

## OBSERVATIONS

## Poor Correlation of Pulse-Wave Velocity and Intima-Media Thickness in Diabetic Subjects

Various noninvasive in vivo assessments have recently been applied to the estimation of atherosclerosis in subjects with diabetes. The measurement of pulse-wave velocity (PWV) has been popular with the advance of apparatus, especially in Japan (1–3). However, it remains unknown whether PWV may be valid and reproducible, especially in diabetic study populations (4). In a recent issue of *Diabetes Care*, Hope et al. (5) addressed the important question of whether it is valid to apply PWV in diabetic subjects. They found that the generalized transfer function, as derived in an index population, did not describe the relationship between peripheral and central arterial waveforms (4,5).

In the present study, we examined the relationship between PWV and another technique to evaluate the early atherosclerotic lesion, i.e., intima-media thickness (IMT) of the carotid artery in subjects with type 2 diabetes and those without it. IMT of the common carotid artery was measured with high-resolution B-mode ultrasonography (SSA-770A; Toshiba, Tokyo, Japan) with an electrical linear transducer (midfrequency 7.5 MHz), as previously reported (6,7). The localized thickness >2.0 mm was excluded as plaque lesion (6). Brachial-ankle PWV (baPWV) was measured with an automated device (ABI-form; Nippon Colin, Komaki, Japan) that can monitor bilateral brachial and ankle-pressure wave forms using the volume plethysmographic method (1–3). The study population included a total of 245 consecutive Japanese subjects with type 2 diabetes (128 men and 117 women, mean age  $65.6 \pm 9.2$  years [means  $\pm$  SD]) and a total of 91 subjects without diabetes (35 men and 56 women, mean age  $62.3 \pm 9.9$  years). Although there was a significant positive correlation between baPWV and IMT in

subjects with diabetes, the coefficient was very small ( $r^2 = 0.033$ ,  $P < 0.005$ ). In contrast, there was a significant correlation with high coefficient between baPWV and IMT in subjects without diabetes ( $r^2 = 0.286$ ,  $P < 0.0001$ ). Furthermore, baPWV was not significantly related to the presence of plaque in either group.

This preliminary result suggests that PWV is not a feasible index for the early atherosclerotic lesion. It is not, at least in diabetic subjects, considered to be an equivalent to IMT or plaque, which are established indexes for early and advanced atherosclerotic lesion, respectively. Our result was in contrast to another report (1) that indicated a significant positive correlation between PWV and IMT in both diabetic ( $r = 0.482$ ) and control ( $r = 0.424$ ) subjects. It remains to be elucidated whether PWV can be used as a reliable index to evaluate antiatherogenic action of some drug in diabetic subjects (3).

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## The Human Insulin Analog Aspart Can Induce Insulin Allergy

The human insulin analog aspart is produced by recombinant technology that replaces the proline at position 28 on the  $\beta$ -chain of insulin with negatively charged aspartic acid. Insulin aspart exists as hexamers that rapidly dissociate into monomers and dimers after the subcutaneous injection (1); it appears that it has a reduced antigenicity. It has been confirmed to be less immunogenic for development of antibodies than human insulin (2). Several case reports indicated that the human insulin analog aspart does not cause insulin allergy and is a safe alternative in insulin allergy (3,4). But a case report showed that the patient developed cutaneous allergic reactions not only to human insulin but also to the analogs aspart and lispro (5). However, here we report two cases of cutaneous allergic reaction to insulin aspart (Novorapid; Novo Nordisk, Bagsvaerd, Denmark) and no allergic reactions to human insulin (Novolin R and Novolin N; Novo Nordisk).

A 48-year-old woman with type 2 diabetes diagnosed 5 years prior was re-



cluding insulin resistance and measures of total and regional adiposity.

