

and for the rest by perceived increased bleeding risk. The last was based on inability to comply with monitoring by international normalised ratio, predisposition to falling or head trauma, persistent blood pressure above 160/100 mm Hg, previous serious bleeding on warfarin, severe alcohol misuse for more than 2 years, peptic ulcer disease, thrombocytopenia, or the need for chronic use of a non-steroidal anti-inflammatory drug. Clearly, these criteria were rather loose, being put forward by either the physician or the patient. Therefore double antiplatelet therapy cannot be seen as an alternative to warfarin for patients with atrial fibrillation in general. Are the patients in ACTIVE-A very different from the patients in ACTIVE-W? The strong risk factors for stroke, such as age and CHADS₂ score, a clinical predictor for stroke in atrial fibrillation,⁹ were almost identical (table). As expected, the stroke rate in patients on double antiplatelet therapy was also similar in the double antiplatelet therapy groups in both ACTIVE-A and ACTIVE-W, which strongly suggests that the patients also had the same baseline bleeding risk. So it seems that the populations of patients in both trials were similar. The lowest stroke rate per year was seen in the warfarin group in ACTIVE-W, with a similar major bleeding rate as double antiplatelet therapy in both ACTIVE-A and ACTIVE-W.

Although ACTIVE-A underscores the role of platelets in stroke in patients with atrial fibrillation, double antiplatelet therapy for stroke prevention should be given only to patients who are definitely ineligible for warfarin. This group could include patients who refuse to undergo monitoring or those mentally not able to

take the various doses of warfarin mandated by the monitoring. Perceived unacceptably high risk of bleeding itself cannot make patients ineligible for warfarin, as clearly shown in the published ACTIVE trials, because the bleeding rate with double antiplatelet therapy in both studies were very similar to the bleeding rate with warfarin. Therefore warfarin should remain the cornerstone of stroke prevention in atrial fibrillation.

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I have received departmental research funding and consultancy fees from Sanofi-Aventis and speakers' honoraria from AstraZeneca.

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Insulin glargine and malignancy: an unwarranted alarm



Insulin glargine is a recombinant insulin analogue that has become widely used, largely because of a lower risk of hypoglycaemia and prolonged stable action. Synthetic insulins differ from human insulins in both metabolic and cell-growth activities, which raises legitimate concerns about risk of malignancy.¹ A recent observational study claimed an increased cancer incidence in people using glargine insulin compared with other human insulins, but this effect was only apparent after adjusting for dose.² Subsequently, three further observational studies³⁻⁵ and one randomised trial⁶ have investigated whether insulin glargine is associated with cancer incidence.

Although observational studies from health databases can usefully detect unexpected drug effects in everyday practice, there is potential for biased conclusions.⁷ The problem is that clinical decisions determining each patient's treatment are not random: people are prescribed different therapies for health-related reasons. Thus health outcomes might differ between people taking different therapies even if the therapies themselves have no such effect. Despite adjustment for confounders, residual selection bias might distort any true (lack of) differences between treatments.⁸

Published Online
July 20, 2009
DOI:10.1016/S0140-6736(09)61307-6

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	Comparator	Adjusted hazard ratio (95% CI)
Randomised trial ⁶	Human insulin	0.63 (0.36–1.09)
German database ²	Human insulin	0.86 (0.79–0.94)
UK THIN database ³	Human insulin	0.81 (0.59–1.11)
Swedish database ⁴	Other insulins	1.07 (0.91–1.27)
Scottish database ⁵	Other insulins	1.02 (0.77–1.36)

Table: Risk of malignancy for patients prescribed insulin glargine compared with other insulins in five prospective studies

So what to make of these studies of insulin glargine and malignancy? First, the main hypothesis: does insulin glargine lead to an increased overall incidence of malignancy compared with other insulins? Looking at all five studies, there is no evidence of an excess risk (table). The randomised trial of insulin glargine versus human insulin (free of such confounding problems) included 1017 patients.⁶ During 4.2 years' follow-up, there were 20 and 31 patients with incident cancer in the insulin glargine and human insulin groups, respectively—reassuring but too small to provide conclusive evidence. We agree with the statement in the *Diabetologia* editorial that “There is no evidence of an overall increase in the rate of cancer development in patients on insulin glargine”.¹

The cohort study set in Germany by Hemkens and colleagues² showed a significantly lower incidence of malignancy for those on insulin glargine—perhaps attributable to selection bias and other statistical deficiencies. 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 unsupported. An essential requirement of any time-to-event (survival) analysis is that allocation to treatment groups and other covariates (such as drug dose) must be determined before follow-up starts. Unfortunately, their classification of patients into treatment groups was based on follow-up information: if a patient changed treatment, or was ever on combined treatment, they were removed from analysis. Any malignancy-free follow-up time before the change is not included. Also, insulin dose was calculated as the mean during follow-up, then included in survival analysis as if it was a baseline covariate. These two serious errors make the article's findings uninterpretable.

There are methods for incorporating changes in treatment and dosage over time, with use of time-update

covariates in Cox's proportional hazard models.⁹ However, selection bias could readily generate artificial associations between treatment and/or dosage and outcomes. For example, as patients' diabetes progresses, their mortality risk increases. But poor glycaemic control might prompt the introduction of insulin, which would create systematic differences between patients receiving oral antidiabetic drugs or insulin and great scope for confounding. Insulin treatment will seem linked to higher mortality compared with oral agents. In turn, higher doses of insulin (whether glargine or other) will be linked to higher mortality. Such findings are an artifact of treatment changes as disease advances, not actual treatment effects. Another issue is reverse causality: cancer often has a long period between biological onset and clinical diagnosis. During the subclinical phase, insulin requirements might be affected by the undetected cancer, and lead to treatment changes. To the unwary observer, it can appear that treatment change produces cancer, when in reality cancer produces treatment change.

