Article
Use of insulin glargine and cancer incidence in Scotland: A study from the Scottish Diabetes Research Network Epidemiology Group

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Abstract

Aims/hypothesis: The aim of the present study was to examine whether patients with diabetes in Scotland using insulin glargine have a greater cancer risk than patients using other types of insulin.

Methods: We used a nationwide diabetes clinical database that covers the majority of the Scottish population with diagnosed diabetes, and examined patients with diabetes who were exposed to any insulin therapy between 1 January 2002 and 31 December 2005. Among these we defined a fixed cohort based on exposure during a 4 month period in 2003 (n=36254, in whom 715 cases of cancer occurred) and a cohort of new insulin users across the period (n=12852 in whom 381 cancers occurred). Records from these cohorts were linked to cancer registry data up to the end of 2005. We used Cox proportional hazards models for survival analyses.

Results: Those receiving any insulin glargine (n= 3959) had the same incidence rate for all cancers as those not receiving insulin glargine (HR 1.02, 95% CI 0.77–1.36, p=0.9 in the fixed cohort) The subset of patients using insulin glargine alone (n=447) had a significantly higher incidence of all cancers than those using other insulins only (n=32295) (HR 1.55, 95% CI 1.01–2.37, p=0.045), and those using insulin glargine with other insulins (n=3512) had a slightly lower incidence (HR 0.81, 95% CI 0.55–1.18, p=0.26). There were important differences in baseline characteristics between these three groups, although the risk ratios were broadly unaltered on adjustment for these. Overall, there was no increase in breast cancer rates associated with insulin glargine use (HR 1.49, 95% CI 0.79–2.83). Among type 2 diabetic incident insulin users, no significant difference between the three groups was observed with respect to all cancer or breast cancer. All the above HRs are adjusted for age, calendar time prior cancer and type of diabetes, as appropriate, and are stratified according to sex.

Conclusions/interpretation: 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. Given the overall data, we consider the excess of cases of all cancers and breast cancer in the subgroup of insulin glargine only users to more likely reflect allocation bias rather than an effect of insulin glargine itself.

ISD, Information and Services Division
NICE, National Institute for Clinical Excellence
SCI-DC, Scottish Care Information-Diabetes Collaboration
SDRN, Scottish Diabetes Research Network

Introduction

Insulin glargine (A21Gly,B31Arg,B32Arg human insulin) is a long-acting insulin analogue that is used as basal insulin in people with diabetes and is given once daily. It is produced by recombinant DNA technology and differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the B chain. This renders it less soluble at physiological pH so that it has a prolonged action such that serum concentrations are relatively constant over a 24 h period [1].

Insulin glargine was first recommended for restricted use in Scotland in October 2002 by the regulatory body, the Scottish Medicines Consortium [2]. These guidelines recommended that insulin glargine be used for patients who had problems with nocturnal or recurrent hypoglycaemia or for once daily use in patients requiring carer administration of their insulin. Routine use in patients with type 2 diabetes was not recommended. This advice was reiterated in 2008. In England and Wales, the National Institute for Clinical Excellence (NICE) recommended insulin glargine as a treatment option for type 1 diabetes and recommended restricted use in type 2 diabetes, as in Scotland, but with the added recommendation that it could be used in type 2 diabetic patients who would otherwise need twice daily basal insulin injections in combination with oral glucose-lowering drugs [3]. These recommendations were updated by The National Collaborating Centre for Chronic Conditions, commissioned by NICE, in 2008, with the main change being a widening of the type 2 recommendations to allow consideration of insulin glargine use in those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering drugs [4]. A recent implementation report from NICE illustrates an annual increase in insulin glargine use since 2002, such that an estimated 42.6% of patients with type 1 diabetes and 4.4% with type 2 diabetes of patients received a prescription for insulin glargine in the 12 months up to 31 March 2008 [5].

Since modifications to the structure of the insulin molecule can alter binding to the insulin and IGF receptors, this provides a theoretical basis for concern about potential carcinogenicity of insulin analogues. Systematic reviews of the effects of insulin analogues on glycaemic outcomes have identified the absence of trials of sufficient duration to evaluate cancer rates [6] and have concluded that more studies are needed to better understand the effect of insulin analogues on long-term diabetes complications and the safety of these agents [7].

Following the concerns raised by the paper by Hemkens et al [8] in this issue of Diabetologia we were asked by the EASD to examine whether there was any evidence of an association between cancer incidence and insulin glargine use in Scotland. The Editor was aware that the Scottish Diabetes Research Network (SDRN) Epidemiology Group were preparing Scottish-wide data on diabetes care and outcomes for research purposes including pharmacovigilance. Scotland has a national register of patients with diabetes, which includes prescribing data and has excellent capacity for anonymised linkage to routine health data, including cancer registry and mortality data [9]. The first linkage was recently carried out by the Information and Services Division (ISD) of NHS National Services Scotland in a project funded by the Scottish Government. In view of the lack of good quality evidence from randomised controlled trials on this issue, we considered that such an observational analysis was warranted.

Methods

Overview

We used the Scottish Care Information-Diabetes Collaboration (SCI-DC), a clinical diabetes database that covers the majority of the Scottish population with diagnosed diabetes, to define a cohort of patients with diabetes that were exposed to any insulin therapy from 1 January 2002 (the year of introduction of insulin glargine) up until 31 December 2005. Data for all patients receiving an insulin prescription during this period were extracted from the SCI-DC database and linked to cancer registry data that were available up to

the end of 2005. The incidence of all cancers and cancers at specific sites (breast, colon, prostate, pancreas, lung) was compared between those who did and did not receive insulin glargine.