Thus, these results show that hypo-adiponectinemia is closely associated with nonalcoholic hepatic steatosis in obese healthy individuals, thus suggesting that hypo-adiponectinemia might be, at least partly, responsible for hepatic steatosis and liver test abnormalities found in these subjects. Interpretation of our results, however, requires care because of the relatively small number of patients. Future studies using larger cohorts will be needed to validate this hypothesis.

This clinical finding, however, is consistent with a recent study demonstrating that adiponectin administration was effective in alleviating obesity-induced hepatomegaly, steatosis, and serum ALT abnormality in mice (3). The potential hepatoprotective mechanisms include induction of hepatic fatty acid oxidation, inhibition of fatty acid synthesis, and suppression of tumor necrosis factor- $\alpha$  production in the liver. Therefore, in addition to its antidiabetic and antiatherogenic potentials, adiponectin or its agonists may represent a novel agent for the treatment of liver diseases.

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## COMMENTS AND RESPONSES

### Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

#### Response to consensus statement

I commend the authors of the consensus statement in *Diabetes Care* for focusing our attention on the physical health of people with schizophrenia and serious mental illnesses and on the need for glucose monitoring (1). There is little consensus about the risk of diabetes in people with schizophrenia and the role of atypical antipsychotic drugs (2–4). Recently I was a member of a group of international psychiatrists and diabetologists who reviewed the evidence surrounding this issue (proceedings have been published in a supplement to the April 2004 issue of the *British Journal of Psychiatry*). I was, therefore, interested to see that the conclusions published in *Diabetes Care* differed in some respects from our deliberations and those of the U.S. Food and Drug Administration (FDA). In September 2003, the FDA wrote to the manufacturers of all atypical antipsychotic drugs to ask that their respective labels be changed to recommend regular glucose testing for all schizophrenia patients at risk of diabetes. The FDA went on to explain that “[p]recise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.”

The *Diabetes Care* consensus statement suggests that the risk of hyperglycemia for some “atypicals,” such as clozapine and olanzapine, is greater than for others (1). It is unclear how this opinion was reached, because although a bibliography was given, the work was unreferenced. One may speculate that the weight given to the 35 retrospective studies was greater than that for the prospective trials (4); the placebo-controlled studies (5–7) and the longest prospective

study (8), which assessed glucose over 1 year and compared clozapine and chlorpromazine, are not mentioned in the bibliography.

None of the retrospective studies can state how many patients given each drug received blood tests. This is a crucial confounder, as patients receiving typical antipsychotics have less blood monitoring than those receiving “atypicals” (9). Any study that introduces glucose screening will undoubtedly find new previously undiagnosed diabetes because of the high prevalence of undiagnosed type 2 diabetes.

I am unaware of any prospective trial showing any difference among “atypicals” in terms of emergent glucose abnormalities. The best trial data comparing aripiprazole with olanzapine over 6 months found that emergent glucose abnormalities were identical (4.7 vs. 4.5%) (5,7). The use of placebo cohorts is critical to understanding what part of the risk of glucose abnormalities is attributable to drugs. There are two such datasets, and the incidence of diabetes in the placebo cohorts does not differ from that in the active-drug group (5,6).

Interestingly, during the randomized control trials, weight gain was not associated with the development of diabetes and the incidence of diabetes did not differ among the various “atypicals,” despite differing propensity for weight gain. Linking short-term weight gain to the risk of diabetes ignores the many other genetic and environmental reasons why people with schizophrenia develop diabetes (10,11).

Antipsychotic medication is essential for people with schizophrenia, and effectiveness should be the most important consideration when selecting treatment. The FDA was nearer to the mark in its judgement, and choosing an antipsychotic drug on the basis of its potential to worsen glycemia is failing to understand the available data.

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## Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

### Response to consensus statement

The report from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes Consensus Panel (1) contains valuable advice for the appropriate and prudent monitoring of patients who are at risk for type 2 diabetes. The recommendations made are similar to a prior consensus conference (2) and, if they are followed, will benefit our vulnerable patients by the early identification and treatment of metabolic disorders.

