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Cancer risks of anti-hyperglycemic drugs for type 2 diabetes treatment- a clinical appraisal

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Abstract

A clinical appraisal of existing scientific literature sought to assess the need for long-term prospective epidemiological studies to investigate an increased cancer risk of anti-hyperglycemic medication in type 2 diabetes. A focus statement was formulated as: “With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks.” Field surveys were sent to practicing physicians and endocrinologists to identify the currently prevalent level of acceptance of this statement. Subsequently, a meeting with a six-member panel of key opinion leaders was held to discuss published evidence in support and against the statement. This publication reviews the publications and discussion points brought forth in this meeting and their effect on statement acceptance by the panel. Whereas the majority of field survey responders primarily agreed with the statement, panel members were divided in their statement support. This division remained intact after review of the literature. While there was evidence that type 2 diabetes is associated with an increased risk of cancer, existing studies seemed insufficient to definitively demonstrate a link between cancer risk and use of specific anti-hyperglycemic therapies.

Keywords:

Type 2 diabetes

Cancer

Anti-hyperglycemic drugs

Introduction

According to the Centers for Disease Control and Prevention (CDC), approximately 29 million people in the US have diabetes mellitus, with 90%–95% of the cases comprised type 2 diabetes mellitus (T2DM) (CDC, 2014). T2DM can lead to blindness, renal failure, cardiovascular disease, amputation of extremities, and premature death. In the last decades, many new therapies have become available for treating T2DM. The main T2DM drug classes include agents that either stimulate insulin secretion/improve beta cell function (sulfonylureas, DPP4 inhibitors, GLP1 receptor agonists), reduce hepatic glucose production (biguanides), delay digestion of carbohydrates (alpha-glucosidase inhibitors), improve insulin action (thiazolidinediones), or decrease glucose reabsorption by the kidney (SGLT2 inhibitors) (American Diabetes Association, 2015). Because some of these drugs have been in use for only a short time, concerns of potential long-term adverse effects have not been addressed by a large body of research as yet.

Evidence suggests that diabetes may be associated with an increased risk of cancer (Andersen, 2013; Ching Sun, Kashyap, & Nasr, 2014). The mechanisms are yet to be fully understood, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis (Perseghin, *et al*., 2012). The treatments that cause hyperinsulinemia, such as sulfonylurea and exogenous insulin, have been suggested to increase cancer risk (Azar & Lyons, 2010; Bonelli, *et al*., 2003; Bowker, *et al*., 2006; Maisonneuve, *et al*., 2010), while treatments that decrease insulin resistance, such as metformin, may reduce the risk of cancer development (Chaiteerakij, *et al*., 2012; Lee, *et al*., 2011; Li, *et al*., 2009; Libby, *et al*., 2009; Michaud, *et al*., 2001).

Notwithstanding these suggested links, clinical studies have generated conflicting data on the effects of these and other specific anti-hyperglycemic drugs on cancer risk. A clinical appraisal meeting was

therefore held in December 2014 to investigate the current status and perceptions. A focus statement was formulated and members of a six-person panel of experts were then asked to present an extensive literature review either in support of or in opposition to the statement. Here, we discuss the contents, flaws, and effects of the various studies brought forth in the appraisal meeting to validate or refute a statement related to the link between T2DM medications and cancer risk, and the effect of the panel discussions and presentations on panel members' opinions.

1. Appraisal design

To critically examine the perceptions of practicing physicians in the field regarding statements relevant to T2DM treatments, an online survey was sent out to 40,000 primary care physicians, family practitioners, internal medicine specialists, and endocrinologists, 1.1% of which responded. After elimination of doctors without T2DM treatment experience, responses from 402 physicians (210 primary care physicians, family practitioners or internal medicine specialists, and 192 endocrinologists) were summarized. The physicians were asked to grade their level of support regarding the following statement: "With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks." Support levels are shown in **Table 1** and were defined to be on a scale of 1 to 6, with 1 representing complete support and 6 representing complete rejection.

Subsequently, an expert panel of six subject-matter experts gathered in December 2014 to discuss the statement. With the focus on safety, the goal of that meeting was to create an unbiased, critical, systematic scientific review of existing data, guidelines, and practices. One panel member was selected to present the current literature in support of the statement, and another panel member was tasked

with presentation of the literature in opposition of the statement. In these panel presentations, particular attention was paid to study design, methodologies, and numbers and types of patients involved. Following the presentation of evidence for each statement, the panel evaluated the overall nature of evidence that was presented, which included the following categories: (1) Evidence obtained from meta-analysis, including at least 1 large, randomized controlled trial (RCT); (2) Evidence obtained from either meta-analysis, including at least 1 small RCT, or from at least one well-designed, large RCT; (3) Evidence obtained from well-designed cohort or case-controlled studies; (4) Evidence obtained from case series, case reports, or flawed clinical trials; (5) Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees; (6) Insufficient evidence to form an opinion.

The panel members were also asked to indicate their degree of acceptance of the statements before and after the presentation, using the level definitions presented in **Table 1**.

2. Literature review

2.1 Rationale and definition of statement

The statement was developed to challenge the notion that long-term, prospective epidemiological studies are necessary to evaluate the cancer risks of every hyperglycemic drug involved in T2DM treatment regimens. Although it does appear that T2DM is associated with an increased cancer risk, it remains unclear whether: (i) the association is largely due to shared risk factors; (ii) diabetes itself alters cancer risk; (iii) the risk of cancer development is modified with medications administered to combat T2DM; or (iv) a combination of all three of these assumptions applies.