Data used

SCI-DC Across Scotland, almost all adult patients with a diagnosis of type 1 or type 2 diabetes are registered on the SCI-DC database. The SCI-DC database has been available Scotland-wide since 2000. The estimated coverage of the total adult diabetic population is approximately 99%. This database exists at Health Board level for all Health Boards in Scotland, and each patient record contains a unique identifier, the Community Health Index number. The database captures key diabetes-related data items from hospital clinics, most of which use SCI-DC as their main clinical record system for diabetes. Some hospital clinics use other systems, but these update key items in the SCI-DC database. The database also receives updates of certain data fields nightly from primary healthcare systems, including prescriptions that have been issued. The prescribing data available for this analysis were restricted to the name of the drug prescribed and the date of prescription. Data on dose and directions for use are not yet available. In addition to data from the first date of a patient record into the database onwards, it also contains extensive retrospective data uploaded from other electronic healthcare records at the initial entry of a patient onto the database. The fields extracted from SCI-DC for patients included in this analysis included all prescribed diabetes-related drugs (British National Formulary section 6.1.1 and 6.1.2, i.e. all insulin, biguanides, sulfonylureas and other oral glucose-lowering drugs), age, sex, BMI, age at diagnosis, type of diabetes as designated by clinician, smoking history and Scottish Index of Multiple Deprivation (SIMD) score derived from postcode. The SIMD score is a geographic indicator of deprivation that is based on 37 indicators across the domains of current income, employment, health, education, skills and training, housing, geographic access and crime [10]. In the present study, quintiles of the SIMD score have been used, with the lower quintile representing the most deprived of our cohort. As of 2009, 219,965 live patients with diabetes in Scotland are registered on this database. For the purpose of these analyses, type of diabetes was categorised as definite type 1 if age at diagnosis or use of first insulin therapy was below 30 years, as definite type 2 if age at diagnosis and use of first drug treatment were 35 years or above, and indeterminate if age at diagnosis was 30-35 years.

Cancer Register (Scottish Morbidity Record) The Scottish Cancer Registry was set up in 1958 and has been managed by the Information Services Division of NHS National Services Scotland since 1997. The registry receives notification of cancer from hospital systems, including discharges, radiotherapy, oncology, haematology and pathology records, prospective audit datasets, deaths from the General Register Office for Scotland, and paper records from private hospitals. Other staff verify the notification, validate the information already held and abstract additional information from hospital medical records and local hospital systems before the data are finalised. Data quality is monitored using routine indicators, computer validation, ad hoc studies of data accuracy and completeness of ascertainment, and through data exchange with specialist registries. A recent study estimated that breast cancer ascertainment exceeds 98% [11]. Of the data items reported, we used the following in this analysis: date of diagnosis, site of tumour and mortality. The International Classification of Diseases, 9th and 10th revisions (ICD-9 and -10), were used to code the site of previous and incident cancers. For this analysis, all non-melanoma skin cancer tumours were captured; all C codes in ICD-10 codes except non-melanoma skin cancer C44. Incident prostate cancer was defined as ICD-10 code C61 and subcodes; colorectal cancer was defined as ICD-10 codes C18, C19 and C20 and their subcodes; pancreatic cancer was defined as ICD-10 code C25 and its subcodes. Breast cancer was defined as ICD-10 code C50, and lung cancer was defined as ICD-10 codes C33, C34 and their subcodes. There is typically a lag time of about 2-3 years in availability of validated data for research purposes, so data were only available up to the end of 2005. The completeness and accuracy of the Cancer Register data have been extensively validated: recent estimates for accuracy and sensitivity for breast cancer are 95.7% and 97.8%, respectively [12].

Deaths (General Registrar's Office for Scotland-deaths) All deaths that occur in Scotland are captured into the death register of the General Registrar's Office for Scotland (GROS), on completion of a death certificate. For each death, the GROS assigns a single code for the underlying cause of death and, depending

on what was written on the death certificate, may assign several other codes for other factors that contributed to death. The ICD-10 coding system is used for data from 2000 onwards. For this analysis, we extracted all death records when there was any mention of cancer in the fields concerning underlying cause of death and contributory cause of death.

Governance and ethics
As part of the core programme of work of the SDRN Epidemiology Group, approval was obtained for anonymised linkage of SCI-DC data to specified, centrally held health data sets. Approval was obtained from the Scotland A Research Ethics Committee, Caldicott Guardian for all 14 Health Boards and the ISD Privacy Advisory Committee including linkage to cancer registration data held at ISD.

Linkage methods
Linkage is carried out by ISD, and researchers only have access to anonymised data. Two approaches to linkage were used: exact linkage and probabilistic linkage. Exact linkage was performed using the Community Health Index number, which is noted on all SCI-DC records and most cancer registry records but not GROS death records. When the record did not have a Community Health Index number, probabilistic linkage was performed using a selection of identifiers common across datasets. In Scotland, both the false-positive rate (the proportion of pairs that are incorrectly linked) and the false-negative rate (the proportion of pairs that the system fails to link) for this approach is less than 3% [13].

Statistical methods
There are several possible ways to test the hypothesis of an association between insulin glargine prescription and cancer incidence in these observational data, each of which can be subject to different biases. Thus, we analysed the data in three ways, each of which potentially yields different information. Our approach did not assume any induction time and assumed that the effects, if any, of exposure would continue beyond the exposure period. Associations were declared as statistically significant if p value was <0.05.
All analyses were performed using STATA/MP version 10.0 for Unix (StataCorp, College Station, TX, USA); using the Cox, stset and stsplit procedures for survival analysis.

Fixed cohort analysis In this analysis we chose a 4 month period between 1 July 2003 and 31 October 2003 during which insulin glargine prescription was widespread and reasonable follow-up time remained. All patients receiving any type of insulin at any time over these 4 months were entered into the analysis. Patients were defined as being exposed to insulin glargine or not during this 4 month period and were then followed-up without regard to any subsequent change in exposure status (akin to an intention-to-treat analysis). By ignoring transition to other exposures, this can minimise possible reverse causation bias in some circumstances but can bias towards the null. We used Cox proportional hazards models to examine our primary hypothesis of whether the incidence of any cancer (and cancer at specific sites) varied by exposure to insulin glargine. As the analysis by Hemkens et al. [8] was restricted to insulin glargine only users, we also examined effects in insulin glargine only users and non-glargine plus glargine insulin users separately. We used attained age as the timescale of the model, and the entry time was 31 October 2003. The follow-up for each person was continued to the first of the following: date of first cancer registration or cancer death, date of death from any cause, or 31 December 2005. For analysis of specific types of cancer, the right censoring event date was the date of the first cancer of that type. For all analyses, confirmation that the patient was still under observation within Scotland was confirmed by the availability of other data items in the database throughout the follow-up period (HbA$_{1c}$, BMI, BP and prescription records). We included type of diabetes, calendar year and prior cancer as covariates (we also confirmed that omitting those with prior cancer gave similar results). We then extended these models by including covariates that differed substantially between the exposure categories at baseline, including BMI, systolic and diastolic BP, smoking, glycaemic control, other concurrent diabetes medications and socioeconomic status. We used models that adjusted for type of diabetes and checked the effects in models for each type of diabetes separately. For all models, we confirmed that the assumption of proportional hazards was not violated by testing for a non-zero slope in a regression of scaled Schoenfeld residuals against time; a non-zero slope is an indication of a violation of the proportional hazards assumption. Individual tests by covariate were

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performed, as well as a global test. As there was some departure from proportionality of hazards by sex, the models were stratified by sex.

