Expert opinion

Safety of insulin analogues in diabetes: the lessons of summer 2009

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On Friday 26 June, 2009, the diabetes community was suddenly confronted with an important but highly controversial story of potential great relevance to patients with diabetes treated with insulin, which was largely unexpected at least outside Germany. The European Association for the Study of Diabetes (EASD) and its journal *Diabetologia*, published four registry studies on-line,[1-4] that analyzed the association of insulin glargine with cancer risk and were accompanied by a well written lengthy editorial.[5] The editorial[5] comprehensively reviewed the issue of cancer in diabetes and the basic science for the possible mechanistic interaction of insulin with cancer growth and potentially with pre-cancer cells. Unfortunately the editorialists gave too much emphasis to the conflicting data of the four papers,[1-4] ignoring the serious methodological deficiencies of most of the data and the flawed analyses of the German paper, and concluded that a possible link between insulin glargine and cancer may exist. This prompted headlines, a press release and an urgent webcast presentation that included patient recommendations by EASD representatives. Of note, the scientific papers[1-5] had to be promptly released in electronic format under pressure from the financial community in view of increasing rumors over the internet, as a result of an apparent violation of the confidential peer-review process, predicting major financial losses for sanofi-aventis due to the alleged link between insulin glargine and cancer.[6]

The EASD press release[7] and the document for "patient information"[8] that immediately followed online publications further raised the level of alarm. Indeed, the decision to bring the four *Diabetologia* papers[1-4] to the attention of the medical and patient community in a webcast presentation for consideration of poten-

tial treatment decisions, without giving the opportunity to a scientific body of experts to previously discuss and analyze the data in order to reach consensus and objective conclusions, has been seriously questioned. These actions were interpreted by some physicians and patients to indicate that there could be a real emergency relating cancer risk and the use of insulin glargine.

Notably, on the same day 26 June, only few hours after the online information from *Diabetologia*, the American Diabetes Association (ADA) which was not informed by the EASD of the existence of the these studies until the day of their online publication, promptly reviewed the studies and released a concise and most sensible statement[9] "findings from these research papers are conflicting and inconclusive, and the American Diabetes Association cautions against over-reaction until more information is available. Four different population based studies were reported and published in *Diabetologia* and the data within these studies and between these studies are conflicting and confusing. Until more information is available, the American Diabetes Association advises patients using insulin not to stop taking it. For patients using glargine and considering switching to another form of insulin, the data in these studies make it unclear as to whether any one type of insulin increases the risk of cancer more than other types of insulin".

Outside EASD, similar conclusions and statements were subsequently released by regulatory agencies (European Medicines Agency [EMEA] and the United States Federal Drug Administration [FDA] and also international organizations such as the International Diabetes Federation (IDF), the Endocrine Society and most national diabetes organizations in the UK, France, Spain, etc.[10-13] To the best of our knowledge, only the position statement of the Australian Diabetes Society on 1st July[14] differs slightly from the above and warns about cancer risk with glargine, suggesting use of alternative insulin preparations in cancer patients or in patients at risk for cancer despite the lack of evidence to substantiate such as statement.

As the dust continues to settle following more critical and rigorous analysis of the data by several editorial and expert commentaries,[15-17] it is important that some facts and premises be discussed and clarified so that the use of insulin in general, insulin analogues, and insulin glargine in particular can be put in the proper clinical perspective.

Abbreviations:
ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; EMEA: European Medicines Agency; FDA: Federal Drug Administration; HR: hazard ratio; IDF: International Diabetes Federation; IGF-1: insulin growth factor 1; IGF-1R: IGF-1 receptors; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IR: insulin receptor; MAPK: mitogen-activated protein kinase; NPH: neutral protamin Hagedorn; ORIGIN: Outcome Reduction with an Initial Glargine Intervention; RR: relative risk; THIN: The Health Information Network.