However, the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes. Although clear differences exist in liability for weight gain (and consequently dyslipidemias), quantifiable risk differences among the second-generation antipsychotics regarding an association with diabetes have been inconsistent in large published pharmacoepidemiological studies (3). For this reason, the U.S. Food and Drug Administration has notified the manufacturers of the second-generation antipsychotics that product labeling for all drugs in that class will require a new warning about hyperglycemia and diabetes (4). Furthermore, the risk attributable to antipsychotics appears small compared with established risk factors such as family history and advancing age. From the evidence, choosing a second-generation antipsychotic medication does not, in and of itself, have significant predictive value for treatment-emergent diabetes.

Moreover, the report did not adequately address the complex issues regarding antipsychotic efficacy. Although clinical trials may not show big differences in efficacy among antipsychotic groups, modest differences do exist, favoring not only clozapine but also risperidone and olanzapine (5). Although the consensus panel report acknowledged the

primacy of appropriate treatment, for example with clozapine having unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior, other antipsychotics may also have a favorable efficacy profile among treatment-refractory patients in specific treatment domains such as cognitive dysfunction (favoring risperidone and olanzapine) (6). Efficacy considerations are particularly important among patients with persistent aggressive behavior (again, favoring clozapine). Further complicating the risk-benefit equation is the observation that weight gain may be associated with response in about half of the responders to clozapine or olanzapine (7). In addition, interindividual differences in response may be huge, leading to patients receiving several sequential medication trials over the years to find the optimal regimen for that individual.

As clinicians and researchers in a state-operated psychiatric center, where the average patient has failed a number of medication trials, we find obtaining an adequate antipsychotic medication response to be a major challenge. When such a response is achieved, a major focus is to manage somatic problems should they emerge. Efficacy is the prime mover for treatment decisions (8). A switch from a beneficial antipsychotic regimen is usually the last resort after other management approaches have not been successful. Taken out of context, the consensus conference report might lead the inexperienced practitioner to switch medications prematurely and thus expose the patient to the risk of a deterioration in their symptoms and, ultimately, relapse.

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there is greater variance in the accuracy and repeatability of fetal AC measurements than in this study. This reduces the utility of this measurement in standard clinical practice as a criterion for insulin treatment.

The concept that some marker of fetal hyperinsulinemia should be the indicator for aggressive therapy in GDM is an old idea (7,8). The authors stated that fetal AC <75th percentile for gestational age as a marker of minimal adiposity reliably excludes elevated amniotic fluid insulin levels on the day of amniocentesis. However, Kainer et al. (9) found that the sensitivity of excess AC to predict pathological amniotic fluid insulin was only 67% and the specificity was 53%, and Schaefer-Graf et al. (10) originally found that 11 of 74 fetuses with AC <75th percentile had amniotic fluid insulin >97th percentile for 822 nondiabetic control subjects in the landmark study of Weiss (11). Schaefer-Graf et al. also originally showed that the majority of fetuses with AC >75th percentile had normal amniotic fluid insulin. The variance between fetal AC and amniotic fluid insulin is not surprising, since amniotic fluid insulin can vary with time of day and maternal-fetal glycemia in metabolically unstable women.

One wonders why 75 infants of GDM mothers in the German study (1), with normal fetal AC and no hyperglycemia on 2 days/week, had a 19% rate of neonatal hypoglycemia and 17% transfer to NICU. Perhaps it was related to the inclusion of subjects who smoked up to five cigarettes per day, or perhaps it was related to hyperglycemia on the nonmonitored days. The concept that all we have to worry about in GDM is fetal adiposity ignores the long-established fact that nonmacrosomic infants of diabetic mothers can have neonatal morbidity. Furthermore, recent data show that maternal-fetal hyperglycemia can affect fetal/placental gene expression, which might be important in short- and long-term outcomes. Finally, measurement of glycemic responses to daily food intake in GDM is attractive for its educational value in women at high risk of developing type 2 diabetes.