In the past, public awareness had been raised to the possibility of cancer risks associated with certain treatments such as insulin glargine. Evidence from observational studies suggested that, in addition to glargine, other glucose-lowering oral agents are also associated with either an increased or reduced risk of cancer (Azar & Lyons, 2010; Bonelli, *et al*., 2003; Bowker, *et al*., 2006; Chaiteerakij, *et al*., 2012; Lee, *et al*., 2011; Li, *et al*., 2009; Libby, *et al*., 2009; Maisonneuve, *et al*., 2010; Michaud, *et al*., 2001). However, these studies were unable to reliably determine whether the observed associations were real (ie, whether glucose-lowering medications had a direct harmful or beneficial effect on cancer risk) and/or due to confounding factors.

In light of this, the statement was developed to investigate whether a general need for long-term prospective epidemiological evaluation of possible carcinogenic properties of any hyperglycemic drug exists. An in-depth examination of existing scientific literature was performed to provide guidance and help determine whether there is a direct link between cancer risk and use of specific anti-hyperglycemic therapies.

2.2 Literature search criteria

Literature in support of the statement was identified through a PubMed search in October 2014 using the keywords “anti-diabetic drugs,” “cancer,” “risks,” and “diabetes.” Studies published from 2010 onwards involving human subjects were considered. From the 845 titles, 252 abstracts were selected for further review. Of these, 40 abstracts were found to be most relevant to the research question. The panelist then selected twelve publications for presentation in the meeting.

Literature refuting the statement was also retrieved through a PubMed search in October 2014 using the key phrases “type 2 diabetes mellitus,” “anti-hyperglycemic therapy,” “cancer,” and “neoplasms.” Additional keywords included “glucose-lowering drugs,” “hypoglycemic agents,” and “anti-diabetic drugs.” Results were limited to human studies with a publication date of 2008 or later. From the 603 titles, 196 abstracts were selected for further review. Of these, 53 abstracts were found to be most relevant to the research question. The panelist finally selected 22 publications to be presented at the meeting.

2.3 Literature in support of the statement

The first papers presented in support of the statement established the existence of an increased cancer risk for T2DM patients. According to a review authored by Andersen (Andersen, 2013), epidemiologic evidence strongly suggests that people with diabetes are at significantly higher risk for several forms of cancer, in particular pancreatic ductal adenocarcinoma. Cannata, *et al.,* (Cannata, *et al.*, 2010) sought to establish the reason, and postulated that in T2DM, insulin resistance results in elevated insulin levels, which may lead to cancer through direct effects on cancer cells via the insulin receptor (IR) and the insulin-like growth factor I receptor (IGF-IR).

The following paragraphs discuss the presented literature that investigated cancer risks for specific drug types.

2.3.1 Insulin and insulin analogs

A meta-analysis of observational studies assessed the risk of cancer during insulin treatment (Janghorbani, Dehghani, & Salehi-Marzijarani, 2012), and summarized that six out of ten cohort studies and one out of five case-control studies found a statistically significant positive association between insulin treatment and cancer.

The only RCT to address this issue, ORIGIN (Outcome Reduction with Initial Glargine Intervention), was an international, long-term RCT comparing insulin glargine with standard care in a 2x2 factorial design that included n-3 fatty acids and placebo in 12,537 T2DM patients with a prospective follow-up of up to 7 years (ORIGIN Trial Investigators *et al.*, 2012a and 2012b; Bordeleau, *et al*., 2014). Both insulin glargine and n-3 fatty acids were found to have a neutral association with both cardiovascular and cancer-specific outcomes, including cancer-specific mortality. These findings do not support previous epidemiologic studies that have linked insulin glargine to incident cancers (see below), although it should be noted that metformin was used by 47% of the insulin-glargine group. Of note is the fact that the number of new cancers exceeded the number of myocardial infarctions.

2.3.2 Metformin

A meta-analysis of RCTs, cohorts, and case-control studies published through July 2012 assessed the effects of metformin and/or sulfonylureas on cancer risk (Thakkar, *et al*., 2013). Cohort and case-control studies showed that metformin use is associated with a reduced cancer risk, but this finding was not supported by RCTs. In addition, cohort studies showed that sulfonylurea use is associated with an increase in all-cancer risk, but RCTs and case-control studies did not demonstrate a statistically

significant effect. The authors noted that more well-designed, large-scale RCTs are necessary if the findings of this study are to be translated to changes in clinical practice.

A meta-analysis of seven observational studies examined the effect of metformin on breast cancer incidence (Col, *et al*., 2012). Six out of seven studies reported an association between metformin use and lower breast cancer risk, but only three of the associations were statistically significant. The findings were limited by the observational nature of the study designs, suggesting that longer, prospective randomized studies were necessary to identify real associations.

Metformin was also associated with improved outcomes in cancer patients, and Rizos & Elisaf (Rizos & Elisaf, 2013) proposed possible mechanisms of that effect that included an increased insulin sensitivity coupled with decreased insulin growth factor-1 levels and an activated AMP kinase pathway. However, the favorable cancer association was mostly supported by data from retrospective studies. The authors concluded that larger studies with pathology endpoints needed to be designed to effectively evaluate the effect of metformin use on cancer development and progression.

2.3.3 Thiazolidinediones (TZDs)

A meta-analysis of observational studies examined the effect of TZDs on the risk of bladder cancer, other selected cancers, and overall cancer in T2DM patients (Bosetti, *et al*., 2013). TZD use was not associated with an elevated overall cancer risk. However, a modest excess risk of bladder cancer was reported with pioglitazone. The authors concluded that, assuming this association is real, the potential implications on the risk-benefit analysis of TZD use should be evaluated. TZDs were introduced to the market in the late

1990s, so only short-term exposures can so far be evaluated, with limited information on the cancer association and treatment duration or cumulative dose.

