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ORIGINAL RESEARCH ARTICLE

Fibrates and Risk of Cancer in Tissues with High PPAR-α Concentration: A Nested Case–Control Study

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Abstract

Background Fibrates are lipid-lowering agents that act as peroxisome proliferator-activated receptor (PPAR)-α agonists. They have been associated with cancers in experimental models, but data in humans are rare, and among published studies none has investigated cancers in tissues with high PPAR-α concentrations.

Methods A nested case–control study was performed in a French population-based healthcare database. Adults aged ≥45 years, and free of cancer for 3 years, were followed for 5 years for incident cases of melanoma, non-melanoma skin cancers, thyroid, pancreas, bladder, and kidney cancers. Cases were matched with up to ten controls for age, sex, and diseases that could increase the risk of cancers. Conditional logistic models, adjusted for drug-use as potential confounders, were used to estimate the risk (odds ratio [OR]) of cancers of interest (and individual cancers) associated with cumulative exposure to fibrates (defined daily doses [DDD]).

Results Among the 147,338 eligible subjects, 3,331 (2.3 %) cases of studied cancers were identified. Only use of fibrates >550 DDDs was associated with an increased risk (OR 1.26; 95 % CI 1.12–1.42), and similar results were found for statins (≥1,460 DDDs; OR 1.15; 95 % CI 1.03–1.28). When considering cancers individually, the association was significant for non-melanoma skin-cancer (OR 1.35; 95 % CI 1.14–1.60), and close to significance for bladder cancer (OR 1.26; 95 % CI 0.96–1.64); similar associations with the use of statins were found.

Conclusions The associations found between fibrate exposure and cancers of tissues with high PPAR-α concentrations were most likely related to residual confounding as similar associations were found for statins.

Key Points

Use of fibrates was associated with cancers in tissues with high peroxisome proliferator-activated receptor (PPAR)-α concentration.

A similar association was found for statins, suggesting a potential residual confounding effect.

These results do not provide evidence of a carcinogenic effect of fibrates in humans.

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1 Introduction

Pioglitazone, a thiazolidinedione with both peroxisome proliferator-activated receptor (PPAR)-γ and PPAR-α agonistic properties, has been associated with bladder cancer [1–4], whereas rosiglitazone, which is of the same class but an agonist only for the PPAR-γ isoform, has not been associated with such risk [5, 6]. The underlying mechanism for the carcinogenic effect of pioglitazone is hypothesised to be related to the agonism of both PPAR-γ and PPAR-α [7], or specifically PPAR-α, which increases intracellular oxidative stress [8–10].

Fibrates are lipid-lowering agents that act mostly as PPAR-α agonists. The majority of these drugs have demonstrated their efficacy in cardiovascular secondary prevention; they remain of interest in that indication, especially in patients presenting with adverse events related to the use of statins [11]. They have been associated with cancers in experimental models [12–15], yet data concerning fibrates and cancers in humans are rare [16–18]. Furthermore, studies have not considered the proposed mechanism of action; if the risk of cancer was to be modified by the use of fibrates, this should mostly concern primary cancers of tissues with a high concentration of PPAR-α, such as melanoma, non-melanoma skin cancers, thyroid, pancreas, bladder, and kidney cancers [19–22]. To address this, we conducted a large observational study to investigate the association between fibrates and these cancers.

2 Methods

2.1 Participants, Design, and Settings

We conducted a nested case–control study using the Echantillon Généraliste des Bénéficiaires (EGB), a representative permanent 1/97 sample of the French National Insurance Healthcare System database, which covers over 75 % of the French population. EGB includes approximately 600,000 subjects for whom it provides basic demographic data and prospectively collected reimbursed medical expenses since 2003. These medical expenses include information on all reimbursed medicines, including dates of prescription, dispensing, and quantities dispensed, information for certain costly long-term diseases (Affections de Longue Durée [ALD]) for which 100 % of related healthcare expenses are reimbursed, and, from 2005 onwards, information on hospitalisations. Medical diagnoses associated with ALD long-term disease and hospitalisations discharge summaries are coded using the International Classification of Diseases, 10th Revision (ICD-10). Medicines are coded according to the Anatomical Therapeutical Chemical (ATC) classification.