Incident insulin cohort It could be argued that a caveat of the fixed cohort approach above, especially in type 2 diabetic patients, is that observed differences between exposure categories in the fixed cohort could reflect differences between groups in the stage of progression of their diabetes and prior treatments, for which we have incomplete information. Therefore, we also undertook an analysis among type 2 diabetes patients that was restricted to those who starting insulin therapy for the first time during follow-up from 1 January 2002 (the year insulin glargine was first prescribed) to the end of 2005. In this analysis, exposure was classified based on insulin treatment in the first 4 months of use. The entry time to the cancer incidence models was the end of the 4 month period (to ensure that the period during which exposure is defined is separate from the observation period). The follow-up for each person was continued to the first of the following: date of first cancer or cancer death, date of death from any cause, or 31 December 2005. The timescale of the model was attained age. The same covariate adjustments were made as for the fixed cohort analysis.

Analysis with exposure classification across the follow-up period The fixed cohort analysis described above is an intention-to-treat analysis and ignores the reality that patients transition between exposure categories. Therefore, we also categorised patients on the basis of their exposure across their entire follow-up period. In this analysis, those on insulin glargine only never received insulin glargine concomitantly with any other type of insulin, those on non-glargine insulin only never had any insulin glargine at any time during follow-up, and those on non-glargine plus glargine insulin were using insulin glargine concomitantly with another type of insulin for at least some of the time. This analysis uses the data available more completely and defines actual exposure more accurately but at the cost of being more prone to reverse causation bias. As before, Cox proportional hazards models were used, with entry time being date of first insulin use.

Results
All the HRs reported in the text below are adjusted for age (since age was the timescale of the model), calendar time, prior cancer and type of diabetes, as appropriate, and are stratified by sex, unless stated otherwise.

Fixed cohort
Baseline characteristics A total of 36,254 people were receiving any type of insulin therapy during the 4 month exposure evaluation period (July to October 2003). There were 3959 people on insulin glargine; the majority (n=3512) were receiving insulin glargine with another insulin and the remaining 447 patients were receiving insulin glargine as their sole insulin. Table 1 shows the baseline characteristics of those included in the fixed cohort analysis according to insulin glargine exposure. There were significant and large differences in baseline characteristics across the three exposure groups especially, of course, with respect to the prevalence of type 1 diabetes. When these comparisons were restricted to the 19,899 insulin users with definite type 2 diabetes (Table 2), compared with users of non-glargine insulin alone, those on non-glargine plus glargine insulin were younger, and values adjusted for age and sex indicated that they had a lower BMI and less CVD, but worse glycaemic control and a longer duration of diabetes. For diabetes duration, the non-glargine plus glargine insulin group had a lower prevalence of diabetes duration at least 5 years, but, adjusted for age, they had a higher prevalence (OR 1.38, 95% CI 1.25-1.52, p<0.0001). They also had a lower prevalence of ever smoking and were less likely to be on any concomitant oral therapy at baseline. Compared with users of non-glargine insulin alone, insulin glargine only users were older, had similar BMI but higher diastolic BP, worse glycaemic control but shorter duration of diabetes, and were much more likely to be on concomitant oral therapy at baseline (Table 2).

All cancers A total of 715 incident cancers occurred in this cohort during follow-up in 36,254 subjects (1.97%, 0.95 events per 100 person-years at risk). Among those receiving any insulin glargine (regardless of whether they received any other type of insulin), 1.29% had a cancer compared with 2.06% of those on non-glargine insulin alone. There was no overall difference in all cancer rates in those receiving vs those not receiving insulin glargine (HR 1.02, 95% CI 0.77–1.36, p=0.9). For breast cancer, there was no significant

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difference between insulin glargine users vs users of non-glargine insulin alone (HR 1.49, 95% CI 0.79–2.83, p=0.22). None of the other site-specific cancer rates were associated with insulin glargine use.

Table 3 shows the shows the number of cancers that occurred, together with their cumulative incidence (%), plus the age- and sex-adjusted HR for the fixed cohort for the three insulin exposure categories. Compared with those using non-glargine insulin alone, those who were using non-glargine plus glargine insulin had a slightly, but non-significantly, lower rate of cancer, but those using insulin glargine alone (all of whom would have type 2 diabetes) had a higher rate of cancer, which was of borderline statistical significance. Adjusting for further covariates in those on insulin glargine only made very little difference to the HR (change from 1.55 to 1.73, most of which was due to slight differences in the numbers available for the models; the HR for model 1 restricted to those with complete data for model 4 was 1.63, 95% CI 0.95–2.78, p=0.074). Restricting the model to those without any prior cancer only slightly altered the HRs for those on non-glargine plus glargine insulin (0.78, 95% CI 0.53–1.16) and those on insulin glargine alone (1.64, 95% CI 1.05–2.54). In another model we examined the same associations conditional upon survival for the first year (to examine whether all the effects are early after treatment initiation or conversely affected by a lag time) but this made no difference (data not shown).

