Inclusion of Ever vs Never terms in Modelling

Real world scenarios

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Origins/Background

- Pharmacoepidemiology
- Dose response studies
- Bias in Epi studies
  - Allocation
  - Immortal time
  - Detection time
  - Time varying covariates

Sanofi drug may increase cancer risk, studies find

BY BEN HIRSCHLER

LONDON | Sat Jun 27, 2009 5:46am EDT

Logo of the French drugs group Sanofi Aventis company seen at the shareholder's meeting in Paris in this file photo from April 17, 2009.

CREDIT: REUTERS/CHARLES PLATIAU

RELATED TOPICS

Health »

(Reuters) - Sanofi-Aventis's diabetes drug Lantus may increase the risk of cancer, according to European studies involving som 300,000 insulin-treated patients, prompting a call from experts for more research.

The European Association for the Study of Diabetes (EASD), which released details online four studies from its journal Diabetologia, said they were "far from conclusive but they do indicate the need for further investigation of this issue."

The new research was released after mounting speculation that damaging data was about to be published over a cancer link with Sanofi's modern long-acting insulin analog, sinkin the the French drugmaker's share price by 12.3 percent in two days.

Lantus, which sold 2.45 billion euros (2.1 billion pounds) in 2008, is a key driver for Sanof as top drugs like Plavix and Lovenox face the threat of generic competition. Analysts have

EXPRESS Home of the Daily and Sunday Express

Diabetes pill beats cancer...and costs just 2p a day

A DIABETES pill that costs just 2p a day could prevent thousands dying from Britain's biggest cancer killers every year.

By: Jo Willey
Published: Sat, March 16, 2013

Metformin is already taken by millions of diabetes patients

The drug, already taken by millions of patients to control blood sugar levels, is thought to be capable of starving some cancer cells to death.

New research suggests it can slash the risk of developing liver cancer by an astonishing 78 per cent, breast cancer by a third, pancreatic cancer by 46 per cent and bowel cancer by

Use of observational studies vs clinical trials

Risks (as well as benefits) associated with a specific drug depend on the dose, duration & timing of treatment

Rare outcomes

Models need to be specified correctly to avoid confounding and allocation bias

Q: Why not use propensity scores? Or extend to marginal structural models?