The cohort of origin for our nested case–control analysis comprised all subjects included in the EGB as of 1 January 2004, aged 45 years or over at this date, with complete follow-up from this date onwards, and without history of cancer (any type) identified through the medical diagnoses associated with ALD long-term diseases or hospitalisations recorded before 1 January 2007. This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (see electronic supplementary material [ESM] 1).

2.2 Case Definition and Identification

We considered all cancers from tissues with high PPAR-α concentration or existing evidence of potential association with fibrate use. The selected cancers included melanoma, non-melanoma skin cancers, thyroid cancers, pancreas cancers, bladder cancers, and kidney cancers [19–22]. We could not study lung cancer, liver cancer, or brain cancer as the level of ICD-10 code in the EGB did not allow the differentiation between primary and metastatic cancers. Furthermore, we did not consider leukaemia as hospitalisation codes included in the EGB do not allow the differentiation between blood cancer types.

For the selected cancers, we included all incident cases identified between 1 January 2007 and 1 January 2012. The date of first record of ALD long-term disease or hospitalisation associated with an ICD-10 diagnostic code corresponding to one of these cancers constituted the index date for cases. If more than one cancer of interest was diagnosed in the same patient, only the first diagnosed cancer and its diagnosis date were considered. The ICD-10 codes used to identify the cases are reported in eTable 1 in the ESM 2.

2.3 Control Identification and Selection

For each case we selected up to ten potential controls from the cohort who were free of any cancer over the whole study period. Controls were assigned the same index date as their respective case.

We matched controls to cases on age (±1 year), sex, and on each of the following medical conditions: type 1 diabetes, type 2 diabetes and its first diagnosis date (±1 year), alcoholic liver disease, toxic liver disease, hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver, HIV and its complications, schistosomiasis, heart failure, cardiac ischaemic disorders, atherosclerosis, arterial embolism and thrombosis, chronic obstructive pulmonary disease, and asthma. The ICD-10 codes used to identify the medical conditions considered for matching are reported in the ESM 2 (see eTable 2). Their existence in cases and controls

was identified from the diagnostic codes associated with ALD long-term disease or hospitalisation events in the database for the period ranging from the start of the follow-up period to 180 days before the index date.

Cases were never considered as potential controls. Each control was only used for a single case because of the multiplicity of matching variables. Controls could therefore not be matched to different cases with different index dates.

2.4 Exposure of Interest Definition and Assessment

All fibrates (ATC code C10AB) marketed in France during the study period were considered. The exposure was assessed considering for each patient all reimbursements identified for the period ranging from the start of the follow-up period (1 January 2005) to 180 days before the index date. The information regarding the 6-month period preceding the index date was censored.

For each fibrate, the cumulated exposure was calculated considering the total number of defined daily doses (DDDs) that had been reimbursed (number of DDDs per packet multiplied by the number of reimbursed packets). According to the WHO definition, the DDD for bezafibrate (ATC code C10AB02) is 0.6 g, for gemfibrozil (C10AB04) it is 1.2 g, for fenofibrate (C10AB05) it is 0.2 g, and for ciprofibrate (C10AB08) it is 0.1 g [23]. The total cumulated exposure to fibrates was then calculated by summing, for each patient, the estimated cumulated exposure to each fibrate.

2.5 Potential Confounders

As cases and controls were matched for age, sex, and medical conditions, the studied potential confounders concerned exposure to medicines that had already been associated with any cancer, including those related to PPAR-α, such as pioglitazone, as well as those being studied. This led to consider, as potential confounders, exposure to aspirin, insulin, metformin, sulfonamides, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, glinides, and statins. As statins share relatively similar indications as fibrates, associations between the studied cancers and exposure to statins was considered as a marker of a potential indication bias. If an association was found for fibrates that was not found for statins, the association was considered to be less likely to be consecutive to an indication bias. Cumulated exposure to each of these classes was estimated in DDDs using the method described for fibrates. ATC codes used to identify exposure to each drug of these classes are provided in the ESM 2 (see eTable 3).