When the analyses were restricted to the 19899 definite type 2 diabetic patients there was no difference in cancer rates between insulin glargine users (irrespective of whether they were using any other type of insulin) vs users of non-glargine insulin (HR 1.08, 95% CI 0.78–1.49, p=0.64). When the three exposure categories were examined, a pattern similar to that in the cohort as a whole was seen, with higher rates in those using insulin glargine alone (HR 1.58, 95% CI 1.03–2.42, p=0.037) compared with those using non-glargine insulin alone. There was no significant effect of baseline exposure to any of the oral diabetes drugs on cancer rate when evaluated separately, and adjusting for these variables made no difference to the effects of insulin glargine. When the analyses were restricted to type 1 diabetic patients, the HR for non-glargine plus glargine insulin users was closer to, and not statistically significantly different from, unity (HR 1.02, 95% CI 0.50–2.09, p=0.9).

Site-specific cancers Table 4 shows the HRs for site-specific cancer associated with exposure to insulin glargine and the effect of adjusting for covariates in the fixed cohort. The number of cancers by site is so small that power is low. However, 92 cases of breast cancer occurred in the women, six of which were in insulin glargine only users. Overall, insulin glargine use was not associated with an increased risk of breast cancer (HR 1.49, 95% CI 0.79–2.83, p=0.2), but as shown in Table 4, the pattern seen for all cancers combined was replicated: there was a significantly higher rate in insulin glargine only users compared with users of non-glargine insulin alone. Adjustment for covariates generally made little difference. When restricted to type 2 diabetes, the same pattern was observed. For lung and colon cancer, a similar pattern of HRs above 1 in insulin glargine only users and HRs below 1 in non-glargine plus glargine insulin users was observed, but none of the HRs was statistically significant.

Incident cohort analysis:
There were 12,852 definite type 2 diabetic patients who received insulin for the first time between 1 January 2002 and 31 December 2005, 12, 845 of which had follow-up data Electronic supplementary material (ESM) Table 1 shows the baseline characteristics in the three exposure categories. The characteristics of these incident users differ from those of the fixed cohort, and the between-group differences in baseline characteristics are different to those seen in the fixed cohort. Compared with those on non-glargine insulin only, insulin glargine only users were, like those in the fixed cohort, older and had a higher BP but, unlike those in the fixed cohort, they had a slightly longer duration of diabetes, similar glycaemic control and less CVD.

A total of 378 cancers occurred in this incident cohort (Table 5). Overall, the incidence of cancer was not different between insulin glargine users (regardless of what other type of insulin was used by them) vs users of non-glargine insulin alone (HR 0.93, 95% CI 0.70–1.25, p=0.64). Unlike in the fixed cohort analysis, the incidence rate in insulin glargine only users was not higher than in users of non-glargine insulin alone (HR

0.87, 95% CI 0.63–1.21, p=0.41), and this was also the case when adjustment for covariates was made (Table 5). Restricting the analysis to only include patients with type 2 diabetes did not alter this pattern. For site-specific cancers, the numbers are very small, but show no significant difference in breast cancer rates, although the HR is 1.47 for insulin glargine only users vs non-glargine insulin only users. It should be noted that the number of insulin glargine only users in this analysis is higher than that in the fixed cohort, which is expected given that insulin glargine use has increased since its introduction.

Analysis summarising exposure across the entire follow-up
In the analysis in which we summarised exposure across the entire follow-up period overall (see ESM), We included 49197 patients who received a prescription for insulin therapy at some point between 1 January 2002 and 31 December 2005, in whom 1523 cancers occurred (see ESM Tables 2–4). Overall among those receiving any insulin glargine (regardless of what other insulin was used by them), there was a significantly lower rate of total cancers (HR 0.66, 95% CI 0.57–0.76, p<0.0001) when adjustments were made for sex, prior cancer, calendar period and type of diabetes. When we further examined whether the years of cumulative exposure to insulin glargine was associated with cancer rate, this lower HR was lowest in those with at least 2 years of exposure (HR 0.60, 95% CI 0.51–0.70). Those on non-glargine plus glargine insulin had a significantly lower incidence rate of cancers than those on non-glargine insulin only (HR 0.53, 95% CI 0.45– 0.63), and those on insulin glargine alone had a significantly higher incidence rate of cancer than those on non-glargine insulin only (HR 1.28, 95% CI 1.04–1.59). The same pattern was seen when those with prior cancer were excluded and when the analysis was restricted to type 2 diabetes. For breast cancer, there was a slightly higher incidence among those on insulin glargine alone compared with those on non-glargine insulin (HR 1.33, 95% CI 0.69–2.56); this difference was non-significant.

Discussion
In this analysis of Scotland-wide data, we found no difference in the rate of total cancers or site-specific cancers between those exposed to insulin glargine therapy vs those not exposed to insulin glargine therapy. Cancer rates were not positively associated with cumulative years of exposure to insulin glargine therapy. Thus, our primary hypothesis that exposure to insulin glargine was associated with an adverse effect on total cancer rates or site-specific cancer was refuted, and these data are reassuring in this regard.

When we subdivided our exposure categories into those who, during the observation period, used insulin glargine as their only insulin vs those who used insulin glargine with other insulins or used non-glargine insulin alone, a different pattern was seen. We subdivided the categories in this way because the analysis by Hemkens et al [8], which reports a concern regarding the carcinogenicity of insulin glargine, was restricted to users of insulin glargine who were not using any other insulins concurrently. We wanted to understand whether restricting the analysis to such a subgroup could lead to a biased estimate of any overall relationship between cancer and insulin glargine, not because we were hypothesising differential effects of insulin glargine that are dependent on concomitant insulin. In this analysis, those using insulin glargine as their only insulin were found to have a higher cancer rate for all cancers and a higher rate for breast cancer specifically, compared with those using non-glargine plus glargine insulin or those using non-glargine insulin alone. This was demonstrated in the fixed cohort users but not in the incident insulin users. A similar pattern was found for lung and colorectal cancer, with HRs above 1 observed in insulin glargine only users and HRs below 1 seen in those using non-glargine plus glargine insulin. This lower rate among the combined users was more extreme in the analysis in which exposure was summarised across the entire follow-up period.