Another review found a higher risk of bladder cancer associated with pioglitazone use but no association with rosiglitazone (Tseng, 2014a). However, evidence from the completed RCTs may not be informative or conclusive because none of them were designed to specifically investigate the cancer risk associated with TZDs. In addition, the author cautioned that the small numbers of events of bladder cancer did not provide sufficient power for statistical analysis.

2.3.4 Incretin-based therapies

New incretin-based therapies, including dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon like peptide 1 (GLP1) receptor agonists, are popular among clinicians and T2DM patients because they are not associated with weight increase and hypoglycemia. However, analyses of adverse events databases suggested higher incidences of pancreatic and medullary thyroid carcinoma in patients treated with DPP4 inhibitors and GLP1 agonists (Vangoitsenhoven, Mathieu, & Van der Schueren Vangoitsenhoven, 2012). However, such databases have numerous limitations, including incomplete patient characteristics and reporting bias. Long-term, prospective RCTs were therefore deemed necessary to further evaluate the effects of these drugs.

2.3.5 Dapagliflozin

Dapagliflozin works by inhibiting sodium glucose cotransporter 2 (SGLT2) and blocking reabsorption of glucose in the kidney. Because a numeric increase in bladder cancer was observed in one clinical trial,

the FDA asked Bristol-Myers Squibb to evaluate and respond to the perceived event imbalance for bladder cancer. New data presented at a December 2013 advisory committee meeting showed that the overall cancer incidence ratio risk was 1.03 (0.71, 1.51) (Bristol-Myer Squibb & AstraZeneca, 2013). The study concluded that the evidence does not support a causal link between dapagliflozin and bladder cancer although this is being assessed in the large DECLARE RCT (clinicaltrials.gov identifier NCT01730534).

In a summarizing study, Lutz, *et al.* (Lutz, *et al.*, 2014) evaluated cancer risks of the major glucose-lowering drug classes and confirmed the trends mentioned above. Favorable effects of metformin on several site-specific cancers were fairly significant, whereas insulin glargine had no effect. Remaining concerns were expressed for sulfonylureas and incretin-based therapies (pancreas and thyroid cancers) as well as for sodium glucose cotransporter-2 inhibitors and pioglitazone (bladder cancer). However, the authors concluded that more large-scale, well-designed RCTs with long follow-up times are necessary to get more reliable answers.

Of note is the fact that, overall, each of the authors of each presented paper called for more RCTs to evaluate the effect of anti-hyperglycemic medications on cancer risk.

2.4 Literature in opposition of the statement

Literature in opposition of the statement centered around the fact that trials, even if well designed, failed to unequivocally ascertain a connection between an elevated risk of cancer and use of a particular T2DM drug. Gallagher & LeRoith (Gallagher & LeRoith, 2013) posited that epidemiological studies have generated conflicting results regarding the associations between specific anti-hyperglycemic

medications and cancer development. They surmised that the few studies proposing an association between therapeutic agents and cancer risk in patients with diabetes have been clearly validated. Giovanucci, *et al.* (Giovannucci, *et al.*, 2010) stressed that the association between cancer and T2DM may partly be due to shared risk factors between the two diseases, including aging, obesity, diet, and physical activity. Furthermore, illustrating the difference in interpretation of existing literature, the study by Andersen (Andersen, 2013), presented in support of the statement earlier, was also discussed as evidence refuting the statement. The focus in the panel presentation was shifted onto the conclusion of the author that there is no definitive, prospective data indicating that the currently available T2DM therapeutics increase the incidence of cancer beyond the inherent increased risk in this population.

The following paragraphs discuss specific drug classes and the quality of evidence for their role in increasing the risk for cancer in patients with T2D.

2.4.1 Thiazolidinediones (TZDs)

The PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) was the first study to prospectively evaluate the effects of a TZD on cardiovascular outcomes in high-risk T2DM patients and pre-existing macrovascular disease. During the initial double-blind treatment period of PROactive (mean observation time of 34.5 months), there was a higher number bladder malignancies reported in the pioglitazone group compared with the placebo group (n=14 versus 6); however, a ten-year follow-up of 3,599 patients who completed PROactive found no significant difference in bladder malignancies between the two groups (Erdmann, *et al.*, 2016). Although five-year interim analysis results of a ten-year epidemiology study conducted by the University of Pennsylvania and Division of Research at Kaiser Permanente Northern California showed a small but statistically significant elevated risk of bladder

cancer among patients receiving more than 2 years of pioglitazone treatment, the final ten-year results of this study found no statistically significant association between use of pioglitazone and bladder cancer risk, irrespective of duration and dose of treatment (Lewis, *et al.*, 2015).

A retrospective cohort study utilized databases of all Taiwanese T2DM patients who received oral anti-diabetic agents or insulin from 1996 to 2009 (Tseng, 2014b). A total of 1,093,675 patients were followed up for kidney cancer incidence until the end of 2009. Pioglitazone and kidney cancer were not significantly associated in unadjusted, age-sex-adjusted, and fully adjusted models. In addition, none of the dose-response parameters showed a significant trend of risk association.

