



Cardiovascular Risk of Oral Antidiabetic Drugs: Current Evidence and Regulatory Requirements for New Drugs

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Abstract

Background: Better control of diabetes mellitus reduces microvascular complications, but has limited effect on macrovascular complications including cardiovascular mortality. A spate of controversial reports has shown that some new oral antidiabetic drugs may paradoxically increase cardiovascular events and mortality. We review here published data on cardiac safety of currently available oral antidiabetic drugs.

Methods: Literature search was performed for “cardiovascular risk” and “antidiabetic drugs” or individual oral antidiabetic drugs.

Results: Some sulfonylureas increase cardiovascular risk presumably by preventing protective ischemic cardiac preconditioning. Rosiglitazone increases risk of myocardial infarction and death possibly by increasing serum triglycerides and LDL-cholesterol levels. Muraglitazar increased risk of cardiovascular death, myocardial infarction, or stroke due to as yet unidentified reasons. Only insulin sensitizing drugs like metformin and pioglitazone have been consistently shown to reduce cardiovascular risk. Beneficial effects of tight glucose control with insulin or insulin secretagogues on macrovascular complications are inconsistent; their benefits may be negated by increased risk of hypoglycemia which in turn increases adverse cardiovascular events. Increased cardiovascular risk of some antidiabetic drugs was missed during drug development and detected only on meta-analysis of clinical trial data. Regulatory agencies in North America and Europe have therefore proposed stringent guidelines for study design, data analysis and quantification of cardiovascular risk of new antidiabetic drugs.

Conclusions: Physicians should weigh the cardiovascular risk against potential benefits when prescribing antidiabetic medications. The proposed regulatory measures will ensure approval of safer drugs, but may also lengthen the drug development cycle or even deter development of potentially useful drugs.

Introduction

More than just a disorder of glucose metabolism, diabetes mellitus is now known to encompass other physiological derangements like lipid abnormalities, endothelial dysfunction, microvascular changes and accelerated atherosclerosis.^{1,2} Epidemiological studies show that 65% of deaths in patients with diabetes are caused by cardiovascular events associated with atherosclerosis. The overall mortality risk from cardiovascular events is 2 to 4 times higher in diabetics than in healthy individuals.¹ In fact, diabetes is also termed ‘coronary heart disease risk equivalent’ as the risk of cardiovascular mortality in Type 2 diabetes mellitus (T2DM) is the same as in patients with previous myocardial infarction.³⁻⁶

The primary endpoint in most studies on treatment of T2DM is a reduction of blood levels of glycated haemoglobin (HbA1c), which provides a reliable estimate of glycaemic control over the previous three months. High levels of HbA1c are strongly associated with microvascular complications like retinopathy, nephropathy and neuropathy. An increase of 1% in HbA1c is associated with an 18% increase in the risk of cardiovascular events⁷ and 12 to 14% increase in the risk of death.^{8,9} Furthermore, studies have shown that reduction in HbA1c levels results in decrease in microvascular complications. Current treatment strategies are, therefore, designed to achieve near-normal levels of HbA1c.¹⁰⁻¹⁴ However, reduction of HbA1c has not been found to decrease macrovascular complications.^{10,15,16} While the absence of a beneficial effect on macrovascular complications could be

accepted as an unfortunate limitation of presently available antidiabetic drugs, a spate of reports in the past few years have shown that new antidiabetic drugs reduced HbA1c levels but paradoxically increased cardiovascular events or mortality. We, therefore, reviewed published data on cardiac safety of currently available oral antidiabetic drugs and the proposed regulatory guidelines to ensure cardiac safety of new antidiabetic drugs.

Methods

Literature search was performed using PubMed and Google Scholar using the keywords “cardiovascular risk” and “antidiabetic drugs.” Only English language articles were included. For individual drugs or class of drugs, a combination of “cardiovascular risk” and the specific drug or class were used as keywords. Additional references cited in these articles and regulatory guidelines were also included.

Cardiovascular Risk of Antidiabetic Drugs

Many antidiabetic drugs including sulfonylureas, rosiglitazone, muraglitazar and even insulin have, at some time or the other, been suspected to have adverse cardiovascular effects.