As there are few events in these subgroup analyses the observed association may reflect chance. The p values are based on large sample approximations, and these are less valid when events are sparse. They, nonetheless, warrant discussion and interpretation in view of the paper by Hemkens et al. [8]. Our analysis of baseline characteristics shows that insulin glargine only users differ substantially as a group from those using non-glargine plus glargine insulin or those using non-glargine insulin alone. Even restricting comparisons to those with type 2 diabetes, they are clearly an older group with worse glycaemic control, and were on more intensive oral therapy. Adjusting for these potential confounders did little to explain, in a

statistical sense, the higher observed cancer rate for this group. It should be noted that for past and current oral drugs these adjustments do not fully capture all retrospective exposure with precise quantification, as this is not possible with the dataset. In our view, the potential for allocation bias (otherwise termed confounding by indication) here is very high, i.e. that those generally less healthy patients were more likely to have been prescribed this simple-to-use once daily insulin glargine regimen than other insulins that require more frequent injections or have a greater risk of nocturnal hypoglycaemia. Less healthy patients might also be less likely to be prescribed additional non-glargine insulin on top of insulin glargine. Therefore, we cannot exclude allocation bias as the most likely reason for observing this higher cancer rate in insulin glargine only users and, similarly, the slightly lower rate in those using non-glargine plus glargine insulin. Furthermore, we cannot fully disentangle any potential effect of insulin glargine from the other drugs that are more commonly used in this group. It would only be possible to conclude that the rate differences between subgroups were likely to be real if the baseline characteristics had been similar between exposure groups. We performed an analysis of incident users of insulin in an attempt to improve the comparability of the three exposure groups, at least in terms of what might broadly be termed stage of progression of diabetes (though, of course, there remains variability in the timing of initiation of insulin therapy [14]). That these subgroup effects were less apparent in this analysis supports our interpretation that the effects are not likely to be causal. Importantly, we would expect that if exposure to insulin glargine were harmful, this effect would be seen regardless of use of other insulin. Instead, we found that there was no increased risk associated with insulin glargine and, indeed, in the analysis that summarises exposure across the entire follow-up period, the opposite was observed. The short period of time between exposure and events in these analyses also argues strongly against a causal relationship.

Consistent with allocation bias, as described in the introduction, the clinical guidelines operant in Scotland during this period have encouraged limiting insulin glargine use in type 2 diabetes to those requiring assistance with insulin or with problems of nocturnal hypoglycaemia. Whilst the data show that clinicians in Scotland are actually prescribing insulin glargine to a much wider range of patients than this it is also clear that such patients will be over-represented in the insulin glargine only group.

Another limitation of our analysis is that we do not yet have data available on drug dose; thus, we were not able to test the hypothesis that higher doses of any insulin are associated with higher cancer rates or whether the slope of such a relationship varies by insulin type. A third important methodological aspect of this observational analysis is that the use of other drugs varies substantially by insulin glargine exposure status. As shown, those using insulin glargine without any other insulin have, not surprisingly, a much higher rate of current use of oral hypoglycaemics. Once again, adjusting for use of these drugs had little effect on the risk ratios observed for insulin glargine use, but the possibility of residual confounding through other drug effects remains, and we have not fully captured cumulative exposure in the past to other drugs, which may be relevant [15].

One of the limitations of our analysis is that we only had cancer registry data through to the end of 2005, with first insulin glargine exposure occurring in 2002. Therefore, follow-up time was short for evaluating cancer effects. Another aspect is that our linkage for this current study does not contain people with diabetes who are not on any insulin. A fuller analysis of cancer rates across all diabetic patients and their therapeutic subgroups compared with the general population is what is warranted, and this will now be carried out.

So where does this leave the concern about the mitogenicity of insulin glargine? The concern arises from the fact that modifications to the structure of the insulin molecule can alter binding to the insulin IGF receptors, theoretically altering carcinogenicity. Data from cell and animal model studies are conflicting [16-21]. In contrast to these numerous studies in cell and animal models, powerful studies of cancer effects in humans using insulin glargine are lacking. Systematic reviews of the effects of insulin analogues on glycaemic outcomes have pointed to a lack of trials of sufficient duration to evaluate cancer rates (or, indeed, even beneficial effects on hard clinical outcomes of complications rates) [6], and have concluded that more studies are needed to better understand the effect of insulin analogues on long-term diabetes complications and the safety of these agents [7]. As this analysis of our large dataset also highlights, observational analysis

of drug effects is not a substitute for randomised trials because, fundamentally, one can never completely rule out allocation bias except by random allocation. Observational analyses can raise hypotheses about harm and in many cases they can provide reassurance about harm. Whilst our data do not provide complete reassurance about cancer rates and insulin glargine use, neither do they point to unequivocal evidence of harm. Had we found evidence of increased cancer rates among all categories of insulin glargine use we would have been much more concerned, and, conversely, lower rates among all categories of use would have been more reassuring. Nonetheless, what this emphasises is that continuing controversy over potential carcinogenic concerns can probably only be addressed by randomised trial data. Where there is equipoise about beneficial effects of new drugs, as the systematic reviews of the effectiveness of insulin analogues demonstrate, then clear demonstration of lack of harm should become even more critical to clinical decision making. In the meantime, clinicians should inform patients being prescribed insulin glargine about the relative lack of safety information for newer insulins when considering whether potential benefits with regard to ease of administration or management of nocturnal hypoglycaemia are worthwhile.

Roles of SDRN Epidemiology Group members in this study
Study design and data analysis specification: H. Colhoun, S. Livingstone, S. Wild, R. Lindsay, K. Greig, A. Morris.
Data analysis code: S. Livingstone.
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Table 1 Baseline characteristics of the fixed cohort by insulin glargine exposure group (*n*=36,254)