Using the same database, another retrospective cohort study followed 887,665 patients for thyroid cancer incidence (Tseng, 2013). Rosiglitazone and thyroid cancer were not significantly associated in unadjusted, age-sex-adjusted, and fully adjusted models. However, in dose-response analyses, the adjusted hazard ratios were significantly lower during the last third of the duration of therapy and cumulative dose, for patients at age 50 or greater. The author concluded that rosiglitazone may reduce the risk of thyroid cancer by ~50% if the duration of therapy is greater than 14 months or the cumulative dose is greater than 1,800 mg. However, users of rosiglitazone had a significantly higher probability of receiving insulin or other oral agents, so indication bias related to these therapies could not be excluded.

2.4.2 Metformin

A meta-analysis of 15 observational studies suggested a protective association between metformin use and colorectal cancer risk in patients with diabetes mellitus (Singh, *et al.,* 2013a). Metformin use might

therefore be associated with a lower risk of colorectal cancer, while the same study also concluded that sulfonylureas and insulin do not significantly increase colorectal cancer risk.

A second meta-analysis by the same authors found that metformin use might also be associated with a 50% relative risk reduction in hepatocellular cancer, while sulfonylurea use may be associated with a 62% increase in the relative risk (Singh, *et al.,* 2013c). Lastly, the group found that metformin, thiazolidinediones, and insulin use had no significant effect on pancreatic cancer risk, while sulfonylurea use was associated with a 70% increase in the odds of pancreatic cancer (Singh, *et al.,* 2013b). The authors went on to caution readers that one major caveat in these meta-analyses consisted of considerable heterogeneity across the compared studies, which was only partly explained by study setting, location, and whether the studies adjusted for the concomitant use of other anti-diabetic medications. Post-hoc analysis of RCTs alone did not reveal any significant association. The authors concluded that while definitive and randomized prospective trials are necessary, they are impractical because of the required sample size and duration of follow-up.

Another meta-analysis of cohort and case-control studies also concluded that metformin is associated with the lower risk for colorectal and pancreatic cancer, but not breast and prostate cancer (Soranna, *et al*., 2012). However, the authors proceed to point out evidence of publication bias and occasional substantial between-study heterogeneity.

A meta-analysis of the ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) RCTs assessed the efficacy and/or safety of metformin in comparison with sulfonylurea and rosiglitazone (Home, *et al*.,

2010). The authors found that metformin does not offer any particular protection against malignancy compared with rosiglitazone, but may perform better than sulfonylureas.

2.4.3 Insulin and insulin analogs

A Barcelona case-control study evaluated the impact of glucose-lowering agents on cancer risk in a large T2DM patient population (n = 275,164) (Simó, *et al*., 2013). No differences in cancer risks were observed between case and control subjects, when evaluating drug proportion, drug dose, or duration of exposure to each treatment. None of the types of insulin and oral agents analyzed showed a significant increase in cancer risk, including glargine alone or in combination with metformin. Confirming this finding, a meta-analysis of 19 RCTs compared the use of insulin glargine with any other active comparator and found that it is not associated with an increased incidence of cancer (Home & Lagarenne, 2009).

In line with these findings, a retrospective cohort study reported no evidence of an increased risk of cancer associated with insulin glargine as compared to intermediate-acting insulin as observed in thousands of diabetic patients aged ≥20 years (Chang, *et al*., 2011). This was also supported by a meta-analysis based on a Scottish database, which found that insulin glargine is not associated with an increased cancer risk (Colhoun & SDRN Epidemiology Group, 2009). The authors noted that the excess of cases of all cancers and breast cancer in the subgroup of insulin glargine only users most likely reflected allocation bias rather than an effect of insulin glargine itself.

However, a few dissenting studies were also presented. A cohort study that investigated malignancy risk using data provided by a German database of patients treated with human insulin or with insulin

analogs found that cancer incidence with glargine was higher than expected compared with human insulin (Hemkens, *et al*., 2009). Another meta-analysis using a Swedish registry found that women using insulin glargine alone had an increased incidence rate of breast cancer compared with women using other types of insulin (Jonasson, *et al*., 2009). No statistically significant results were obtained in that study for any other individual cancer site or for the outcome "all malignancies." Lastly, a retrospective cohort study utilizing data from a UK database found that patients treated with insulin or insulin secretagogues were more likely to develop cancer than those on metformin, and that a combination of insulin with metformin abolished most of this excess risk (Currie, 2009). Insulin analogs were not associated with increased cancer risk as compared with human insulin.

In a comparative meta-analysis of RCTs, the cancer risk during treatment with insulin detemir, a long-acting insulin analog, was assessed (Dejgaard, *et al*., 2009). Patients treated with insulin detemir had a lower or similar occurrence of a cancer diagnosis compared with patients treated with NPH insulin or insulin glargine. Finally, a nested case-control study found an association between cancer incidence and higher insulin glargine doses (≥0.3 IU/kg/day), even after adjusting for confounders (Mannucci, *et al*., 2010), and suggested that dosage of the treatment should always be considered in future risk association studies.

In summary, the few studies that seemed to provide some support to an association between cancer risk and specific T2DM treatment classes and types were either meta-analyses (ie, retrospective in nature) or observational/case-control studies. Statistical relevance for prospective studies was only achieved in large meta-analyses

2.5 Grading of literature evidence and level of statement support

Literature presented in support of the statement was evaluated by five of the six panelists to stem from either a meta-analysis including at least one RCT or from one well-designed, large RCT (**Fig. 1**, categories 1 & 2). The remaining panelist thought that the decisive evidence was obtained from a well-designed cohort or case-controlled study (category 3). The papers discussed in opposition to the statement were graded slightly lower: three panelists thought that the most important evidence was of category 2 quality; and the other three evaluated the evidence to be from category 3.