Sulfonylureas

Sulfonylureas have been used for over five decades as a therapy for T2DM and act by increasing insulin release from pancreatic beta cells. The University Group Diabetes Program (UGDP) study was initiated in 1960 and patients were treated

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with the sulfonylurea tolbutamide alone, or placebo, fixed dose insulin or variable dose insulin.¹⁷⁻¹⁹ Surprisingly, an excess of cardiac deaths was found in the tolbutamide group (12.7%) compared to 4.7% with placebo, 6.2% with fixed dose insulin and 5.9% with variable dose insulin; the tolbutamide arm of the study was prematurely terminated. This led some experts to conclude that sulfonylureas, as a class, were associated with increased cardiovascular mortality while others criticized the design and analysis of the UGDP study and questioned its conclusions.¹⁹ More than a decade later, animal studies revealed that sulfonylureas exert their effect by binding to sulfonylurea receptors (SUR), which are closely linked to ATP-dependent potassium channels. By binding to SUR1 receptors on pancreatic beta cells sulfonylureas exerted their insulinotropic effect.²⁰⁻²³ Some sulfonylureas also act on SUR2A/B receptors on the myocardium and coronary smooth muscle and prevent development of protective ischemic preconditioning.²³ The adverse cardiac effects of sulfonylureas are probably due to interference with adaptive ischemic preconditioning — a phenomenon where repeated exposure to mild or moderate ischaemia protects the myocardium against damage during subsequent episodes of severe ischemia.²³

The next-generation sulfonylureas like gliclazide or glipizide exhibit lower SUR2 affinity (SUR1/SUR2A ratio of gliclazide is 16000)²³ and have shown favorable cardiovascular outcomes when used as initial pharmacotherapy.²⁴ Retrospective studies have also shown that glibenclamide (SUR1/SUR2A ratio of 6.4)²³ and glimepiride (SUR1/SUR2A ratio of 1.35),²³ which have lower SUR1 selectivity, are associated with an increase in cardiovascular events including angina, myocardial infarction, stroke, peripheral vascular disease.²⁴ In a one-year retrospective study of 9876 diabetics with acute myocardial infarction, Jorgenson et al found that the hazard ratio for cardiovascular mortality and/or nonfatal MI was 1.19 (95% CI 1.06-1.32) with glimepiride and 1.31 (95% CI 1.17-1.46) with glibenclamide and 1.03 (95% CI 0.88-1.22) with gliclazide when compared with metformin.²⁴ However, differential affinity of individual sulfonylureas for pancreatic and cardiac receptors cannot explain why tolbutamide, with a SUR1/SUR2A ratio of 314.8, is associated with increased cardiac mortality. Besides, in the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, targeting lower blood glucose (in the range of 7.0 to 7.9% HbA1c) with drugs that included gliclazide did not significantly increase cardiac morbidity or mortality.²⁵ In balance, considering the efficacy of sulfonylureas like glimepiride, glipizide or gliclazide in reducing HbA1c and improved glucose control, and the uncertain adverse cardiac risk associated with their use, sulfonylureas are currently recommended by the American Diabetes Association (ADA) for patients with T2DM in whom glycaemic control is not satisfactory with diet and metformin.²⁶

Metformin

Metformin belongs to the class of biguanides and reduces blood glucose levels through suppression of gluconeogenesis, stimulation of peripheral glucose uptake by tissue (mainly skeletal muscles) in the presence of insulin, and decreases absorption of glucose from the gastrointestinal tract.²⁷ The United Kingdom Prospective Diabetes Study (UKPDS) 34 showed that metformin therapy was associated with risk reduction of 32% (95% CI, 13% to 47%) for any diabetes-related (microvascular and macrovascular) endpoints when compared to insulin or sulfonylureas (chlorpropamide or glibenclamide).^{11,28} It also showed a 42% reduction in diabetes-related deaths (95% CI, 9%

to 63%), and 36% reduction in all-cause mortality (95% CI, 9% to 55%).¹¹ Metformin is therefore recommended by the ADA as the first line drug in patients with T2DM not controlled with diet and lifestyle modification. However, metformin should be avoided in heart failure, renal insufficiency (creatinine clearance <30ml/min), hepatic dysfunction, metabolic acidosis and acute illness as it may cause lactic acidosis in these patients.²⁶

Muraglitazar

Muraglitazar, a dual peroxisome proliferator-activated receptors (PPAR) agonist, binds to PPAR-gamma and PPAR-alpha receptors. PPAR-gamma activation results in insulin sensitization and antidiabetic action while PPAR-alpha activation increases HDL cholesterol synthesis, stimulates “reverse” cholesterol transport and reduces triglycerides.²⁷ In Phase II studies, muraglitazar, improved glucose and lipid homeostasis although it caused weight gain, fluid retention and edema. Based on results of Phase II and Phase III studies, in 2005 an advisory committee for the FDA recommended approval of the drug for treatment of T2DM.²⁹ Soon after this, a meta-analysis was published, which included one Phase II and four Phase III trials from the muraglitazar clinical development program.³⁰ Patients receiving metformin or glyburide were randomized to receive muraglitazar or pioglitazone or placebo in addition to their original antidiabetic medication.³⁰ Death, MI, or stroke occurred in 35 of 2374 (1.47%) muraglitazar-treated patients, compared with 9 of 1351 (0.67%) patients in the placebo and pioglitazone groups (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; P=0.03).³⁰ Further development of muraglitazar was discontinued. While the exact reason for increased mortality with muraglitazar is not clear, some authors hypothesize that it may be due to its effect on inflammation.³¹⁻³³

