. Endocrine Published on line 16 August 2019]

Risk of Thyroid Cancer



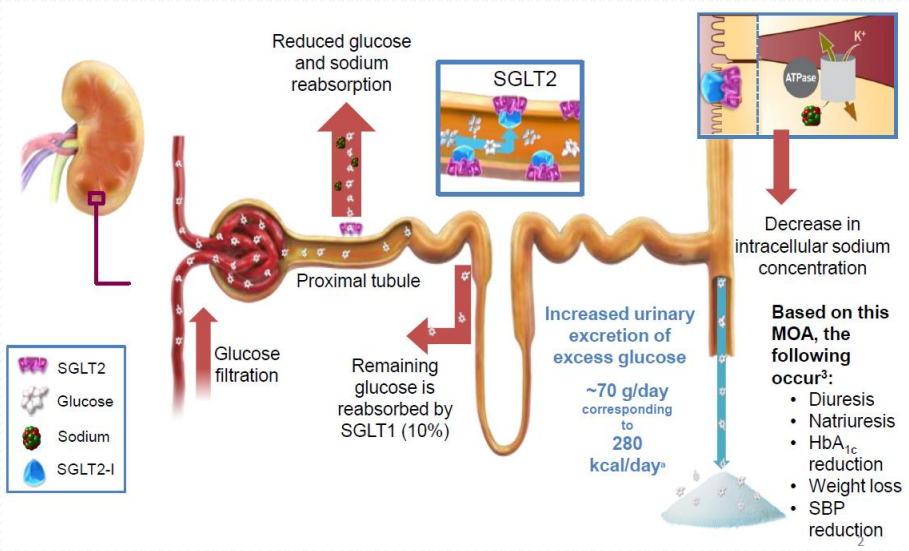
Risk of Pancreatic Cancer



SGLT2-I

- **Medications in Class**
  - Canagliflozin - Dapagliflozin – Empagliflozin –Ertugliflozin

- **MOA**
  - Block glucose reasorption by the kidney, increasing glicosuria



SGLT2-I and Cancer – Clinical Evidence

- Placebo-controlled CVOT including > 30,000 T2DM pts indicate no significant increase in overall cancer risk in SGLT2-I users
- Excess numbers of female breast cancer and male bladder cancer noted in early clinical trials with dapagliflozin NOT confirmed from results of dapagliflozin DECLARE-TIMI CVOT
  - bladder cancer incidence actually lower than placebo and breast cancer similar to placebo
- Possible increased risk of bladder cancer with empagliflozin at 25 mg dose noted in EMPA-REG CVOT - based on very low numbers - not supported by pooled analysis of phase I-III trials

[Neal B et al. N Engl J Med 2017; 377:644-657] [Kohler S et al Diabetologia 2017; 60:2534–2535]
[Kohler S et al Adv Ther 2017; 34:1707–1726] [Wiviott SD et al. N Engl J Med 2019; 380:347-357]