As illustrated in **Fig. 2**, approximately 80% of field survey responders agreed with the statement to some extent (categories 1–3, **Table 1**). Prior to presentation of the literature review, two out of six panelists primarily agreed with the statement (categories 2 & 3, **Table 1**), while the four remaining panelists rejected the statement either with major reservations or completely (categories 5 & 6, **Table 1**). Following presentation of the literature review, the panelists shifted towards more acceptance of the statement, but remained divided: four out of six panelists now agreed with the statement with minor or major reservations (categories 2 & 3), whereas one subject matter expert still completely rejected the statement, and one panelist rejected the statement with minor reservations. Overall, the panelists remained skeptical of the statement, despite a tendency towards more acceptance. As illustrated in **Fig. 3**, the weighted mean of the level of acceptance/rejection shifted from 4.3 to 3.3.

3. Discussion

The majority of clinicians in the field supported the notion, as posed in the focus statement, that *"…all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer*

risks." Conversely, prior to the appraisal meeting, panel members predominantly rejected the notion, although the reasons for this varied. After presentation of the literature review, the panelists were split as to whether to accept or reject the statement. Different interpretations and emphasis were put on the statement that caused the panel members to be divided in their views. Some panelists focused on the prohibitive cost/benefit calculations regarding such a stipulation, while others heeded the general demand of experts in the field to provide more well-designed RCTs to properly address the question. Some panelists emphasized the fact that trends, if in fact present, were safely observed in smaller cohort studies as well as in big RCTs, while others regarded the high rate of well-designed costly studies that failed to unearth a statistically relevant correlation between any T2DM therapy and cancer risk. A prominent opinion involved the idea that high quality, cost-efficient research methods using registries may be satisfactory and provide as much quality data as prospective RCTs that require much more resources.

There was general agreement that diabetes is indeed associated with an increased cancer risk. However, it remains unclear whether the association between diabetes and risk of certain cancers may be largely due to shared risk factors, such as obesity, or whether diabetes itself alters cancer risk (ie, hyperglycemia, insulin resistance, and hyperinsulinemia). The risk for cancer development associated with diabetes treatments cannot, in itself, be viewed separately from this consideration.

Overall, existing studies were deemed largely insufficient to demonstrate a clear link between cancer risk and use of specific anti-hyperglycemic therapies. This is not surprising given the long latency of cancer development after carcinogen exposure and the fact that many clinical trials did not have the duration of follow-up to match this latency. High-quality evidence for or against such a link should be obtained, but there was dissent on the best possible strategy to achieve this. RCTs are deemed the gold

standard but concerns were raised as to their monetary feasibility given the required sample size and duration of follow up to obtain any statistical significance. While epidemiological studies can provide more “real world” generalizable data on the potential associations between the use of specific anti-hyperglycemic agents and risk for cancer than RCTs, confounders, both known and unknown, may affect those study results. Perhaps broad population-based studies using high-quality databases that include a maximum amount of (legally protected and voluntarily provided) patient information can be used to best compare incidences of specific cancers between patients and correlate these more clearly with specific treatment regimens.

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References

American Diabetes Association (ADA). What are my options? (2015). http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options Accessed 22.02.15.

Andersen, DK (2013). Diabetes and cancer: placing the association in perspective. *Current Opinion in Endocrinology, Diabetes, and Obesity, 20*(2), 81–86.

Azar, M, & Lyons, TJ (2010). Diabetes, insulin treatment, and cancer risk: what is the evidence? *F1000 Medicine Reports*, 2, pii 4.

Bonelli, L, Aste, H, Bovo, P, Cavallini, G, Felder, M, Gusmaroli, R, Morandini, E, Ravelli, P, Briglia, R, Lombardo, L, De Micheli, A, & Pugliese, V (2003). Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in northern Italy. *Pancreas, 27*(2), 143–149.

Bordeleau, L, Yakubovich, N, Dagenais, GR, Rosenstock, J, Probstfield, J, Chang Yu, P, Ryden, LE, Pirags, V, Spinas, GA, Birkeland, KI, Ratner, RE, Marin-Neto, JA, Keltai, M, Riddle, MC, Bosch, J, Yusuf, S, Gerstein, HC; ORIGIN Trial Investigators (2014). The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care, 37*(5), 1360–1366.

Bosetti, C, Rosato, V, Buniato, D, Zambon, A, La Vecchia, C, & Corrao, G (2013). Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. *Oncologist, 18*(2), 148–156.

Bowker, SL, Majumdar, SR, Veugelers, P, & Johnson, JA (2006). Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care, 29*(2), 254–258.

Bristol-Myers Squibb & AstraZeneca. Dapagliflozin BMS-512148. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. December 12, 2013. (2013).

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM379659.pdf Accessed 06.09.2015.

Cannata, D, Fierz, Y, Vijayakumar, A, & LeRoith, D (2010). Type 2 diabetes and cancer: what is the connection? *Mount Sinai Journal of Medicine, 77*(2), 197–213.

Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report. (2014). http://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport Accessed 22.02.15.

Chaiteerakij, R, Yang, JD, Harmsen, WS, Slettedahl, SW, Mettler, TA, Fredericksen, ZS, Kim, WR, Gores, GJ, Roberts, RO, Olson, JE, Therneau, TM, & Roberts, LR (2012). Risk factors for intrahepatic cholangiocarcinoma: association between metformin use and reduced cancer risk. *Hepatology, 57*(2), 648–655. doi: 10.1002/hep.26092.

Chang, CH, Toh, S, Lin, JW, Chen, ST, Kuo, CW, Chuang, LM, & Lai, MS (2011). Cancer risk associated with insulin glargine among adult type 2 diabetes patients--a nationwide cohort study. *PLOS One, 6*(6), e21368.