2.6 Statistical Analysis

We used numbers and proportions to describe the qualitative characteristics of cases and controls, and medians and interquartile range (IQR) to describe quantitative ones. We classified the studied medicine exposures (fibrates and other drugs) with regards to their distribution characteristics to search for potential cumulated dose effects whenever possible (see eTable 3 in the ESM 2); categorical thresholds for statistical analyses were defined to reflect meaningful cutoffs (e.g. 365 DDDs corresponding to 1 year of cumulated exposure; 550 DDDs corresponding to around 1.5 years of cumulated exposure, etc.) that would be the closest to the distribution parameters (e.g. quartiles, median). For drugs to which few patients were exposed, patients were categorised as being either exposed or not to the drug in question. To take into account individual matching, we used bivariate conditional logistic regression models to compare these characteristics.

We used conditional logistic models adjusted for all studied potential confounders to estimate the association between exposure to any fibrate and any of the cancers of interest. The dependent variable was the existence of any of the studied cancers. Exposure to fibrates was the main explanatory variable and non-exposure constituted the reference. We thus obtained adjusted odds ratios (ORs) for the association, using non-exposure to fibrates as the reference. In the secondary analyses, the association between exposure to fibrates and each cancer type of interest was tested using similar conditional logistic models adjusted for all potential confounders.

We used the SAS statistical package, version 9.3 (SAS Institute, Cary, NC, USA) for all analyses. All reported p-values were two tailed, and we considered $p < 0.05$ to be statistically significant; 95 % confidence intervals (CIs) were calculated for all ORs.

3 Results

In the EGB database, 147,338 subjects meeting the inclusion criteria were selected for this study (Fig. 1). Among these, 3,331 incident cases of a cancer of interest were identified between 2007 and 2011, and matched to 31,460 controls; all cases were matched to at least one control. Characteristics of cases and controls are summarised in Table 1. Overall, 595 cases had been exposed to fibrates, 224 were in patients exposed to <550 DDDs of fibrates, and 371 in patients exposed to ≥550 DDDs of fibrates. After adjusting for the selected covariates, exposure to fibrates was found to be associated with the studied cancers in patients with exposure to ≥550 DDDs (OR 1.26; 95 % CI 1.12–1.42) [Table 2] but not when exposure was <550

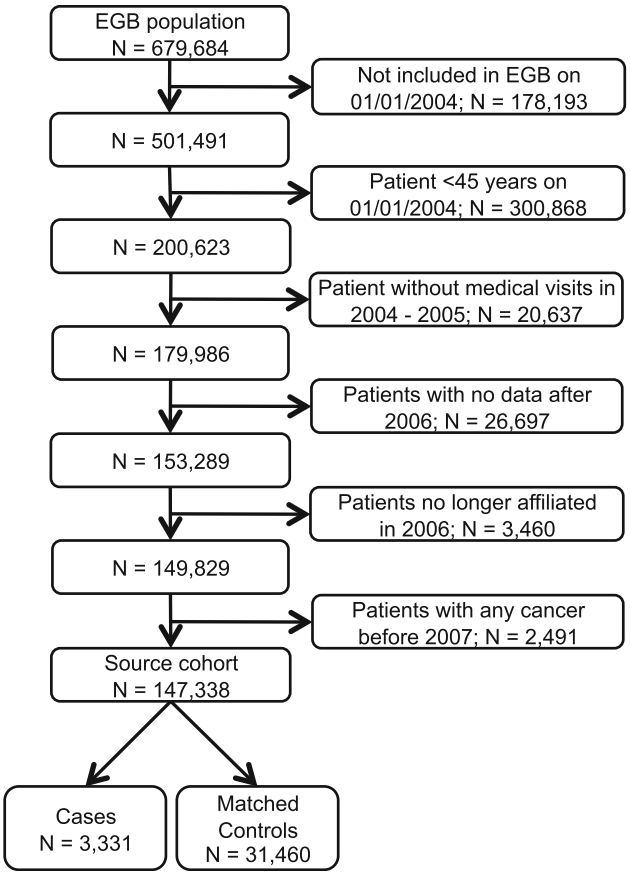

Fig. 1 Selection of the study population. Among the source population, subjects included in the EGB in 2004 aged ≥45 years, with a minimum amount of healthcare information and free from any cancer before the study period, composed the source cohort. Within the latter, cases were patients who were diagnosed with at least one cancer of interest (melanoma, non-melanoma skin cancer, pancreas, thyroid, bladder, kidney) from 1 January 2007. These were matched with up to ten controls who were selected among patients without any cancer diagnosis during the study period. *EGB* Echantillon Généraliste des Bénéficiaires

DDDs (OR 1.02; 95 % CI 0.88–1.18). Exposure to statins was associated with cancer only for the highest level of exposure (≥1,460 DDDs; OR 1.15; 95 % CI 1.03–1.28) [Table 2].