SGLT2-I and Cancer – Clinical Evidence

Pooled analysis of Phase I-III trials with Empagliflozin

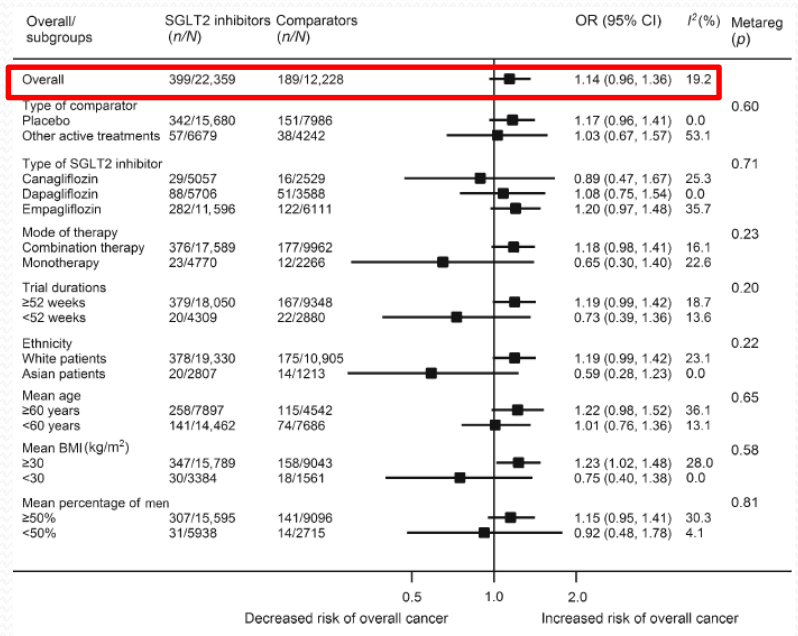
	Placebo (N = 4203)			Empagliflozin 10 mg (N = 4221)			Empagliflozin 25 mg (N = 4196)		
	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years
Cancer events[e]	95	2.3	1.3	121	2.9	1.6	119	2.8	1.5
With onset ≥6 months from start of treatment/participants with exposure ≥6 months	76/3159	2.4	1.4	103/3270	3.1	1.8	86/3203	2.7	1.5
Bladder cancer[f]	2	0.1	0.0	4	0.1	0.1	7	0.2	0.1
Renal cancer[g]	5	0.2	0.1	4	0.1	0.1	3	0.1	0.1
Breast cancer[h]	4	0.1	0.1	3	0.1	0.1	3	0.1	0.1
Melanoma[i]	2	<0.1	<0.1	4	0.1	0.1	3	0.1	0.1
Lung cancer[j]	7	0.2	0.1	11	0.3	0.2	9	0.3	0.2

[Modified from: Kohler S et al Adv Ther (2017) 34:1707–1726]

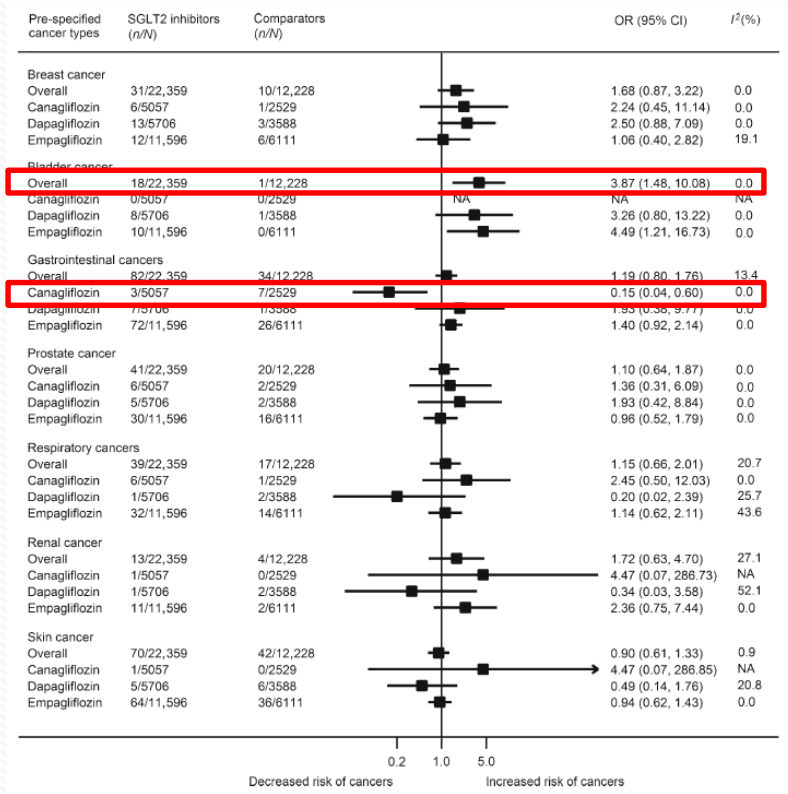
SGLT2-I and Cancer – Clinical Evidence

- 2017 metanalysis of 46 RCTs with canagliflozin, dapagliflozin, emplagliflozin (34,569 pts)
  - Overall cancer risk not increased with SGLT2-I
  - Risk of bladder ca might be increased with SGLT2 inhibitors
  - Canagliflozin might be protective against GI cancers