Characteristic		Non-glargine insulin	Non-glargine plus glargine insulin	Insulin glargine only	*p* value[a]
Subjects	% (n)	89.1 (32295)	9.7 (3512)	1.2 (447)	
Sex, % women	% (n)	46.9 (15,153)	50.3 (1,765)	52.1 (233)	<0.0001
Age, years	median (LQ, UQ)	55 (38,68)	41 (30,54)	68 (58,76)	<0.0001
BMI, kg/m^2	mean (SD)	28.9 (6.2)	26.8 (5.0)	30.0 (6.3)	<0.0001
Systolic BP, mmHg	mean (SD)	135.0 (22.1)	130.1 (19.1)	139.8 (20.4)	0.6
Diastolic BP, mmHg	mean (SD)	75.2 (11.9)	75.1 (11.0)	77.0 (12.6)	0.008
HbA$_{1c}$, %	mean (SD)	8.6 (1.7)	8.9 (1.6)	9.4 (1.8)	<0.0001
Duration of diabetes					
≥5 years	% (n)	83.0 (26,724)	83.1 (2,907)	75.1 (334)	<0.0001
Prior insulin					
≥5years on insulin	% (n)	48.1 (15,525)	58.3 (2,046)	5.4 (24)	<0.0001
Prior cancer					
Ever		4.7 (1,531)	2.6 (90)	8.7 (39)	0.92
≤5 years ago		2.3 (754)	1.5 (52)	5.4 (24)	0.24
Prior CVD	% (n)	12.1 (3,919)	5.6 (196)	21.5 (96)	0.014
Ever smoked	% (n)	30.5 (7,553)	27.9 (812)	26.1 (89)	0.0008
Diabetes type					<0.0001
Type 1	% (n)	35.8 (11,547)	62.2 (2,184)	3.4 (15)[b]	
Type 2	% (n)	57.2 (18,455)	29.4 (1,033)	92.0 (411)	
Undefined type	% (n)	7.1 (2,293)	8.4 (295)	4.7 (21)	
Age at diagnosis, years	median	41	25	57	<0.0001
In the two most deprived SIMD quintiles	% (n)	44.4 (14,351)	36.7 (1,288)	53.7 (240)	0.0001

Missing values for BMI, Systolic BP, Diastolic BP, HbA$_{1c}$, Duration of diabetes and ever smoked

[a]Age- and sex-adjusted. Values are for tests of whether the overall variation between groups is significant and are taken from linear and logistic regressions of continuous and binary variables ,respectively

[b]These are likely to be type 2 misclassified as type1

LQ, Lower quartile; UQ, upper quartile

Table 2 Baseline characteristics of the fixed cohort by insulin glargine exposure group: type 2 diabetic patients only (n=19,899)

Characteristic	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin	Insulin glargine only	p value[a]
Subjects	% (n)	92.7 (18,455)	5.2 (1,033)	2.1 (411)	
Sex, % women	% (n)	48.8 (8,996)	48.5 (501)	52.6 (216)	0.13
Age, years	median (LQ, UQ)	65 (56,72)	57 (49, 66)	69 (59,77)	<0.0001
BMI, kg / m^2	mean (SD)	30.4 (6.1)	27.9 (5.7)	30.1 (6.2)	<0.0001
Systolic BP, mmHg	mean (SD)	139.3 .2(22)	136.1 (19.5)	140.5 (20.5)	0.19
Diastolic BP, mmHg	mean (SD)	76 (12)	77 (12)	77(13)	0.006
HbA$_{1c}$, %	mean (SD)	8.5 (1.7)	9.0 (1.7)	9.3 (1.8)	<0.0001
Duration of diabetes					
≥5 years	% (n)	83.2 (15,360)	76.8 (793)	75.2 (309)	<0.0001
Prior Insulin					
≥5years on insulin	% (n)	37.2 (6,867)	47.1 (487)	4.6 (19)	<0.0001
Age at diagnosis, years	median	53	46	59	<0.0001
Prior cancer					
Ever	% (n)	7.4 (1,357)	5.0 (52)	9.3 (38)	0.59
≤5 years ago	% (n)	3.6 (664)	2.7 (28)	5.6 (23)	0.35
Any CVD	% (n)	18.6 (3,441)	12.1 (125)	22.1 (91)	0.016
Ever smoked	% (n)	29.9 (4,335)	28.4 (247)	24.8 (77)	0.001
Use of oral glucose-lowering drugs at baseline[b]	% (n)	28.9(4559)	23.4 (169)	80.0 (295)	<0.0001
On three or more oral glucose-lowering drugs at baseline	% (n)	4.0 (745)	3.1 (32)	29.4 (121)	<0.0001
In the two most deprived SIMD quintiles	% (n)	47.1 (8,686)	35.4 (366)	54.0 (222)	<0.0001

[a]Age- and sex-adjusted. Values are for tests of whether the overall variation between groups is significant and are taken from linear and logistic regressions of continuous and binary variables, respectively

[b]Denominator for oral glucose lowering drugs excludes 3005 (15%) of subjects for whom oral drug prescription is not known with certainty

LQ, Lower quartile; UQ, upper quartile

Table 3 Total cancers by insulin glargine group in the fixed cohort

	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin		Insulin glargine only	
All cancers	n (%)	664 (2.1)	29 (0.8)		22 (4.9)	
	Incidence rate per 100 person-years	1.0	0.39		2.6	
Model 1[a] (n=36254)	HR (95% CI)	Reference	0.80 (0.55–1.17)	p=0.26	1.55 (1.01–2.37)	p=0.045
Model 2[b] (n= 36254)	HR (95% CI)	Reference	0.80 (0.55–1.17)	p=0.26	1.56 (1.00–2.45)	p=0.052
Model 3[c] (n=28696)	HR (95% CI)	Reference	0.87 (0.59–1.30)	p=0.51	1.65 (1.02–2.66)	p=0.038
Model 4[d] (n=21,813)	HR (95% CI)	Reference	0.88 (0.55–1.40)	p=0.58	1.73 (0.98–3.05)	p=0.057

[a]Model 1 adjusts for prior cancer, type of diabetes and calendar year, and is stratified by sex ; timescale is age

[b]Model 2 further adjusts for metformin, sulfonylurea and other oral hypoglycaemic drugs at baseline

[c]Model 3 further adjusts for diabetes duration, HbA_{1c}, diastolic BP, systolic BP and deprivation quintile

[d]Model 4 further adjusts for smoking ever and BMI, but note the reduction in available sample size