Unmeasured confounding
Data availability/model assumptions

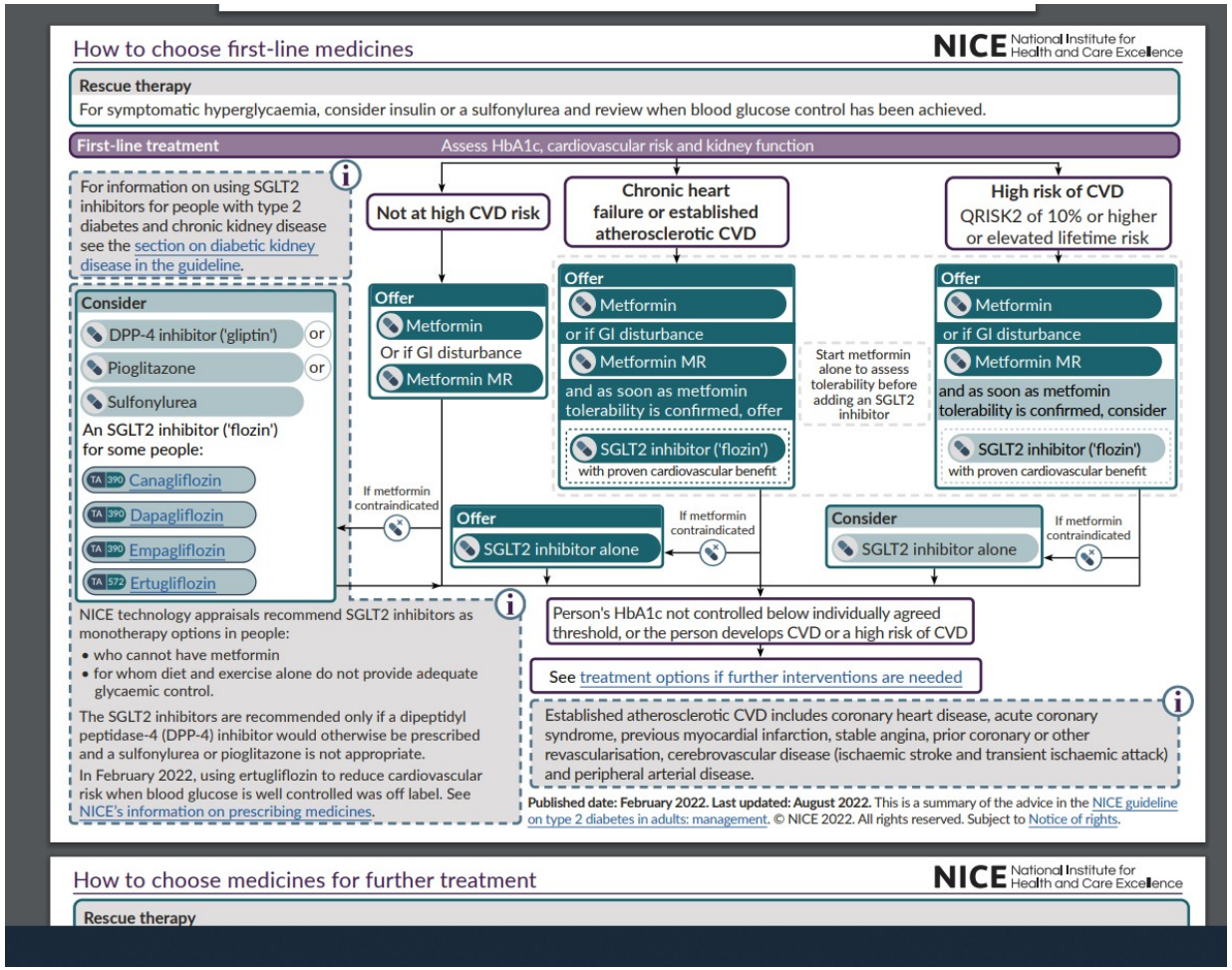
Human Insulin Therapy Is Associated With an Increased Risk of Lung Cancer: A Population-Based Retrospective Cohort Study (single author)

rsin.org/files/Articles/466513/tendo-10-00443-HTML/image_m/tendo-10-00443-t002.jpg

Exposure to human insulin	Case number	Incident lung cancer	%	Person-years	Incidence rate (per 100,000 person-years)	Adjusted hazard ratio	95% Confidence interval	*P*
Never-users	850,897	13,677	1.61	4,361,227.25	313.60	1.000		
Ever-users	156,720	3,007	1.92	708,441.33	424.45	1.545	(1.478–1.614)	<0.0001
TERTILE CUTOFFS								
Time since starting insulin (months)								
Never-users	850,897	13,677	1.61	4,361,227.25	313.60	1.000		
<25	50,771	974	1.92	232,470.92	418.98	1.518	(1.419–1.624)	<0.0001
25–57	51,254	977	1.91	234,151.75	417.25	1.469	(1.373–1.573)	<0.0001
≥57	54,695	1,056	1.93	241,818.67	436.69	1.656	(1.549–1.772)	<0.0001
P trend								<0.0001
Cumulative dosage of insulin exposure (units)								
Never-users	850,897	13,677	1.61	4,361,227.25	313.60	1.000		
<328	51,739	1,070	2.07	245,321.33	436.16	1.368	(1.283–1.459)	<0.0001
328–16,166	51,717	979	1.89	229,593.17	426.41	1.518	(1.418–1.625)	<0.0001
≥16,166	53,264	958	1.80	233,526.83	410.23	1.902	(1.771–2.041)	<0.0001
P trend								<0.0001
Cumulative duration of insulin exposure (months)								
Never-users	850,897	13,677	1.61	4,361,227.25	313.60	1.000		
<0.57	52,245	1,105	2.12	241,256.17	458.02	1.401	(1.315–1.492)	<0.0001
0.57–8.63	51,118	944	1.85	233,903.33	403.59	1.458	(1.361–1.563)	<0.0001
≥8.63	53,357	958	1.80	233,281.83	410.66	1.945	(1.810–2.089)	<0.0001
P trend								<0.0001