The premises focusing on cancer risk based on *in vitro* and *in vivo* preclinical studies in animals

After the demonstration that the rapid-acting insulin analogue AspB10 produced mammary tumors in rats,[18] all insulin analogues synthesized thereafter are required to be extensively investigated for safety *in vitro* and *in vivo* before commercialization. *In vitro,* AspB10 exhibited two key differences as compared to human insulin due to the modification in the B region: greater affinity to IGF-1 receptors (IGF-1R), and a prolonged residency time on the insulin receptor (IR).[19] Insulin analogues such as lispro, aspart and detemir, overall do not differ from human insulin with respect to these aspects.[19] In contrast, insulin glargine, due to extension of the B-chain by addition of two arginine residues at B31 and B32 position, has 6-8 fold greater affinity for IGF-1R in the model of human osteosarcoma cells,[19] a malignant cell line, which expresses nearly exclusively IGF-1R, and not IR on its surface. This finding raised an initial concern about the safety of glargine *in vivo* since in osteosarcoma cells glargine promotes mitogenesis about 7-8 times more than human insulin,[19] but it is important to emphasize that experiments demonstrating increased mitogenesis do not necessarily translate into increased oncogenesis. Of note, in other cell lines expressing a more physiological ratio of IGF-1R/IR, such as skeletal muscle, glargine is no longer different from human insulin in promoting DNA synthesis.[20] More importantly, a critical difference between glargine and AspB10 is that glargine has a much shorter residency time on the IR as compared to AspB10 as well as compared to human insulin itself,[19] which confers a safer characteristic to insulin glargine as compared to AspB10. Indeed, the faster dissociation rate from the IGF-1R rather than its binding affinity, is likely more important to exert lesser potential for growth stimulation and mitogenesis *in vivo*.[21]

Another important fact to consider is that in clinical practice*,* the plasma insulin concentrations following insulin glargine administration are usually about 20-40 µU/ml, which is 10-20 times lower than the levels shown *in vitro* to have increased IGF-1R binding (>500 µU/ml) vs. human insulin.[20] Indeed, even the increased affinity of glargine for IGF-1R is still much lower than IGF itself.[20] In addition, most of the injected insulin glargine in the subcutaneous tissue, is rapidly degraded to metabolites (M1 and M2) which fully retain insulin activity, but are both deprived of the di-arginine molecules B31 and B32.[22,23] Thus, it is estimated that at least 50% of the insulin concentration circulating in plasma after s.c. injection of glargine, is not glargine as such, but M1 and M2 which do not differ from human insulin in terms of binding affinity to IGF-1R and mitogenic activity.[19,22]

Moving from *in vitro* cell to *in vivo* animal experiments, the data on glargine are reassuring since no tumor development has been observed for up to two years in rodents at the maximal tolerated insulin dose of 12.5 U/kg/day.[24] The critique by Smith and Gale[5] that sanofi-aventis has not explored higher insulin glargine doses proven to be carcinogenetic with AspB10 (i.e. 10 and 200 U/kg/day) is valid, but these doses could not be used because of the greater glucose-lowering potency of insulin glargine. When doses of glargine larger than 12.5 U/kg/day were given, animals died after severe brain damage caused by hypoglycemia.[24]

Recently, it has been shown that growth of the malignant mammary epithelial cell line MCF7 (with high ratio IGF-1R/IR) was promoted more by insulin glargine vs. human insulin already at the concentration of 0.3 nM (~50 µU/ml) which may be relevant to the human situation of insulin treatment in diabetes mellitus.[25] Human insulin and the other insulin analogues (aspart, lispro and detemir) had a similar effect at higher concentration (1.5-15 nM, ~250-2,500 µU/ml). Such an effect was related to activation of the IGF-1R and MAPK pathway.[25] However, no difference between glargine and the other insulin analogues was observed regarding growth stimulation of MCF10A cells showing low IGF-1R/IR ratio. While these results have to be reproduced, they reiterate the well known concept that certain cell lines abundant in IGF-1R may be more responsive to lower concentration of glargine as compared to human insulin and other insulin analogues. However, the fundamental question remains as how to translate these *in vitro* findings dealing from a single, homogeneous, malignant cell-line, into the complexity of the *in vivo* situation. Safety in animals is well proven; the question now is to prove safety in humans. Smith and Gale openly state that insulin glargine does not promote mutation of non-cancer cells into cancer cells, but they speculate that under extreme conditions (e.g. supraphysiological insulin concentrations) it might accelerate growth of pre-existing cancer cells.[5]

The facts and fallacies of the Diabetology Registry Studies

The story started with the German cohort study[1] from the Institute for Quality and Efficiency in Health Care (IQWiG), widely known to be overtly biased against insulin analogues, and a German health insurance (AOK) with an obvious conflict of interest. They reported an increased risk of malignancies with insulin glargine over a median period of 1.4 years only after applying a flawed statistical analysis to adjust for insulin dosage but notably with no body weight information. The authors basically ignored that the overall cancer risk was reduced for insulin glargine as indicated by the unadjusted hazard ratio (HR) of 0.85 (0.79-0.93). However, since the dose of glargine (IU/day) was nearly half of that of human insulin, the authors introduced a highly questionable statistical adjustment of the results per insulin dose without data on body weight, after which the cancer risk for glargine significantly increases vs. human (with 50 IU, HR 1.31, 95% CI 1.20-1.42).