Table 4 Site-specific cancers by insulin glargine group in the fixed cohort

Site	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin		Insulin glargine only	
Breast Cancer	n (%)	81 (0.5)	5 (0.3)		6 (2.6)	
Model 1[a] (n=17151)	HR (95% CI)	Reference	0.87 (0.34–2.17)	p=0.76	3.39(1.46–7.85)	p=0.004
Model 2[b] (n=17151)	HR (95% CI)	Reference	0.85 (0.34–2.14)	p=0.73	3.92(1.58–9.70)	p=0.003
Model 3[c] (n=13635)	HR (95% CI)	Reference	1.07 (0.42–2.73)	p=0.88	5.04 (1.95–13.03)	p=0.001
Model 4[c] (n=10307)	HR (95% CI)	Reference	1.10 (0.36–3.00)	p=0.86	3.65(1.05,12.68)	p=0.042
Prostate	n (%)	44 (0.26)	3 (0.17)		1 (0.47)	
Model 1[a] (n=19103)	HR (95% CI)	Reference	1.76 (0.54–5.74)	p=0.35	1.16 (0.16–8.50)	p=0.88
Colorectal		104 (0.32)	2 (0.06)		3 (0.67)	
Model 1[a] (n=36254)	HR (95% CI)	Reference	0.36(0.09–1.48)	p=0.16	1.43 (0.45–4.53)	p=0.54
Lung	n (%)	140 (0.43)	5 (0.14)		4 (0.89)	
Model 1[a] (n=36254)	HR (95% CI)	Reference	0.47(0.18–1.25)	p=0.13	1.43 (0.53–3.88)	p=0.70
Pancreatic n(%)		38 (0.12)	1 (0.03)		0	
	HR (95% CI)				No events	
Model 1[a] (n=36254)		Reference	0.57 (0.08–4.20)	p=0.60		

[a]Model 1 adjusts for prior cancer, type of diabetes and calendar year, and is stratified by sex ; timescale is age
[b]Model 2 further adjusts for metformin, sulfonylurea and other oral hypoglycaemic drugs at baseline
[c]Model 3 further adjusts for diabetes duration, HbA_{1c}, diastolic BP, systolic BP and deprivation quintile
[d]Model 4 further adjusts for smoking ever and BMI, but note the reduction in available sample size due to missing covariates

Table 5 Cancers by insulin glargine group in the incident insulin users cohort: type 2 diabetic patients only

	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin		Insulin glargine only	
All cancers	n (%)	320 (3.1)	14 (2.0)		44 (2.3)	
	Incidence rate per 100 person-years	1.7	1.6		1.9	
	HR (95% CI)					
Model 1 (n=12,845[a])		Reference	1.20 (0.69 2.09)	p=0.53	0.87 (0.63–1.21)	p=0.41
Breast cancer	n (%)	29 (0.61)	0 (0)		6 (0.65)	
	Incidence rate per 100 person-years	0.3			0.5	
	HR (95% CI)					
Model 1 (n=5,963)		Reference	No events		1.47 (0.59–3.64)	p=0.41

[a]Excludes seven subjects without follow-up data

Electronic supplementary material

Methods

Analysis summarising exposure across the entire follow-up period

All patients who were prescribed insulin at any time during the follow-up period were included. The entry time was defined as 1 January 2002 for those receiving insulin on that date or date of first non-glargine insulin or insulin glargine thereafter. Subjects were classified as non-glargine insulin only if they did not use insulin glargine at any time in the study period, as non-glargine plus glargine insulin if they ever used insulin glargine in combination with another insulin, or as insulin glargine only if, when they were on insulin glargine, they did not use any other type of insulin. The follow-up for each person was continued to the first of the following: date of first cancer or cancer death, date of death from any cause, cessation of all insulin therapy, or 31 December 2005. Analysis was using Cox proportional hazards models adjustment for other covariates, as shown in the tables.

Electronic supplementary material

ESM Table 1 Baseline characteristics of cohort of incident insulin users by insulin glargine exposure group: type 2 diabetic patients only

Characteristic	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin	Insulin glargine only	p value[a]
Subjects, n=12852	% (n)	79.8 (10,262)	5.4 (690)	14.8 (1900)	
Sex, % women	% (n)	46.4 (4,761)	40.4 (279)	48.7 (926)	0.050
Age, years	median (LQ, UQ)	63 (54,71)	58 (46, 69)	67 (58, 75)	<0.0001
BMI, kg/m^2	mean (SD)	29.9 (6.3)	29.3 (6.9)	30.5 (6.3)	<0.0001
Systolic BP, mmHg	mean (SD)	137.7 (21.9)	135.3 (22.6)	139.8 (23.2)	0.070
Diastolic BP, mmHg	mean (SD)	76.8 (12.3)	77.6(13.1)	77.8 (12.5)	<0.0001
HbA1c, %	mean (SD)	9.9 (2.1)	9.8 (2.2)	9.9 (1.9)	0.10
Duration of diabetes					
≥5 years	% (n)	67.8 (6,962)	58.0 (400)	82.7 (1,571)	<0.0001
Age at diagnosis, years	median	55	50	57	0.0001
Prior cancer					
Ever	% (n)	8.7 (894)	6.4 (44)	9.8 (187)	0.51
≤5 years ago	% (n)	5.2 (530)	4.6 (32)	5.5 (105)	0.73
Prior CVD	% (n)	39.6 (4,066)	30.0 (207)	40.3 (765)	<0.0001
Ever smoked	% (n)	30.3 (2,391)	29.9 (159)	29.6 (370)	0.08
Use of oral glucose-lowering drugs at baseline[b]	% (n)	89.0 (6,835)	89.8 (371)	97.6 (1,641)	<0.0001
In the two most deprived SIMD quintiles	% (n)	47.5 (4,872)	39.4 (272)	49.5 (940)	<0.0001

[a]Age- and sex-adjusted p values are for tests of whether the overall variation between groups is significant and are taken from linear and logistic regressions of continuous and binary variables respectively
[b]Excludes 15% of patients in whom oral drug use at baseline was not known with certainty
LQ, Lower quartile; UQ, upper quartile

Electronic supplementary material

ESM Table 2 Baseline characteristics of all insulin users during follow-up by insulin glargine exposure group summarised across follow-up (*n*=49,197)