Hazard ratios are adjusted for all variables in ***Table 1****.*

NICE guidelines



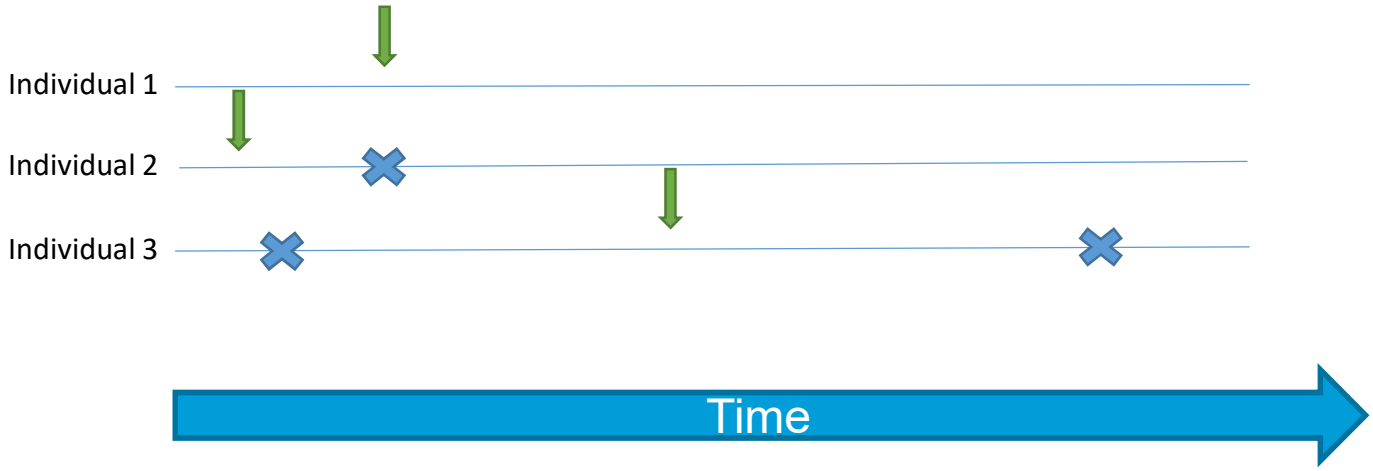
Including ever-vs-never exposure to drugs together with cumulative exposure

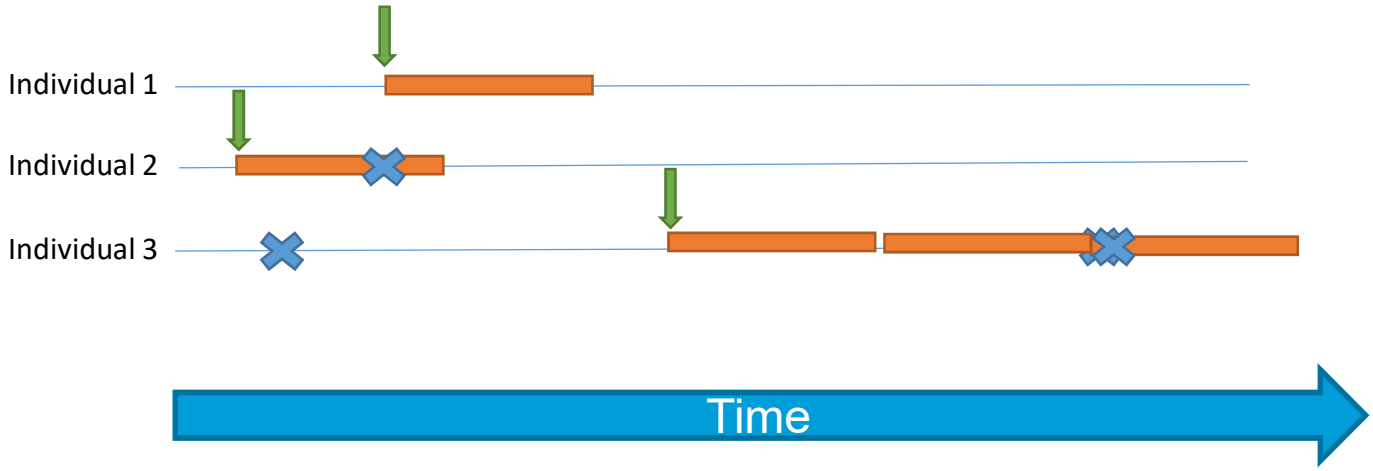
- distinguish causal effects from confounding by allocation