The German study had serious methodological aberrations that were well described recently by two leading epidemiologists from the London School and Tropical Medicine who stated: "Their claim of an increased cancer risk with insulin glargine arises from an unconventional analysis that adjusted for insulin dosage. However, the methods used are fundamentally flawed, making the conclusions unsupportable".[16] Their valid arguments against the German analyses include the lack of allocation by

treatment group at study-entry when the observation was initiated and the flawed calculation of the insulin dose that was the mean estimated over time of follow-up but then was used for adjustments assuming that this was a baseline variable.

Another problem with the German study[1] is that the glargine group had an homogenous treatment (one injection a day of basal insulin) whereas the human insulin control group were on different insulin regimens, i.e. either insulin NPH once or twice daily, or insulin NPH combined with mealtime human regular insulin, or mealtime human regular insulin with no insulin NPH, or twice daily human pre-mixes. This treatment imbalance is the likely reason of major discrepancy between the mean daily insulin dose in the two groups (26 IU with glargine, 44 IU with human insulin) and also the fact that the two treatments are not bioequivalent due to the use of prandial insulin in the human insulin groups which was not present in the glargine group. With basal-bolus insulin regimen by definition the total daily insulin dose is higher than a basal insulin regimen only. So it is expected that dividing the lower "crude incidence" of cancer risk for the dose of glargine (lower than human insulin) the cancer risk apparently increases for glargine and decreases for human insulin ("dose-adjustment").

We further argue that any data on insulin doses without knowing the body weight are useless and most confusing especially when comparing once daily insulin glargine versus human insulin that included NPH and soluble insulin. Indeed, it is highly conceivable that a dose of 50 IU/day of insulin glargine may represent 0.5 IU/kg which is a relatively common dose for a 100 kg person. However, in Germany where the use of prandial insulin is fairly popular, patients using prandial soluble insulin plus NPH or even just 25 IU twice daily premixed human insulin, the same total dose of 50 IU/day may well represent 0.6 IU/kg in an 85 kg person which is not an unusual dose when using these insulin regimens. Thus, the groups very likely differ in weight which not only influences insulin dose and makes the dose-adjustment not acceptable, but also itself is a cancer risk since it is well known that obesity is a risk factor associated with cancer.[26] These confounding factors make any allegation of a dose relationship of insulin glargine with cancer totally invalid in the German paper,[1] as reaffirmed by Nagel et al.[27] and Simon[28] who offer further major criticisms to the dose-adjustment approach. A recent very defensive reply by Grouven et al.[29] did not answer the aforementioned multiple criticisms of the dose-adjustment process in the German paper.[1]

The comparison should have been done between regimens based on basal insulins, i.e. insulin glargine vs. insulin NPH–treated patients which would likely yield a similar daily insulin dose as several clinical studies have shown. This was correctly presented in the UK study[4] which in fact reported no cancer risk with glargine as compared to (basal) human insulin or any other insulins. The UK study was clearly a negative study regarding cancer risk and insulin glargine.

A final argument against the insulin glargine story as recognized even by the German authors,[1] was that the exposure to glargine in the study was quite short, which goes against any biological plausibility.

What the Hemkens' paper only proves is that the incidence of cancer in people initiating insulin (any type) is increased, ranging between 2.13-2.50/100 patient-years,[1] but multiple confounding variables like age, duration of diabetes, glucose control, insulin resistance and obesity could have accounted for the findings. Likely, this is not an effect of diabetes *per se*, but rather it is largely driven by obesity which itself may account for 25 to 30% of major cancers.[30] What the Hemkens' paper *does not prove*, is the causality of relationship between use of insulin (any type) and incidence of cancer.