Ching Sun, GE, Kashyap, SR, & Nasr, C (2014). Diabetes therapy and cancer risk: Where do we stand when treating patients? *Cleveland Clinic Journal of Medicine, 81*(10), 620–628.

Col, NF, Ochs, L, Springmann, V, Aragaki, AK, & Chlebowski, RT (2012). Metformin and breast cancer risk: a meta-analysis and critical literature review. *Breast Cancer Research and Treatment, 135*(3), 639–646.

Colhoun, HM, & SDRN Epidemiology Group (2009). Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia, 52*(9), 1755–1765.

Currie, CJ, Poole, CD, & Gale, EAM (2009). The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia, 52*(9), 1766–1777.

Dejgaard, A, Lynggaard, H, Rastam, J, & Krogsgaard Thomsen, M (2009). No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. *Diabetologia, 52*(12), 2507–2512.

Erdmann, E, Harding, S, Lam, H, & Perez, A (2016). Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. *Diabetes, Obesity and Metabolism, 18*(3), 266–273.

Gallagher, EJ, & LeRoith, D (2013). Diabetes, antihyperglycemic medications and cancer risk: smoke or fire? *Current Opinion in Endocrinology, Diabetes, and Obesity, 20*(5), 485–494.

Giovannucci, E, Harlan, DM, Archer, MC, Bergenstal, RM, Gapstur, SM, Habel, LA, Pollak, M, Regensteiner, JG, & Yee, D (2010). Diabetes and cancer: a consensus report. *Diabetes Care, 33*(7), 1674–1685.

Hemkens, LG, Grouven, U, Bender, R, Günster, C, Gutschmidt, S, Selke, GW, & Sawicki, PT (2009). Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia, 52*(9), 1732–1744.

Home, PD, & Lagarenne, P (2009). Combined randomized controlled trial experience of malignancies in studies with insulin glargine. *Diabetologia, 52*(12), 2499–2506.

Home, PD, Kahn, SE, Jones, NP, Noronha, D, Beck-Nielsen, H, & Viberti, G (2010). Experiences of malignancies with oral glucose-lowering drugs in the randomized controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. *Diabetologia, 53*(9), 1838–1845.

Janghorbani, M, Dehghani, M, & Salehi-Marzijarani, M (2012). Systematic review and meta-analysis of insulin therapy and risk of cancer. *Hormones and Cancer, 3*(4), 137–146.

Jonasson, JM, Ljung, R, Talback, M, Haglund, B, Gudbjornsdottir, S, & Steineck, G (2009). Insulin glargine use and short-term incidence of malignancies- a population-based follow-up study in Sweden. *Diabetologia, 52*(9), 1745–1754.

Lee, MS, Hsu, CC, Wahlqvist, M, Tsai, HN, Chang, YH, & Huang, YC (2011). Type 2 diabetes increases and metformin reduces total, colorectal, liver, and pancreatic incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer, 11*, 20.

Lewis, JD, Habel, LA, Quesenberry, CP, Strom, BL, Peng, T, Hedderson, MM, Ehrlich, SF, Mamtani, R, Bilker, W, Vaughn, DJ, Nessel, L, Van Den Eeden, SK, & Ferrara, A (2015). Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA, 314*(3), 265–277.

Li, D, Yeung, SC, Hassan, MM, Konopleva, M, & Abbruzzese, JL (2009). Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology, 137*(2), 482–488.

Libby, G, Donnelly, LA, Donnan, PT, Alessi, DR, Morris, AD, & Evans, JM (2009). New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care, 32*(9), 1620–1625.

Lutz, SZ, Staiger, H, Fritsche, A, & Haring, HU (2014). Antihyperglycaemic therapies and cancer risk. *Diabetes & Vascular Disease Research, 11*(6), 371–389.

Maisonneuve, P, Lowenfels, AB, Bueno-de-Mesquita, HB, Ghadirian, P, Baghurst, PA, Zatonski, WA, Miller, AB, Duell, EJ, Boffetta, P, & Boyle P (2010). Past medical history and pancreatic cancer risk: Results from a multicenter case-control study. *Annals of Epidemiology, 20*(2), 92–98.

Mannucci, E, Monami, M, Balzi, D, Cresci, B, Pala, L, Melani, C, Lamanna, C, Bracali, I, Bigiarini, M, Barchielli, A, Marchionni, N, & Rotella, CM. (2010). Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. *Diabetes Care, 33*(9), 1997–2003.

Michaud, DS, Giovannucci, E, Willett, WC, Colditz, GA, Stampfer, MJ, & Fuchs, CS (2001). Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA, 286*(8), 921–929.

ORIGIN Trial Investigators, Bosch, J, Gerstein, HC, Dagenais, GR, Díaz, R, Dyal, L, Jung, H, Maggiono, AP, Probstfield, J, Ramachandran, A, Riddle, MC, Rydén, LE, & Yusuf, S (2012a). n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *New England Journal of Medicine, 367*(4), 309–318.

ORIGIN Trial Investigators, Gerstein, HC, Bosch, J, Dagenais, GR, Díaz, R, Jung, H, Maggioni, AP, Pogue, J, Probstfield, J, Ramachandran, A, Riddle, MC, Rydén, LE, & Yusuf, S (2012b). Basal insulin and cardiovascular and other outcomes in dysglycemia. *New England Journal of Medicine, 367*(4), 319–328.

Perseghin, G, Calori, G, Lattuada, G, Raogna, F, Dugnani, E, Garancini, MP, Crosignani, P, Villa, M, Bosi, E, Ruotolo, G, & Piemonti, L (2012). Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up. *Acta Diabetol, 49(6)*, 421–428.