Characteristic	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin	Insulin glargine only	*p* value[a]
Subjects		64.5 (31,752)	30.9 (15,184)	4.6 (2,261)	
Person years		92,743	51,478	3,512	
Sex, % women	% (*n*)	46.3 (14,697)	48.1 (7,298)	49.9 (1,129)	<0.0001
Age, years	median (UQ, LQ)	60 (45,70)	41 (28,54)	68 (58,76)	<0.0001
BMI, kg/m^2	mean (SD)	29.7 (6.3)	27.3 (5.5)	30.3 (6.5)	<0.0001
Systolic BP, mmHg	mean (SD)	137.2 (22.5)	130.2 (20.2)	139.3 (24.0)	<0.002
Diastolic BP, mmHg	mean (SD)	75.5 (12.2)	75.4 (11.5)	77.0 (13.1)	<0.0001
HbA$_{1c}$, %	mean (SD)	8.6 (1.7)	8.9 (1.6)	8.9 (1.8)	<0.0001
Duration of diabetes					
≥5 years	% (*n*)	78.5 (24,609)	77.2 (11,615)	82.6 (1,852)	<0.0001
Prior insulin					
≥5years on insulin	% (*n*)	25.0 (7,922)	37.2 (5,656)	4.2 (95)	<0.0001
Prior cancer					
Ever	% (*n*)	5.9 (1,879)	1.9 (295)	8.7 (197)	<0.0001
≤5 years ago	% (*n*)	3.2 (1,015)	1.0 (155)	5.0 (113)	0.0001
Prior CVD	% (*n*)	24.9 (7,902)	7.2 (1,093)	32.4 (733)	<0.0001
Ever smoked	% (*n*)	30.3 (6,920)	29.3 (3,506)	28.8 (439)	<0.0001
Diabetes type:					
Type 1	% (*n*)	23.0 (7312)	58.6 (8,892)	1.7 (38)	
Type 2	% (*n*)	77.0 (24,440)	41.4 (6,292)	98.3 (2,223)	<0.0001
On three or more glucose lowering drugs	% (*n*)	35.5 (11,277)	13.3 (2,020)	73.2 (1,656)	<0.0001
In the two most deprived SIMD quintiles	% (*n*)	47.9 (15,215)	37.1 (5,634)	50.2 (1,135)	<0.0001

[a]Age- and sex-adjusted *p* values are for tests of whether the overall variation between groups is significant and are taken from linear and logistic regressions of continuous and binary variables respectively

LQ, Lower quartile; UQ, upper quartile

Electronic supplementary material

ESM Table 3 Total cancers by insulin glargine group with insulin exposure, summarised across 147,736 person-years of follow up (*n*=49,197)

Characteristic	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin		Insulin glargine only	
	n	31,752	15,184		2,261	
	Person-years	92,743	51,478		3,515	
All cancers	*n* (%)	1273 (4.0)	156 (1.0)		94 (4.2)	
Model 1[a] (n=49,197)	HR (95% CI)	Reference	0.53 (0.44, 0.63)	*p*<0.0001	1.28 (1.04,1.59)	*p*=0.022
Model 2[b] (n= 49,197)	HR (95% CI)	Reference	0.52 (0.44,0.62)	*p* <0.0001	1.39 (1.11, 1.73)	*p*=0.004
Model 3[c] (n=35,389)	HR (95% CI)	Reference	0.59 (0.49, 0.71)	*p* <0.0001	1.54 (1.20, 1.97)	*p*=0.001
Model 4[d] (n=26,420)	HR (95% CI)	Reference	0.65 (0.53, 0.81)	*p* <0.0001	1.49 (1.09, 2.03)	*p*=0.012

[a]Model 1 adjusts for prior cancer, type of diabetes, calendar year and sex, and has attained age as timescale
[b]Model 2 further adjusts for metformin, sulfonylurea and other oral hypoglycaemic drugs at baseline
[c]Model 3 further adjusts for diabetes duration, HbA$_{1c}$, diastolic BP, systolic BP and deprivation quintile
[d]Model 4 further adjusts for smoking ever and BMI, but note the reduction in available sample size

Electronic supplementary material

ESM Table 4 Site-specific cancers by insulin glargine group with insulin exposure summarised across the follow-up

	Data presented as	Non-glargine insulin	Non-glargine plus glargine insulin		Insulin glargine only	
Breast cancer		132 (0.9)	33 (0.45)		10 (0.9)	
Subjects = 23, 121[e]		14,695	7,298		1,128	
Person years = 70,263		43,261	25,102		1,899	
Model 1[a] (n=23,121)	HR (95% CI)	Reference	0.86 (0.57, 1.29)	p=0.46	1.33(0.69, 2.56)	p=0.39
Model 2[b] (n=23,121)	HR (95% CI)	Reference	0.85 (0.57, 1.28)	p=0.44	1.54 (0.79, 3.02)	p=0.21
Model 3[c] (n=16,756)	HR (95% CI)	Reference	1.00 (0.64, 1.56)	p=0.9	1.93 (0.97, 3.84)	p=0.059
Model 4[d] (n=12,425)	HR (95% CI)	Reference	1.19 (0.72, 1.94)	p=0.50	1.99 (0.88,4.49)	p=0.099
Prostate	n (%)	82 (0.48)	13 (0.16)		5 (0.44)	
Subjects = 26,068[e]		17,1050	7,886		1,132	
Person years = 78,495		50,269	26,550		1,676	
Model 1[a] (n=26,068)	HR (95% CI)	-	1.05 (0.58, 1.91)	p=0.9	1.14 (0.45, 2.84)	p=0.79
Colorectal	n (%)	171(0.54)	20 (0.13)		12 (0.53)	
Model 1[a] (n=49,190)	HR (95% CI)	-	0.58 (0.36, 0.93)	p=0.025	1.13 (0.62, 2.04)	p=0.69
Pancreatic	n (%)	100(0.31)	2 (0.01)		8 (0.35)	
Model 1[a] (n=49,197)	HR (95% CI)	-	0.11 (0.03,0.45)	p=0.002	1.34 (0.64,2.78)	p=0.44

[a]Model 1 adjusts for prior cancer, type of diabetes, calendar year and sex . Timescale is age
[b]Model 2 further adjusts for metformin, sulfonylurea and other oral hypoglycaemic drugs at baseline
[c]Model 3 further includes diabetes duration, HbA$_{1c}$, systolic BP, diastolic BP and deprivation quintile
[d]Model 4 further adjusts for smoking ever and BMI but note the reduction in sample size due to missing covariates
[e]Excludes 53 women and 78 men without follow-up data