Overall Cancer Risk



Site-Specific Cancer Risk

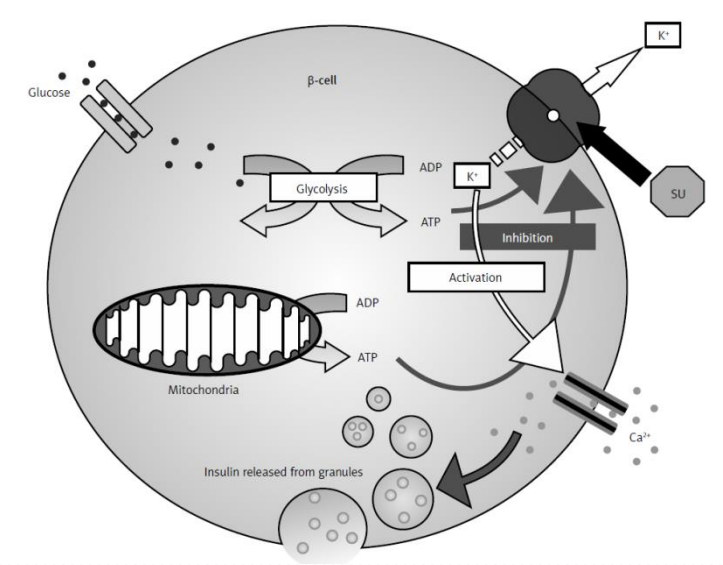


[Tang H et al Diabetologia published on line 19 July 2017]

Sulfonylureas (SU)

- **Medications in class**
  - Glibenclamide – Gliclazide – Glimepiride – Glipizide [tolbutamide and chlorpropamide]

- **MOA**
  - ↑ insulin secretion



Sulfonylureas and Cancer

- Several epidemiological studies reported an **increased risk of cancer incidence and cancer-related mortality** in T2DM pts treated with sulphonylureas compared to metformin

  [Currie CJ et al Diabetologia 2009; 52:1766–1777] [Libby G et al Diabetes Care 2009; 32:1620–1625]

  [Currie CJ et al Diabetes care 2012; 35: 299–304] [Bowker SL et al. Diabetes Care 2006; 29:254–258]

- Metanalysis of observational studies but NOT of RCTs indicate an **association between SU use and increased overall cancer risk** as compared to metformin thiazolidinediones or DPP4-I

  [Chen Y et al. Journal of Diabetes 2017; 9: 482–494]

- As regards **site-specific cancer risk**, results from systematic meta-analyses indicate among SU users
  - increased risk of **pancreatic, hepatocellular and colorectal cancer**

  [Singh S et al. Am J Gastroenterol 2013; 108:881–891]

  [Singh S et al. Cancer Epidemiol Biomarkers Prev 2013; 22: 2258–2268]

  [Singh S et al. Am J Gastroenterol 2013; 108: 510–519]

Sulfonylureas and Cancer

- Within- SU class differences in cancer risk may exist
  - Results from 2 retrospective observational studies reported a significantly higher cancer mortality in glibenclamide Vs gliclazide users

    [Monami M et al. Diab Metab Res Rev 2007; 23:479-84] [Bo S et al. Europ J of Endocrinol 2013; 169: 117–126]
  - Matched case-control study in T2DM pts with an incident cancer matched with T2DM pts unaffected by cancer reported:
    - significant reduction in cancer risk with ≥ 36 mos exposure to metformin or gliclazide
    - increased incidence of malignancies with use of glibenclamide ≥36 mos