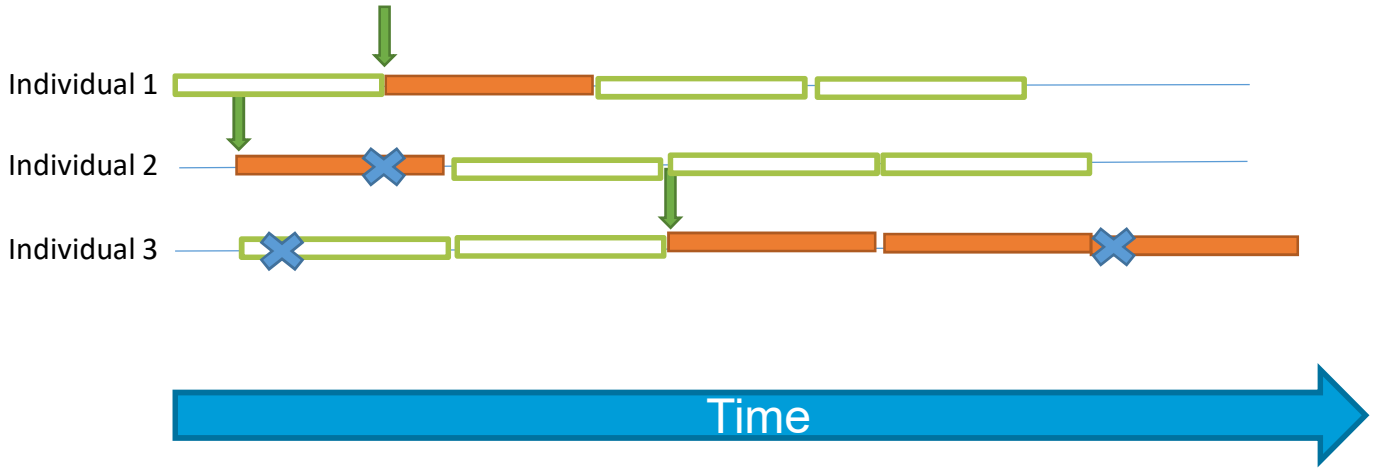
Time periods

Bradford hill criteria


Individual 1
Individual 2
Individual 3
Time


Individual 1
Individual 2
Individual 3
Time


Individual 1
Individual 2
Individual 3
Time


Individual 1
Individual 2
Individual 3
Time

Methods

- Cox regression models for time to failure specified to include drug exposure
- the time-updated ever-never exposure term
- both the ever-never term and a linear term for cumulative exposure
- Where stepwise effects on the risk of adverse events are unlikely (cancer) joint modelling of ever-never and cumulative exposure can be used to study the effects of multiple drugs and to distinguish causal effects from confounding by allocation.

- Or discrete time survival model (allows time periods updated for time varying covariates and exposures)

Modelling cumulative exposure for inference about drug effects

Table 2. Hazard Ratios for Incident CVD Using a Time-Updated Ever-Never Exposure Term Only.