Rizos, CV, & Elisaf, MS (2013). Metformin and cancer. *European Journal of Pharmacology, 705*(1–3), 96–108.

Simó, R, Plana-Ripoll, O, Puente, D, Morros, R, Mundet, X, Vilca, LM, Hernandez, C, Fuentes, I, Procupet, A, Tabernero, JM, & Violán, C (2013). Impact of glucose-lowering agents on the risk of cancer in type 2 diabetic patients. The Barcelona case-control study. *PLOS One, 8*(11), e79968. doi: 10.1371/journal.pone.0079968.

Singh, S, Singh, H, Singh, PP, Murad, MH, & Limburg, PJ (2013a). Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Cancer Epidemiology Biomarkers & Prevention, 22*(12), 2258–2268.

Singh, S, Singh, PP, Singh, AG, Murad, MH, McWilliams, RR, & Chari, ST (2013b). Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *American Journal of Gastroenterology, 108*(4), 510–519.

Singh, S, Singh, PP, Singh, AG, Murad, MH, & Sanchez, W (2013c). Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *American Journal of Gastroenterology, 108*(6), 881–891.

Soranna, D, Scotti, L, Zambon, A, Bosetti, C, Grassi, G, Catapano, A, La Vecchia, C, Mancia, G, & Corrao, G (2012). Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist, 17*(6), 813–822.

Thakkar, B, Aronis, KN, Vamvini, MT, Shields, K, & Mantzoros, CS (2013). Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. *Metabolism, 62*(7), 922–934.

Tseng, CH (2013). Rosiglitazone may reduce thyroid cancer risk in patients with type 2 diabetes. *Annals of Medicine, 45*(8), 539–544.

Tseng, CH (2014a). A review on thiazolidinediones and bladder cancer in human studies. *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis and Ecotoxicology Reviews, 32*(1), 1–45.

Tseng, CH (2014b). Pioglitazone does not affect the risk of kidney cancer in patients with type 2 diabetes. *Metabolism, 63*(8), 1049–1055.

Vangoitsenhoven, R, Mathieu, C, & Van der Schueren, B (2012). GLP1 and cancer: friend or foe?

Endocrine-Related Cancer, 19(5), F77–88.

Table 1

Definition of levels of support for statements.

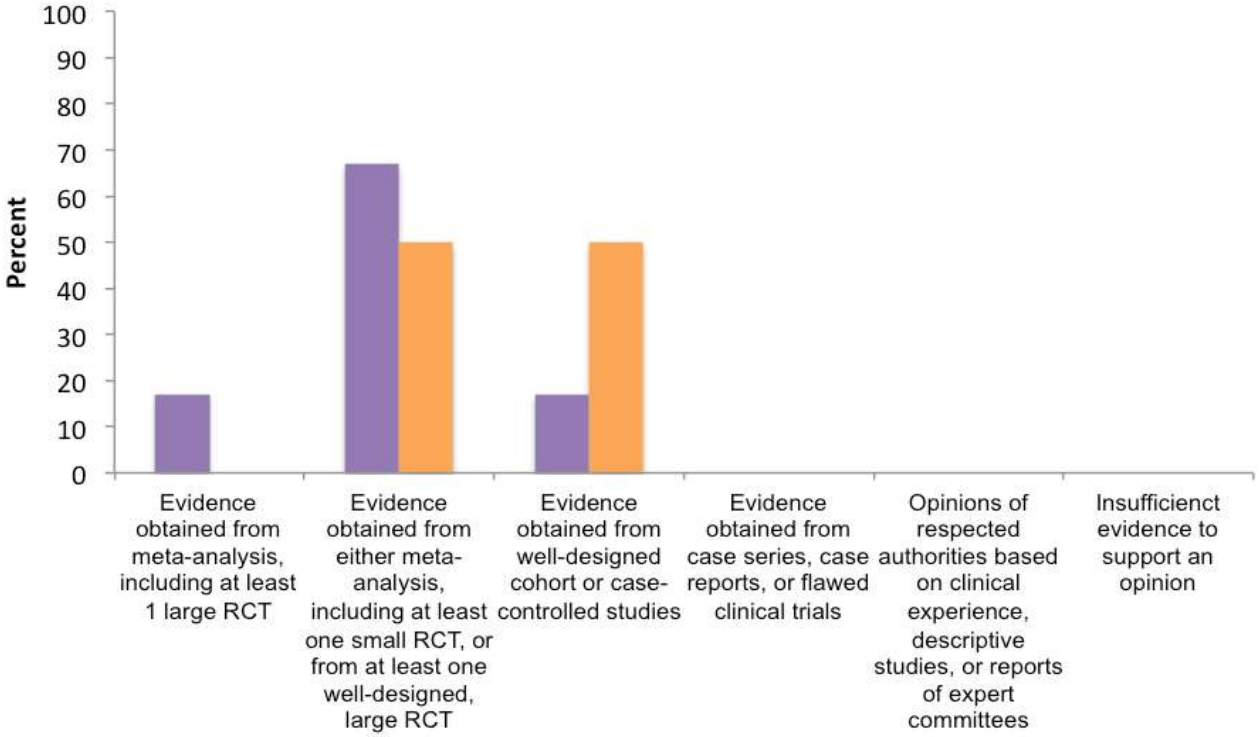
Support level	Definition
1	Agree completely
2	Agree with minor reservations
3	Agree with major reservations
4	Reject with minor reservations
5	Reject with major reservations
6	Reject completely