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## Randomized Trial Evaluating a Predominately Fetal Growth-Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Kitzmiller

We truly understand the concerns raised by our study (1) investigating a mainly fetal growth-based management strategy of gestational diabetes mellitus (GDM), since our data questioned the maternal glycemia-based management that we have used for decades. We are grateful for the opportunity of discussion.

Kitzmillier (2) is right that two profiles per week may not be considered as intensified management and that we might have missed occasional events of hyperglycemia. The large-for-gestational-age (LGA) rate in the standard group might have been slightly lower with more insulin therapy. But then we would have ended up with a rate of LGA newborns lower than the normal 10%. The tight blood glucose treatment in the ultrasound group is part of the concept of ultrasound-based management that concentrates intensive intervention on fetuses at risk (3,4).

In contrast to most areas of medicine, a major dilemma in obstetrics is that there is no direct approach to the fetus. We have to rely on methods of surveillance that give us only indirect information about the well-being of the fetus. This implicates, per se, a lack of reliability. We all know about the high false-positive rate of fetal heart tracing. We are faced with the same problem in the management of GDM. From the Pedersen hypothesis, we know that severe maternal hyperglycemia is harmful for the fetus. Fasting glucose values >95 mg/dl and 2-h postprandial glucose >120 mg/dl are considered as an indication for insulin therapy. But where is the evidence for these values to be accepted as normal? When we look at the glucose values from pregnant women with normal glucose tolerance from Parretti's data (5), our thresholds seem to be too high. Where is the evidence that the





abetic and nondiabetic subjects in the study of Mohanlal and Holman (1) is significant by the criterion of AUC because diabetic subjects have much higher fasting triglyceride levels (1.35 vs. 0.77 mmol/l), but when the criterion of IAUC is used, diabetic subjects do not have a significantly higher postprandial triglyceride response. Thus the greater "exposure" of diabetic subjects suggested in this study is mainly due to higher fasting triglycerides than excessive postprandial increase.

The extremely high ( $r = 0.909$ ) correlation found between postchallenge and fasting triglyceride levels is misleading because fasting levels contribute >70% to the postprandial levels.

We have recently shown (3), using a test meal containing 40 g fat, 19 g protein, and only 10 g carbohydrates in nondiabetic subjects, that the triglyceride increment over the fasting value and the IAUC were not correlated with the fasting triglyceride concentration. Thus postprandial hypertriglyceridemia can occur irrespective of the fasting triglyceride concentrations and is better described by incremental values.

We think that each test meal has its advantages and disadvantages and that until a universally accepted oral triglyceride tolerance test (in analogy to the oral glucose tolerance test) is developed, test meals should be in each study and, moreover, incremental rather than absolute triglyceride values should be used for the evaluation of postchallenge hypertriglyceridemia.

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## A Standardized Triglyceride and Carbohydrate Challenge

Response to Thanopoulou, Karamanos, and Roussi

We welcome the comments by Thanopoulou, Karamanos, and Roussi (1), who emphasize the unmet need for a standardized method to assess triglyceride tolerance. In the absence of an acceptable test meal that could readily be made available worldwide, our oral triglyceride tolerance test (OTTT) (2) provides a practical solution for the reproducible evaluation of postchallenge triglyceride tolerance in diabetic and nondiabetic subjects. The incorporation of 50 g of carbohydrate in the OTTT makes it more akin to everyday meals in that fat is usually ingested with carbohydrate and thus more likely to reflect the daily postprandial situation than an isolated fat load. We agree that careful interpretation and reporting of the lipid profiles observed is essential, particularly given the well-recognized close association between fasting and postchallenge triglyceride levels. The routine use of a standardized challenge such as the OTTT would permit more comparable data to be obtained for both clinical and trial-related evaluations of triglyceride tolerance. This in turn would allow for more precise determination of the relative importance of postchallenge triglyceride levels on clinical outcomes and the potential impact of therapies that might differentially affect them.