    [Monami M et al. Acta Diabetol 2009; 46:279-84]
  - Cohort study in 60103 Hong Kong Chinese patients with T2DM free of cancer
    - Use of gliclazide and glibenclamide associated with dose-dependent reduced risk of cancer

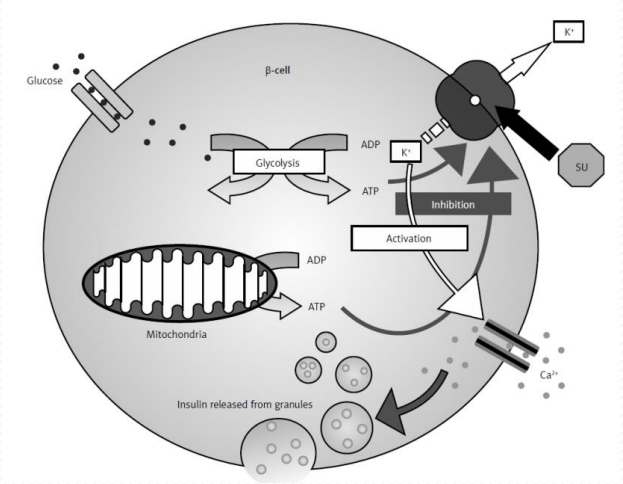
    [Yang X et al. Diabetes Res Clin Pract. 2010; 90: 343-51]

Glinides

- **Medications in class**
  - Repaglinide – [Nateglinide]

- **MOA**
  - ↑ insulin secretion

  (same as sulphonylureas)



Glinides and Cancer – Clinical Evidence [Lacking]

- No comprehensive studies identified exploring the risk of cancer under glinides treatment

- A nested case–control study from Barcelona including 1040 cases with any cancer and 3120 controls based on a cohort of 275,164 T2DM pts could not find evidence for altered cancer risk with repaglinide Vs insulin, metformin, sulphonylureas, or TZD

  [Simo R, et al. PLoS One 2013; 8: e79968]

α-Glicosidase inhibitors

- **Medications in class**
  - Acarbose – [Miglitol, Voglibose]

- **MOA**
  - ↓ carbohydrate digestion/absorption by the GI tract

α-Glicosidase inhibitors and Cancer

- Only few publications investigating α-glucosidase inhibitors and cancer risk exist.
- Most studies carried out in Taiwan population
  - A large study based on National Health Insurance database (495,199 men and 503,748 women) found **no association between acarbose use and bladder or thyroid cancer**

    [Tseng CH et al. Diabetologia 2011; 54: 2009–2015] [Tseng CH et al. PLoS One 2012; 7: e53096]
  - A small population-based case–control (116 pts with kidney cancer and 464 controls) pointed to an **elevated risk of kidney cancer** with use of α-glucosidase inhibitors

    [Lai SW et al. Ann Acad Med Singapore 2013; 42: 120–124]
  - Two larger population-based observational studies (19,624/19,625 cases with newly diagnosed DM and 78,496/78,500 controls) reported **decreased lung and gastric cancer risk** with use of α-glucosidase inhibitors

    [Lai SW et al. Clin Lung Cancer 2012; 13:143–148] [Chen Yl et al. Gastric Cancer 2013; 16: 389–396]
  - Another large population-based study (39,515 pts with newly diagnosed DM and 79,030 controls) reported **lower risk of hepatic cancer** in α-glucosidase users

    [Chiu CC et al. Intern Med 2013; 52: 939–946]
- The Barcelona case–control study including 1040 cases with any cancer and 3120 controls based on a cohort of 275,164 T2DM pts found **no association between the use of α-glucosidase inhibitors and risk of cancer**

  [Simo R et al. PLoS One 2013; 8: e79968]
- **Taken together available data indicate no serious cause for concern regarding cancer incidence under α-glucosidase inhibitor therapy.**