The Swedish study[2] reports greater risk for breast cancer in a sub-population using glargine only vs. non-glargine users, but the risk disappears when glargine is used in combination with other insulins. Notably, the study does not indicate greater cancer risk with increasing glargine dose. The authors were cautious to comment the results since exposure to glargine was relatively short (two years), that the results observed are likely due to "random fluctuation" of risk for breast cancer, and are not attributable to glargine. Of interest, the study reported lower myocardial infarction and mortality in glargine users.

The Scottish study reported no overall differences in cancer risk for glargine and human insulin on a fixed cohort (36,254 people with type 1 and type 2 diabetes) and in an incident cohort analysis (12,852 people with type 2 diabetes).[3] Similar to the Swedish study, they report no difference in cancer risk between users of glargine (alone and in combination with other insulins) vs. non-glargine insulin users. However, the subgroup using glargine alone, which was very small (n= 447) had greater breast cancer risk vs. non-glargine insulin users. The fact that the risk was no longer seen in users of glargine combined with other insulin types, as compared to non-glargine users, lead the authors to propose "allocation bias" between groups, and not to blame glargine itself, as the likely explanation.

Thus, the comments of the Scottish study authors[3] are similar to the Swedish study[2] and were properly cautious in their conclusions which were almost ignored by the editorialists.[5] Curiously, the editorial[5] also ignored that overall cancer risk and mortality were the primary outcomes for all the studies and similar reduced mortality was found in the German and Swedish studies. In addition, both showed no overall increase in cancer risk as did the Scottish study which also demonstrated no increase in overall cancer risk. Unfortunately, much of the editorial emphasis was given to secondary analyses in sub-populations with insufficient data weakened by unknown confounding factors that generated inconsistent and confusing findings. Indeed, as noted above, the transparent Swedish and Scottish authors were the first to recognize the limitations of the registry data. They concluded: "Overall, insulin glargine use was not associated with an increased risk of all cancers or site-specific cancers in Scotland over a 4 year time frame"[3], and the Swedish: "No definitive conclusions regarding a possible causal relationship between insulin glargine use and the occurrence of malignancies can be drawn from the results of this study".[2]

As noted above, the UK study was negative for cancer risk associated to glargine use[4] and still is lumped together with the 4 studies alleging a relationship between glargine and cancer risk. Interestingly, despite the fact that the UK study was also "commissioned" by *Diabetologia* and EASD to explore the possibility of a relationship of insulin analogues and cancer based on the database from the THIN registry, the authors including the editor of *Diabetologia*, put all the major findings to the claim that metformin reduced the risk of cancer in diabetes. This was indeed an interesting finding worth reporting, but the original purpose to conduct the "commissioned study", in light of the German study, was curiously not even mentioned by the authors. As compared with metformin, the main finding of the UK study was greater cancer risk for patients on sulphonylureas and insulin in general but with no differences between glargine and the other types of insulins.[4] However, the insulin group had older age and longer known diabetes duration as compared to the metformin group.

Conceivably, the differences in cancer risk at baseline in the groups (being this a retrospective analysis) might well explain differences in cancer development at follow-up.[1-3] This is similar to the principle of "reverse causality" where it is not insulin use that causes cancer, but rather insulin resistance secondary to initial and/or latent cancer that eventually necessitates insulin use to control hyperglycemia.[16]

Taken together, these four studies[1-4] cannot have a valid unique interpretation and did not justify the alarming webcast conference as the data suffer from important methodological limitations such as lack of randomization, too short exposure to insulin glargine, absence of longitudinal follow-up, and lack of information on multiple confounding factors such as diabetes duration, body weight, degree of glucose control, socioeconomic status, etc. The issues raised by the Smith and Gale editorial[5] and the four *Diabetologia* papers,[1-4] have been defined as "excessive and non justified alarm" by Pocock and Smeeth[16] in the *Lancet* commentary described above. This was followed by a defensive letter by Gale[31] who recognized the major limitations of the German study,[1] but at the same time he expressed his opinion as an editor, saying that he felt forced to publish the German data and to commit additional investigation (Swedish, Scottish and UK registries) because "incomplete information is better than no information".

We respect the opinion of the editor of *Diabetologia*, but as we have already commented about the non existence of link between use of glargine and cancer based on the *Diabetologia* papers, we do not believe that such unusual decision was justified.[27] We disagree with the journal and EASD's decision to "commission" further international registry studies to prove or disprove a flawed German paper. As pointed out in the editorial,[5] 3 reviewers rejected and 3 reviewers felt that the data needed to be reported. Perhaps, the editor of *Diabetologia* should have listened to the three reviewers who recommended rejection of the biased German study from the IQWiG authors who did not even acknowledge their obvious conflict of interest in the publication and still have in their website home page the unsubstantiated statement: "Insulin analogue glargine possibly increases cancer risk"!