In the secondary analyses, no significant association was found for exposure to <550 DDDs of fibrate and any of the cancers of tissues with high PPAR-α concentration (Table 2). The risk of non-melanoma skin cancers was increased with fibrate exposure ≥550 DDDs (OR 1.35; 95 % CI 1.14–1.60), and the association was close to significance for statin exposure ≥1,460 DDDs (OR 1.19; 95 % CI 1.00–1.40). A trend towards increased risk was found for bladder cancer for both exposure to ≥550 DDDs of fibrate (OR 1.26; 95 % CI 0.96–1.64) and exposure to ≥1,460 DDDs of statin (OR 1.25; 95 % CI 0.997–1.58). No association was found for fibrates and the risk of other cancers. The detail of the crude and adjusted OR estimations for the associations between exposure to fibrates and each cancer type is reported in eTables 4–9 in the ESM 2. No significant interaction was found between fibrates and any of the potential confounders in either the primary or the secondary analyses.

Among fibrate users, 2,963 (17.1 %) were also exposed to statins during follow-up. In statin non-users, the association of fibrate exposure with cancer remained significant and was found to be similar to that obtained in the main analysis (eTables 10 and 11).

4 Discussion

We found an association between exposure to fibrates and the risk of cancer in tissues highly expressing PPAR-α that were considered for the study. The risk was increased for exposure to ≥550 DDDs of fibrates, i.e. cumulated exposure that represents at least 18 months of treatment at usual doses. When considering cancers of interest individually, this increase was found significant for non-melanoma skin cancer and close to significance for bladder cancers, but not for other cancer types investigated. Similar results were found for higher exposure to statins, which do not share the pathophysiological rationale to explain the increased risk associated with fibrates [24, 25]. This raises the question of possible residual confounding, whereby the increased risk of cancer may be related to patient characteristics leading to prolonged or more intense use of lipid-lowering agents, rather than to the agents themselves. Such a background risk may be the existence of unmeasured risk factors for cardiovascular disease and cancer, such as smoking or obesity, which would result in more intense cardiovascular prevention. This finding is consistent with recent publications that found no increase in the risk of cancer [16], of all-type cancer mortality [17, 18], and specifically melanoma [26].

The present study was performed using data from a representative sample of the French population for which exhaustive data on medicine reimbursement and hospitalisation are available that lowers the risk of selection bias. The exhaustiveness of the hospitalisation data suggests that cancer identification is reliable, although early-stage skin cancer may not always lead to a hospitalisation. It is thus likely that only the more serious cases of skin cancer were identified through this study. This would be an issue if the severity of the skin cancers differed among the exposure groups. Such a differential misclassification bias could lead to the association found if, for a similar incidence, cancer was identified at a later (more advanced) stage in those exposed to fibrates than in non-exposed ones. This could arise if patients treated with fibrates were less likely to have