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## Role of Simvastatin as an Immunomodulator in Type 2 Diabetes

Response to Lopes-Virella et al.

In reading the article by Lopes-Virella et al. (1), we were rather concerned that the authors referred to "creatinine kinase" as a marker of cardiac injury. We are certain that the authors wanted to refer to creatine kinase, which is usually abbreviated as CK, and not "creatinine kinase," as such an enzyme does not exist. Creatine kinase catalyzes the reversible phosphorylation of creatine to phosphorylcreatine, whereas the conversion of creatine to creatinine requires no enzymatic input.

A Medline search performed on 24 April 2004 for the incorrect term "creatinine kinase" revealed a total of 356 entries. Organizing these entries according to which decade they were published, we could see that from 1964 to 1974 there were 2 entries, from 1974 to 1984 there were 20 entries, from 1984 to 1994 there were 128 entries, and finally (rather worryingly) from 1994 to 2004 there were 206 entries. It is evident that the number of entries for the incorrect term "creatinine kinase" has been steadily increasing. We are deeply concerned about this unjustified increase and wish to make more authors aware of the correct terminology.

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## Improper Insulin Compliance May Lead to Hepatomegaly and Elevated Hepatic Enzymes in Type 1 Diabetic Patients

Response to Yu and Howard

We read with interest the recent letter by Yu and Howard (1) describing recurrent episodes of hepatomegaly and pronounced elevation of liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) in type 1 diabetic patients with poor metabolic control and treated with high daily doses of insulin (1.3–2.2 units

•  $\text{kg}^{-1} \cdot \text{day}^{-1}$ ), considering the extra doses are to correct frequent hyperglycemia and/or diabetic ketoacidosis.

Here we describe similar experiences in our patients affected by autoimmune and nonautoimmune diabetes in the pediatric age range. In particular, we have observed a child with diabetes onset at the age of 66 days that was probably not of autoimmune origin (2) because he did not present with type 1 diabetes–susceptible non–Asp/Arg HLA DQ heterodimers (3) and showed the absence of islet cell antibodies, GAD, insulin autoantibodies, and insulinoma-associated protein 2. These last dosages were carried out on frozen serum because they were not all available at the time of diagnosis.

At age 3 years, he presented with the first episode of hepatomegaly and elevated liver enzymes. Other liver function tests, such as alkaline phosphatase, prothrombin/partial prothombin time, and total bilirubin, were normal. Two other episodes were reported in the following 2 years. Although his metabolic control was acceptable on all three occasions, the insulin dose was maintained at a high level for the best possible HbA<sub>1c</sub> (Table 1). This dose was almost twice the usual dose used at this age and is comparable to the 2.2 units •  $\text{kg}^{-1} \cdot \text{day}^{-1}$  described by Yu and Howard.

Hepatic biopsy during the second episode showed abundant glycogen deposits in the hepatocytes and normal mitochondria. On all three occasions, continuous low-dose intravenous insulin normalized the liver enzymes in just a few days.

Now at age 15 years, aside from diabetes, he is in good health. During adolescence the maximum dosage of insulin was 1 unit •  $\text{kg}^{-1} \cdot \text{day}^{-1}$ , which was lower than the dose described by Yu and Howard, yet we found no other episodes of liver damage.

In three other patients with type 1 autoimmune diabetes, we observed a pattern of liver dysfunction during puberty similar to Yu and Howard. In all patients, diabetes was very poorly controlled despite high insulin dosage (Table 1). Liver size and enzymes in these three patients also returned to normal after intravenous insulin. No liver biopsy was performed in any of these cases.

On the basis of our experience, we agree with Yu and Howard when they indicate the pathogenesis of this liver disease in chronic overtreatment with insulin and self-induced hyperinsulinism rather than low metabolic control or diabetes etiology.