	Model with ever-exposure term only				Model with terms for ever-exposure and cumulative exposure			
	Hazard Ratio	Lower 95% Confidence bound	Upper 95% Confidence bound	p-value	Hazard Ratio	Lower 95% Confidence bound	Upper 95% Confidence bound	p-value
Current age (years) †	1.04	1.04	1.05	<0.001	1.05	1.04	1.06	<0.001
Gender (female vs male)	0.79	0.77	0.80	<0.001	0.79	0.77	0.80	<0.001
Age at diabetes diagnosis (years)	0.98	0.97	0.98	<0.001	0.97	0.97	0.98	<0.001
Statins ever vs never exposure	1.13	1.10	1.16	<0.001	1.20	1.16	1.23	<0.001
Cumulative statin exposure (years)	-	-	-	-	0.97	0.97	0.98	<0.001

† Models included linear and quadratic terms for age

Whats your favourite baseline????

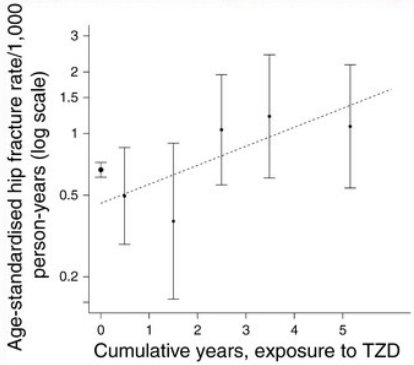
Table 3. Hazard ratios for incident CVD in models with cumulative statin exposure coded as discrete categories, illustrating effect of choice of baseline category. Models include sex, age at baseline, age at diabetes diagnosis, and time-updated calendar time.

	With baseline category as unexposed person-time intervals				With baseline category as exposed person-time intervals with cumulative exposure < 0.5 years			
Years of cumulative exposure	Hazard Ratio	Lower 95% Confidence bound	Upper 95% Confidence bound	p-value	Hazard Ratio	Lower 95% Confidence bound	Upper 95% Confidence bound	p-value
0 < exposure <=0.5	1.29	1.24	1.34	<0.000	NA	NA	NA	NA
0.5< exposure <=1.5	1.13	1.09	1.17	<0.000	0.88	0.84	0.92	<0.001
1.5< exposure <=2.5	1.07	1.03	1.12	0.001	0.83	0.79	0.87	<0.001
2.5< exposure <=3.5	1.09	1.04	1.14	<0.000	0.85	0.81	0.89	<0.001
3.5< exposure <=4.5	1.09	1.04	1.14	0.001	0.84	0.80	0.89	<0.001
4.5< exposure <= 5.5	1.06	1.01	1.12	0.023	0.83	0.78	0.88	<0.001
5.5< exposure <=6.5	1.04	0.98	1.11	0.186	0.81	0.76	0.86	<0.001
6.5< exposure <=7.5	1.05	0.98	1.13	0.157	0.82	0.76	0.88	<0.001
7.5< exposure <=8.5	1.07	0.95	1.20	0.245	0.83	0.74	0.94	0.002

Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs

Fig. 1

From: Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs



Age-standardised rates of hip fracture by cumulative exposure to TZD in women. The error bars indicate the 95% CI for the rates. The x axis shows cumulative years of exposure; the data point at $x = 0$ is for all unexposed person time-periods, and the other data points are for exposure categories $0 < x \leq 1$, $1 < x \leq 2$, $2 < x \leq 3$, $3 < x \leq 4$ and $x > 4$ years. The dotted regression line shows the linear effect of cumulative exposure (x) calculated by weighted least squares from the ever-exposed data points as an approximation to the modelling approach described in the Methods. Whereas the data point at $x = 0$ is the log fracture rate observed for all unexposed person time-periods, the point on the dotted regression line where $x = 0$ is the estimate from the model of the log fracture rate at the point of starting exposure in those exposed. Thus the difference in height between these two points gives the magnitude of the ever-exposed term and is the sum of any immediate stepwise effect of the drug and any difference in prior risk of fracture in ever vs never exposed. Since an immediate stepwise effect of TZD on hip fracture is unlikely the difference in height suggests that those who become exposed have a lower prior fracture risk than the never exposed

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Examples for BiB

Covid?

Cumulative exposures? Pollution??

Rare outcomes?