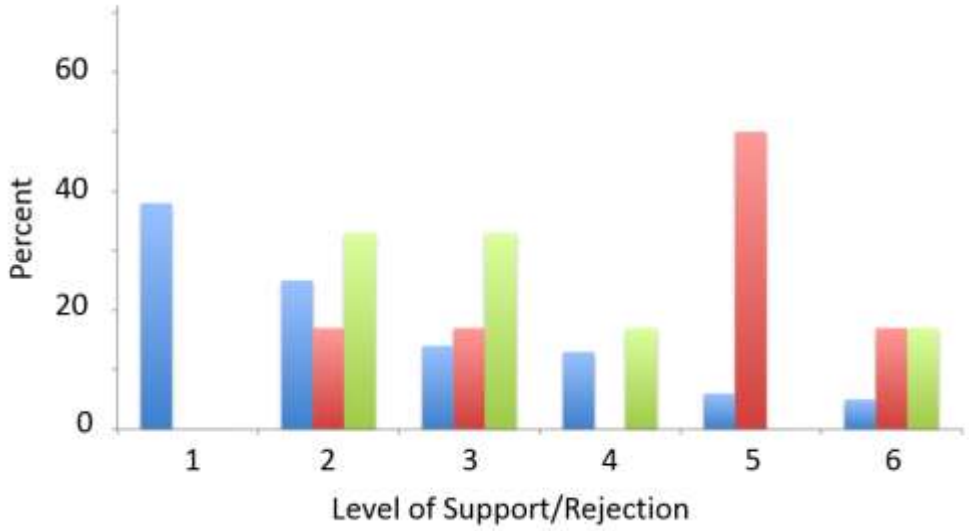
Figure captions

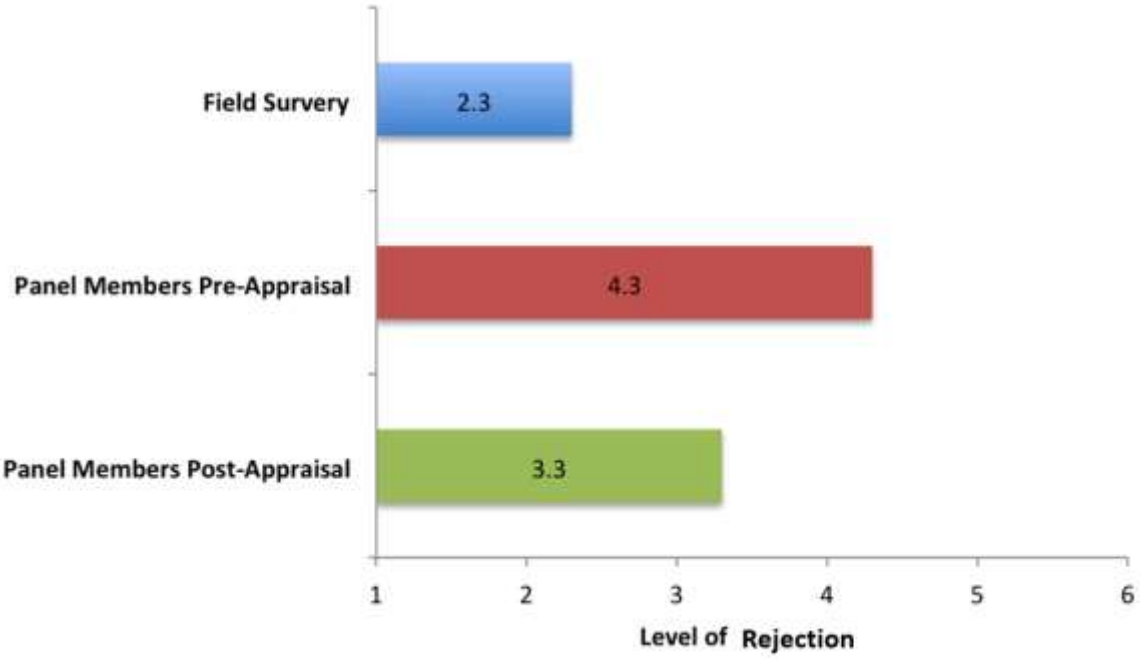
Fig. 1. Grading of evidence. *With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks.* Panel members (n = 6) voted on the nature of the evidence presented at the appraisal meeting. Purple bars: literature presented in support of the statement. Orange bars: literature presented in opposition to the statement.

Fig. 2. Level of support. *With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks.* Blue bars, field survey respondents (n = 402). Red bars, panel members (n = 6) before appraisal meeting. Green bars, panel members (n = 6) after appraisal meeting. Definition of support levels is shown in **Table 1**.

Fig. 3. Weighted mean of acceptance level. *With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks.* Blue bars, field survey respondents (n = 402). Red bars, panel members (n = 6) before appraisal meeting. Green bars, panel members (n = 6) after appraisal meeting. The grading on the x-axis corresponds to the levels of support shown in **Table 1**.


Percent
100
90
80
70
60
50
40
30
20
10
0
Evidence obtained from meta-analysis, including at least 1 large RCT
Evidence obtained from either meta-analysis, including at least one small RCT, or from at least one well-designed, large RCT
Evidence obtained from well-designed cohort or case-controlled studies
Evidence obtained from case series, case reports, or flawed clinical trials
Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Insufficienct evidence to support an opinion


60
40
20
0
Percent
1
2
3
4
5
6
Level of Support/Rejection


Field Survery
2.3
Panel Members Pre-Appraisal
4.3
Panel Members Post-Appraisal
3.3
1
2
3
4
5
6
Level of Rejection