Table 1 Characteristics of cases and controls

	Cases (%) [$n = 3,331$]	Controls (%) [$n = 31,460$]
Matching variables		
Age [years; median (interquartile range)]	74.0 (64.0–81.0)	73.0 (63.0–80.0)
Females	1,464 (44.0)	14,222 (45.2)
Type 1 diabetes	24 (0.7)	33 (0.1)
Type 2 diabetes	333 (10.0)	2,340 (7.4)
Heart failure	39 (1.2)	303 (1.0)
Cardiac ischaemic disorders	274 (8.2)	2,453 (7.8)
Atherosclerosis, arterial embolism and thrombosis	122 (3.7)	995 (3.2)
Chronic obstructive pulmonary disease	7 (0.2)	47 (0.1)
Asthma	20 (0.6)	132 (0.4)
HIV and its complications	7 (0.2)	42 (0.1)
Fibrosis and cirrhosis of liver	5 (0.2)	29 (0.1)
Chronic hepatitis	5 (0.2)	46 (0.1)
Alcoholic liver disease	7 (0.2)	57 (0.2)
Others	0 (0.0)	0 (0.0)
Adjustment variables		
Aspirin, cardiovascular		
1–179 DDD	232 (7.0)	2,104 (6.7)
180–729 DDD	297 (8.9)	2,334 (7.4)
≥730 DDD	660 (19.8)	5,696 (18.1)
Aspirin, painkiller or antipyretic		
1–13 DDD	254 (7.6)	2,590 (8.2)
≥14 DDD	278 (8.4)	2,310 (7.3)
Statins		
1–364 DDD	355 (10.7)	3,296 (10.5)
365–912 DDD	270 (8.1)	2,507 (8.0)
913–1,459 DDD	252 (7.6)	2,314 (7.4)
≥1,460 DDD	616 (18.5)	5,125 (16.3)
Insulines		
1–59 DDD	76 (2.3)	256 (0.8)
≥60 DDD	157 (4.7)	694 (2.2)
Metformin		
1–269 DDD	117 (3.5)	814 (2.6)
≥270 DDD	319 (9.6)	2,350 (7.5)
Pioglitazone	63 (1.9)	438 (1.4)
Sulfamides		
1–1,094 DDD	156 (4.7)	972 (3.1)
≥1,095 DDD	222 (6.7)	1,573 (5.0)
Dipeptidyl peptidase-4 inhibitors	115 (3.4)	950 (3.0)
Glucagon-like peptide-1 agonists	16 (0.5)	88 (0.3)
Glinides	119 (3.6)	702 (2.2)

Data are rendered as *n* (%), unless otherwise specified

DDD defined daily doses

medical/dermatological follow-up than non-exposed ones. As a similar association was found with statins, this is unlikely to have occurred, except if one considers that patients taking lipid-lowering agents are all less likely to be diagnosed with non-melanoma skin cancer early on. Although this cannot be entirely excluded, it appears improbable.

As we considered, for the cohort of origin, all subjects present in the database on 1 January 2005, and matched controls were selected on the date of the case cancer identification, duration of follow-up was similar for each case and its matched controls. Thus, cases and matched controls had, a priori, a similar probability of cumulated exposure and the difference between them for this exposure was unlikely to be related to difference in follow-up duration.

The large sample size provided accurate matching and the consideration of a large number of co-morbidities for control selection, whereas the exhaustiveness of medicine reimbursement allowed adjustment for treatments that are often co-prescribed with lipid-lowering agents and that have been associated with the increased [1, 3, 27] or decreased incidence [28, 29] of certain cancers. For these matching variables, the apparent imbalances in patients characteristics are related to the number of controls that each case can have, which may be up to ten, but not necessarily as many. Thus, the number of controls can vary between cases, and the proportion of controls with a given condition (e.g. diabetes) can differ between the population of controls and the population of cases while, within strata, cases and controls all have the same status for each condition and conditional logistic regression takes unequal numbers of controls per case into account.

Despite this close matching and adjustment, and as for most studies performed from reimbursement databases, many potential confounders could not be studied (e.g. phototype or sun exposure for skin cancers, or smoking for bladder cancer). To compensate this limitation we preferred to use a reference group with similar indications to fibrates rather than to rely on statistical techniques that deal with unmeasured confounders. Statin use was retained to provide a reference risk with similar indications (i.e. dyslipidaemia, high-risk cardiovascular profile, or secondary cardiovascular prevention) [30], and there is a large body of evidence that suggests their use does not increase the risk of cancer [31–39]. Finding a similar risk of the same specific cancers associated with long-term use of fibrates or statins raises the distinct possibility of residual confounding, and casts doubt on the reality of an increased risk of these cancer caused by fibrates.