This German manuscript should have been rejected, but if the decision was to publish it, this should have occurred along with an independent editorial by an epidemiologist and/or oncologist. The paper could have been just another weak epidemiologic publication and investigators around the world would have had the opportunity to analyze the data and decide whether or not to further explore the issue with properly designed studies. However, "commissioning" international registry studies was probably beyond the call of duty for a journal or for EASD, especially without informing regulatory agencies if indeed they had such a major safety concern.

Finally, in the same issue of *Diabetologia*, the results of the longest randomized trial comparing human insulin NPH and glargine in type 2 diabetes was published, reporting no difference in cancer risk.[32] The strength of the randomized trial is that it minimized the effects of measured and non-measured potential confounding variables except for the use of glargine. The study provided a mean cumulative exposure of more than 4 years (2,144 and 2,095 patient-years exposure in the insulin glargine and the NPH insulin groups; respectively). The limitation is the relatively small sample size (~1,000 subjects) but nonetheless no clear signal was detected to support the theoretical concept that insulin glargine may accelerate tumor growth or uncover preexistent silent tumors. There was no excess risk for all neoplasms or breast cancer with insulin glargine and neither was there an increased risk of diabetic retinopathy observed.[33] The overall number of patients with neoplasms was 57 patients (11.1%) in the insulin glargine group vs. 62 patients (12.3%) in the NPH insulin group, with a relative risk (RR) for insulin glargine of 0.90 (95% CI 0.64-1.26). The rate was also similar in both treatment groups for malignant neoplasms reported as serious adverse events: 20 patients (3.9%) in the insulin glargine group vs. 31 patients (6.2%) in the NPH insulin group, with an RR for insulin glargine of 0.63 (95% CI 0.36-1.09).

In a recent publication,[34] cancer risk was analyzed and reported as no different from the comparator insulin in 31 randomized trials previously conducted by sanofi-aventis that included 10,880 patients. The strength of this report is the high number of subjects, but the obvious limitation is the short period of observation (6-12 months).

ORIGIN[35] is a randomized trial with a large population and a long period of observation assessing the impact of early insulin glargine replacement on cardiovascular outcomes. By 2011 the ORIGIN trial will be finished, and data on cancer risk in a population of 12612 patients with type 2 diabetes will also be reported. However, since the glargine arm has no insulin comparator, the results will need to be interpreted with caution. If there is increased cancer risk in the glargine arm, this could be part of the theoretical insulin risk in general, and not necessarily specific for glargine itself. Thus, a positive outcome (more cancer in glargine arm) will be difficult to interpret. A negative outcome (no risk vs. standard treatment) will be very reassuring and could eliminate concerns regarding insulin glargine (and insulin in general) and long-term cancer risk. Of note, the Data Safety Monitoring Com-
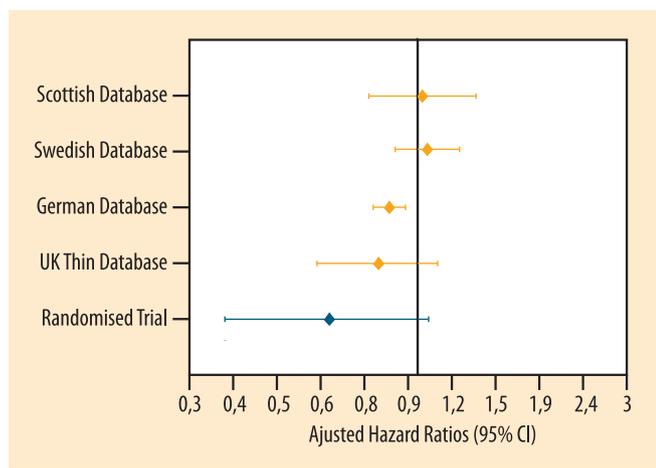
Figure 1. Risk of malignancy for insulin glargine compared with other insulins. Modified from Pocock and Smeeth[16]

mittee that closely supervises the safety of the trial issued a reassuring press release on August 5, 2009 that stated: "In the ORIGIN trial, participants have been followed for an average of 4 years to date for a total exposure of over 50,000 person years. Data are collected related to all major serious health outcomes, including cancers. Accumulating data are reviewed regularly by an Independent Data Monitoring Committee charged with auditing the safety of the trial. In light of the questions raised by the recent publications, this committee of experts has recently reviewed data related to cancers in both treatment groups and has concluded that there is no cause for concern and no reason to alter the design of the study for safety reasons".