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1. Yu YM, Howard CP: Improper insulin compliance may lead to hepatomegaly

Table 1

Patient initials, sex, diabetes onset	First episode age, insulin dose, HbA <sub>1c</sub> (%), AST, ALT (units/ml)	Second episode age, insulin dose, HbA <sub>1c</sub> (%), AST, ALT (units/ml)	Third episode age, insulin dose, HbA <sub>1c</sub> (%), AST, ALT (units/ml)
G.V., male, age 66 days	3.1 years, 1.3 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 5.5, 8,210, 5,880	3.8 years, 1.2 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 7.0, 2,000, 1,000	5.4 years, 1.1 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 8.0, 1,824, 1,604
B.A., female, age 13 years	17 years, 1.5 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 12, 1,420, 1,290		
O.S., female, age 11 years	12 years, 1.5 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 9.8, 1,370, 1,120		
P.V., female, age 7 years	11 years, 1.1 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 13.8, 840, 720	13 years, 1.4 units • $\text{kg}^{-1} \cdot \text{day}^{-1}$ , 12.0, 299, 260 amylase 362	





## Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: a consensus statement from the American Heart Association and American Diabetes Association

Response to Nesto

The introduction of thiazolidinediones (TZDs) has been greeted with enthusiasm in part because of their ability to lower glucose by addressing an underlying pathological feature of diabetes and because TZDs have the potential to ameliorate several cardiovascular markers. This enthusiasm has been tempered by safety concerns. We, therefore, read with interest the American Diabetes Association/American Heart Association consensus statement (1) regarding TZD use, fluid retention, and congestive heart failure (CHF).

We disagree with portions of this statement. In individuals without symptomatic heart disease, we would not start TZDs if the patient had preexisting edema or a history of heart failure, especially since no lower range for a depressed ejection fraction is stated. While this may have a salutary effect on glucose control, it introduces unnecessary complexity and confusion when considering future symptoms and signs. Likewise, we would wait to use TZDs in patients with symptomatic heart failure until ongoing clinical trials establish the safety of these medications in this patient population. We disagree strongly with components of the monitoring section. When someone who is free of CHF develops CHF after the start of a medication known to worsen CHF, a recommendation to “reconsider” or a “dosage change” is unduly restrained, especially given the uncertain time period that is required for the effect of TZDs to dissipate. Additionally, if edema develops after the start of TZDs, the statement invites consideration of alternate causes of edema. While this recommendation is in-

tellectually defensible, it belies the reality that physicians will, with rare exception, stop a medication when a side effect develops that is clearly known to be caused by the medication. In both circumstances, we would stop the medication.

Until ongoing prospective clinical trials ascertain the safety of TZDs in the patients that we cite above, we believe that there should be a strong preference for alternate therapies.

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1. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Winter ML, Porte D, Semenkovich C, Smith S, Young LH, Kahn R: Thiazolidine use, fluid retention and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 27:256–263, 2004

## Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: a consensus statement from the American Heart Association and American Diabetes Association

Response to Elasy and Griffin

We appreciate the letter from Elasy and Griffin (1) containing their approach to the use of thiazolidinediones (TZDs). The goal of our re-

port (2) was to increase awareness of this potentially serious side effect of TZD use. Our recommendations were based on the evidence we reviewed and discussed. We do not disagree with the opinions expressed by Elasy and Griffin and believe that these decisions are always best made by the provider, carefully weighing all of the potential benefits and risks of these medications in their particular patient. We should state that there are many scenarios with individual patients in whom cardiac disease may have been clinically evident or is present at the time TZDs are being considered. The consensus document could not consider all of these and instead aimed to provide the practitioner with general guidelines. The authors of this letter have appropriately come to their own conclusions about the use of TZDs in selected patients with diabetes.

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R.W.N. has received honoraria from GlaxoSmithKline and Takeda.

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