In principle it makes sense to explore specific cancers in such studies. However, the many cancer types generate multiple hypotheses and an increased risk of spurious chance findings. For instance, the report of the Swedish-based study⁴ emphasised findings on breast cancer—a relative risk of 1.99 (95% CI 1.31–3.03)—for patients on insulin glargine alone compared with patients on other insulins, but with no excess in patients using insulin glargine in combination treatment. Because breast cancer was not predefined as the tumour site of primary concern, this finding (not confirmed in the Scottish-based study⁵) needs cautious interpretation.

Overall, we see no conclusive evidence that insulin glargine carries an increased of malignancy. We now need an informed scientific debate on what future evidence can realistically be obtained to further clarify this important public health issue. In general, while society expects due diligence in the detection of serious drug side-effects, claims of harm not backed by adequate evidence can provoke unnecessary alarms and anxieties, and seriously interfere with good medical practice.

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SJP is a member of the data-monitoring committees of the INTENSIVE, TECOS, and ACE trials of diabetic treatments sponsored by Sanofi-Aventis (who manufacture insulin glargine), Merck, and Bayer, respectively, and is a member of the steering committee of the RECORD trial sponsored by GlaxoSmithKline. LS is supported by a senior clinical fellowship from the Wellcome Trust.

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Treatments for nicotine addiction should be a top priority



Cigarette smoking is a leading cause of death in the USA. The practice has been linked to 440 000 preventable deaths per year, mainly due to lung cancer (123 836), coronary heart disease (86 801), and respiratory disease and chronic obstructive pulmonary disease (90 582).^{1,2} These deaths are the outcome of nicotine addiction, which compels individuals to use tobacco despite the known adverse health consequences. Sadly, priorities for investment in clinical trials are directed at treatment of diseases caused by continued tobacco use, rather than addressing the root cause of the diseases: nicotine addiction (figure). Moreover, clinical trials for smoking cessation and treatment of nicotine addiction are not even within the top 25 therapeutic categories in development by the drug industry; anticancer treatments are the first priority.³ 174 pharmacotherapy trials were done for smoking cessation (46 supported by industry) compared with 1490 for lung cancer (544 supported by industry).

The small number of trials for smoking cessation does not correspond to absence of demand. Many smokers would try to quit smoking if effective and inexpensive approaches were available. Of 45.3 million US adult smokers, 43.5% had tried to quit in the past 12 months, and 80% of those who attempted to quit on their own, without pharmacological or behavioural therapies, relapsed within the first month, with only 3% still abstinent at 6 months.⁴

Unless budgets are increased to develop effective treatments for tobacco dependence, and to make these treatments available to an increased number of

people, the Healthy People 2010 goal⁵ to reduce the proportion of US tobacco users from 21% to 12% is unlikely to be met. According to current projections,

Published Online
April 27, 2009
DOI:10.1016/S0140-6736(09)60352-4

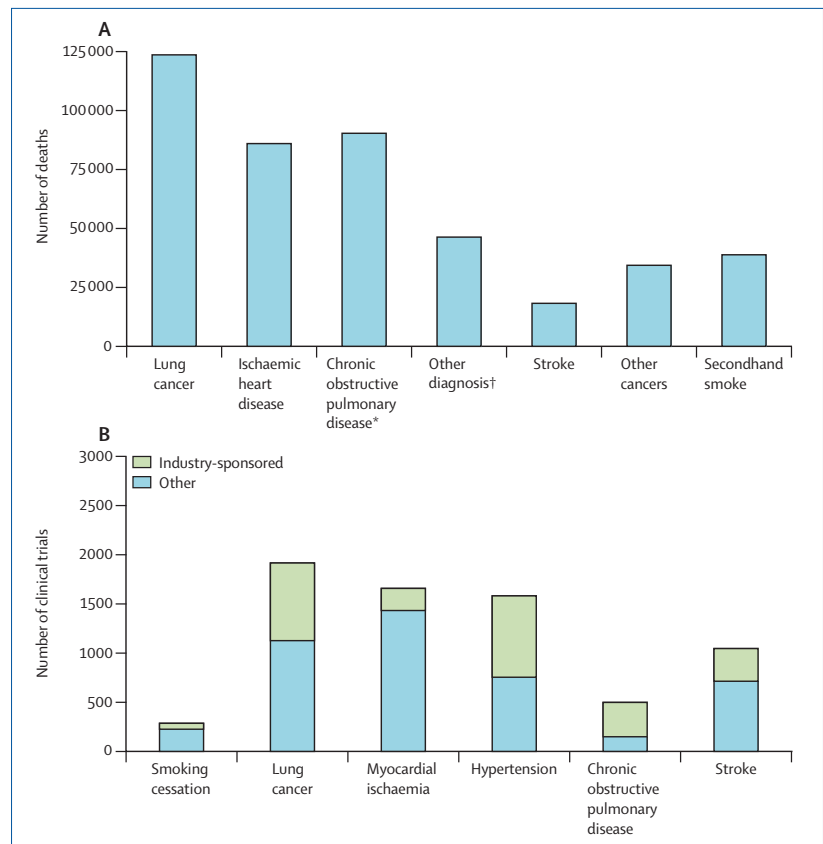


Figure: Research priorities in tobacco addiction (A) Number of deaths per year attributable to smoking-related diseases in USA.² (B) US clinical trials (including treatment, diagnostics, prevention, and supportive care) related to smoking and associated diseases (data from ClinicalTrials.gov, 1987–2008). *Bronchitis, emphysema, and chronic airway obstruction. †Other heart disease, aneurysm, atherosclerosis, other arterial disease, influenza or pneumonia, perinatal conditions, and burn deaths.