At the recent EASD 2009 meeting in Vienna, the issue of cancer and diabetes (as well as pharmacologic diabetes treatments) was discussed in a dedicated symposium. The well known association between cancer and diabetes primarily driven by obesity was reaffirmed, along with the observation that treatment with sulphonylureas and/or insulin is associated with greater cancer risk as compared to metformin. Perhaps this observation may be related to some specific metformin effects on MAPK activity or because people on metformin tend to be healthier with no renal compromise and earlier type 2 diabetes. Likely, this is explained by the principle of reversed causality well known to experienced epidemiologists.[16] The basic mechanisms by which insulin possibly promotes cell growth, especially in cancer cells was reviewed, but at the same time it was quite clear that insulin treatment of diabetes is highly unlikely to stimulate such a theoretical pathways because of the difference between "therapeutic" circulating insulin *in vivo* vs. the elevated insulin concentrations used of *in vitro* experiments. Safety of all insulin analogues was supported in the symposium, and the criticism to the *Diabetologia* papers, especially the German study,[1] reiterated. Surprisingly, despite the overwhelming criticism of the *Diabetologia* papers superbly discussed by Dr. Jay Skyler, still Dr. Edwin Gale in his concluding remarks gave his personal interpretation of the German, Swedish, Scottish studies,[1-3] commenting for a positive as-

sociation between use of glargine and breast cancer risk in these three studies. But this appears as an isolated position in the context of the wide, multi-voice summer debate quite critical on the *Diabetologia* papers,[1-4] especially the German study.[1]

Lesson for diabetologists

The *Diabetologia* story about a possible association between insulin glargine and cancer risk has taught us important lessons and brought to light some important teaching points.

First, this debate has reminded us that cancer is unfortunately more frequent in diabetes, especially in obese people. It is conceivable that with longer survival in diabetes, this risk will increase in future years. Although hyperinsulinemia and insulin resistance related to obesity has been suggested as a possible causative factor in cancer, hyperinsulinemia is merely the marker of insulin resistance, and not necessarily insulin itself might be involved. Clearly, more basic and clinical research will be needed to understand this relationship and to develop strategies for early detection and ideally prevention of cancer in diabetes. This is perhaps the main positive lesson that this debate generated.

Second, the debate has re-opened the discussion about safety of insulin in general vs. insulin sensitizers, and insulin analogues in particular. Of course it is always most appropriate to discuss safety of any drug, and in particular modified insulins, but only if there are studies with valid data without methodological flaws. Unfortunately, the German study[1] which generated the summer debate, does not belong to such a category. Hopefully this debate has stimulated investigators to embark in new registry prospective epidemiological studies with rigorous designs and careful controlled collection of data and of any potential confounders to help bring to light such a controversial issue that remains unsubstantiated today. This is another positive lesson learned. For the time being, we should better look at the hazard ratios calculated by Pocock and Smeeth which appear reassuring (figure 1).[16]

Third, only a few months after the debate emerged, we are now in the position to better understand the serious limitations and weaknesses of the original German paper in *Diabetologia*,[1] thanks to the excellent comments and critiques published thereafter questioning the validity of the *Diabetologia* story.[15-17]

The final message is for clinicians. We understand that insulin glargine has theoretical concerns regarding the IGF-1 binding in some *in vitro* malignant cell lines at high insulin concentrations but with reassuring fast dissociation rates. Moreover, the concentrations realized in plasma in subjects with type 2 diabetes are much lower than those demonstrated in the experimental studies, and furthermore at least 50% of glargine circulates as metabolites M1 and M2 which do not differ from human insulin in the binding affinity to IGF-1R. This solid scientific information, not the sensationalistic emotions or the fears, or political agendas, should guide us to critically conclude that we need to maintain objective confidence in the safety and efficacy of insulin analogues in general, and glargine in particular for our patients. Presence of or risk for cancer should not detract from optimal control of diabetes not only for the

long-term goals to reduce diabetes complications, but also for the everyday quality of life. ■

Declaration of potential conflicts of interest

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