Not all cancers potentially related to PPAR-α could be considered in the database, which limits the generalisation to

Table 2 Estimation of the association between exposure to fibrates and cancers of tissues with high PPAR-α concentration

	Cases (%) [$n = 3{,}331$]	Controls (%) [$n = 31{,}460$]	OR (95 % CI) Crude	p-value	OR (95 % CI) Adjusted[a]	p-value
Fibrates				$<10^{-3}$		$<10^{-3}$
Non-exposed	2,736 (82.1)	26,522 (84.3)	1		1	
<550 DDD	224 (6.7)	2,073 (6.6)	1.04 (0.90–1.20)		1.02 (0.88–1.18)	
≥550 DDD	371 (11.1)	2,865 (9.1)	1.25 (1.11–1.41)		1.26 (1.12–1.42)	
Statins				0.10		0.18
Non-exposed	1,838 (55.2)	18,218 (57.9)	1		1	
<365 DDD	355 (10.7)	3,296 (10.5)	1.05 (0.93–1.19)		1.00 (0.88–1.13)	
≥365 and <913 DDD	270 (8.1)	2,507 (8.0)	1.05 (0.92–1.21)		1.01 (0.89–1.16)	
≥913 and <1,460 DDD	252 (7.6)	2,314 (7.4)	1.05 (0.91–1.21)		1.03 (0.89–1.19)	
≥1,460 DDD	616 (18.5)	5,125 (16.3)	1.17 (1.05–1.30)		1.15 (1.03–1.28)]	

PPAR peroxisome proliferator-activated receptor, *OR* odds ratio, *CI* confidence interval, *DDD* defined daily doses

[a] Adjusted for exposure to:aspirin-cardiovascular, aspirin-painkiller or antipyretic, statins, insulines, metformin, pioglitazone, sulfamides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, and glinides

all tissues with high PPAR-α concentration but does not affect the results of the study. As in most reimbursement databases, the exact date of the cancer diagnosis, and thus exact date of cancer incidence, cannot be ascertained. For this reason, we censored the last 6 months before index date for definition of exposure. The exposure information is, however, plagued by the left censoring of the database used. No distinction was made between prevalent users and incident users in this nested case–control study; the cumulated exposure measured could have been underestimated, and it cannot be ruled out that non-users could be former users of fibrates. The same limits affect exposure to statins. However, as this tends to lower exposure and to misclassify former fibrate users, this should be conservative and is unlikely to have produced the associations found. If associations were found only for fibrates, an incident-user cohort design would have been necessary to ascertain that the cumulated level of exposures found to increase the risk would have been correctly determined. In the present context where residual confounding is much more likely to explain the association than a causal effect of both statins and fibrates, we do not believe that such studies are required.

In addition, due to the limited number of exposed cases and to the very high representation of fenofibrate among fibrate reimbursements in France (>80 %) [40], we could not investigate risks associated with individual drugs as doing so would have led to the power of the analyses being reduced.

5 Conclusion

The associations found between fibrate exposure and cancers of tissues with high concentrations of PPAR-α, and more specifically non-melanoma skin cancer, were most likely related to residual confounding. As this residual confounding is likely to be related to the risk factors in patients with cardiovascular diseases who constitute the majority of patients treated with fibrates, these will need to be taken into account for future research.

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Conflicts of interest declaration Fabienne Bazin, Aude Kostrzewa, Christian Bandre, and Philip Robinson, have had no relationships with companies that might have an interest in the submitted work in the previous 3 years. Francesco Salvo is a consultant of YOLARX Consultants Inc. (Montreal, Canada), and has worked on studies concerning one antifungal, one anticancer drug, and paracetamol. Bernard Bégaud has received investigator-initiated research funding from the French Health Ministry (2011); he is chair of the scientific committee for two pharmacoepidemiological studies conducted by the contract research organisation LA-SER (London, UK)—one on medicines used in osteoarthritis, the other on the use of homeopathic remedies by French practitioners. Nicholas Moore, in the previous 3 years, has had specified relationships on other matters with the following drug companies that might have an interest in the submitted work: Pfizer, Servier, Pierre Fabre, Roche, Merck Serono, Novartis, AstraZeneca, Abbott, Axcan, Bristol-Myers Squibb, Celgene, Cephalon, Vivatec, Lundbeck, GlaxoSmithKline, Leo Pharma, Helsinn Healthcare, Orion, Genevrier, Takeda, Sanofi, and Johnson & Johnson; he has also had, in the previous 3 years, specified relationships on other matters with public regulatory agencies and with healthcare insurance systems that might have an interest in the submitted work. Antoine Pariente, in the previous 3 years, has had specified relationships on other matters with Novartis that might have an interest in the submitted work. The authors' spouses, partners, or children have no financial relationships that may be relevant to the submitted work. All authors have no non-financial interests that may be relevant to the submitted work.

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