Insulin Analogs

- **Medications in class**
  - Long-acting:
    - Detemir - Glargine (U100, U300) – Degludec
  - Rapid-acting
    - Aspart - Glulisine – Lispro (U100, U200)
- **MOA**
  - Activate insulin receptor
  - ↑ Glucose disposal
  - ↓ Glucose production

Insulin Analogs and Cancer – Clinical Evidence

- **Numerous observational studies indicate a neutral effect of insulin analogs on cancer risk**

  [Sturmer T, et al Diabetes Care 2013; 36: 3517–3525] [Fagot JP et al. Diabetes Care 2013; 36:294–301]

  [Simo R et al.PLoS One 2013; 8: e79968]

- **Few observational studies point to a higher risk of cancer among insulin analog users**
  - A large cohort reported a positive correlation between cancer incidence and insulin dose for all insulin types and elevated cancer incidence for glargine compared to human insulin (study with several limitations)

  [Hemkens et al. Diabetologia 2009; 52: 1732–1744]
  - A nested case-control study (1340 insulin-treated pts, median FU 75.9 mos) showed association of the use of insulin glargine with cancer incidence compared to human insulin or other analogues with a dose effect relationship

  [Mannucci et al, Diabetes Care 2010; 33: 1997–2003]

- **Evidence from RCTs do not suggest increased risk of any or specific cancers with insulin analogs detemir, glargine and degludec**

  [Dejgaard A et al. Diabetologia 2009; 52:2507–2512] [Rosenstock J et al Diabetologia 2009; 52: 1971–1973]

  [Gerstein HC et al. N Engl J Med 2012; 367:319-328] [Marso SP N Engl J Med 2017; 377:723-732]

- **Three meta-analyses of RCT, observational, and cohort studies could not find any association between insulin glargine and ↑ cancer risk**

  [Home PD and Lagarenne P. Diabetologia 2009; 52: 2499–2506] [Tang X et al. PLoS One 2012; 7: e51814]
  [Du X et al. Int J Biol Markers 2012; 27: e241–e246]

Antidiabetic Drugs and Cancer – Sum up

- Substantial knowledge gaps exists
- Methodological limitations should be considered when drawing conclusions from available evidence on antidiabetic therapies and cancer
  - Most evidence is based on retrospective observational studies
  - Duration of studies not long enough for carcinogenicity assessment
  - Control groups often using other antidiabetic drugs that may themselves impact cancer risk
  - Many studies reported baseline drug use and did not account for duration of use
  - Available prospective placebo-controlled RCTs not designed to assess products carcinogenicity but CV or renal safety and/or efficacy
    - Relatively short FU
    - Collection of cancer data not homogeneous across studies
    - The low number of incidences is another point to consider
  - Results from meta-analyses are not conclusive since they suffer from the same biases of individual studies

Antidiabetic Drugs and Cancer – Sum up

- **Metformin:** most evidence points to a cancer risk–reducing effect both as monotherapy and when combined with other oral antidiabetic drugs or insulin overall and in several site-specific cancers.
- **Pioglitazone**: its use is associated with increased risk of bladder cancer, possibly dose-and time-dependent
  - It should not be used in patients with current bladder cancer or a history of bladder cancer
- **DPP4-I, GLP1-RA, and SGLT2-I** : clinical data appear reassuring
  - initial concerns regarding pancreatic and thyroid cancers for incretin-based therapies cancer not confirmed in large safety studies and metanalyses
  - concerns about a possible increase in bladder cancer risk in SGLT2 users cannot be completely ruled out based on available evidence
  - Within-class differences in cancer risk may exist
- **Sulphonylureas:** some reason for concern exists
- **Glinides / α-glucosidase inhibitors:** data are scanty and mostly neutral
- **Insulin analogs:** data are reassuring; most evidence do not confirm increased carcinogenic risk with use of glargine

Further investigation needed in well designed clinical trials

GRAZIE PER L'ATTENZIONE!