Meglitinides

Meglitinides are insulin secretagogues and act on the ATP-dependent potassium channels and other receptors on pancreatic beta-cells. Meglitinides have a short duration of action and when taken with meals, produce pronounced dose-dependent reduction of postprandial plasma glucose levels³⁴ while decreasing hypoglycemia during the late postprandial phase.²⁷ Of the two meglitinides currently available, repaglinide decreases HbA1c levels by about 1.5%, while nateglinide is somewhat less effective in lowering HbA1c.^{26,34}

The package insert of repaglinide mentions that “the incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials.”³⁵ However, patients on repaglinide had more severe coronary artery disease at baseline in this study. After adjusting for this baseline difference, the relative risk declined³⁵ and the package insert claims, “In 1-year controlled trials, repaglinide treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agents.” After weighing the risk and benefits, the ADA recommends meglitinides for controlling postprandial blood glucose levels along with metformin.²⁶

Rosiglitazone and the Thiazolidinediones

Introduced in 1997, the thiazolidinediones are insulin sensitizers that bind to PPAR-gamma receptors, which are nuclear transcription factors³⁶ that modulate gene expression, leading to increased glucose transporter expression.²⁷ Troglitazone, the

first agent in this class to receive approval, was withdrawn in 1999 due to hepatotoxicity. Around the same time rosiglitazone and pioglitazone commenced marketing in the US.³⁶ In the data submitted for regulatory approval, rosiglitazone was found to be superior to placebo, metformin or glibenclamide in reducing HbA1c.^{37,38} The drug received approval in 1999 and became one of the 25 best-selling drugs in that year.³⁹ However, in 2007, Nissen and Wolski published the results of their meta-analysis of the long-term cardiovascular risk of rosiglitazone from 42 randomized clinical trials using data available from the manufacturer's website.⁴⁰ As compared with the control group, the odds ratio (OR) for myocardial infarction was 1.43 (95% CI, 1.03 to 1.98; $P = 0.03$) and 1.64 (95% CI, 0.98 to 2.74; $P = 0.06$) for death from cardiovascular causes with rosiglitazone.⁴⁰ Although the OR for death from any cause did not reach statistical significance (OR 1.18; 95% CI, 0.89 to 1.55; $P = 0.24$), this paper raised serious questions about the overall therapeutic benefit of rosiglitazone. A similar meta-analysis was also performed by the FDA in 2007, using patient-level data available with the regulatory agency.^{41,42} This analysis showed that rosiglitazone did not significantly increase risk of myocardial infarction (OR 1.5; 95% CI, 0.9 to 2.7) or death from cardiovascular causes (OR 1.7; 95% CI, 0.7 to 5).⁴² In 2008, Mannucci et al published another meta-analysis that included data from 164 trials with at least 4 weeks of follow-up and showed that the OR for myocardial infarction and death from cardiovascular causes was 1.14 (95% CI, 0.9 to 1.45) and 0.94 (95% CI, 0.69 to 1.29) in the rosiglitazone group as compared with the control group.⁴³ However, this study has limited inferential value, due to inclusion of CV safety trials which were as short as 4 weeks. The differing conclusions from these meta-analyses based on studies that were not designed to assess cardiac safety sparked off considerable controversy, and the pharmaceutical company initiated a larger randomized controlled trial named the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) study to resolve the issue. Cardiac safety and risk of fractures were the primary end points of this study that aimed to enroll 15000 patients between 2009 and 2015.⁴⁴ Meanwhile, in 2010, the FDA released an updated meta-analysis of 52 trials including data from the 'Diabetes reduction assessment with ramipril and rosiglitazone medication' (DREAM) and 'Rosiglitazone evaluated for cardiac outcomes and regulation of glycaemia in diabetes' (RECORD) trials. The OR for myocardial infarction and death from cardiovascular causes was 1.8 (95% CI, 1.0 to 3.3) and 1.5 (95% CI, 0.6 to 3.8) in the rosiglitazone group.⁴² Nissen and Wolski too published an updated meta-analysis which also found that rosiglitazone increased risk of myocardial infarction (HR 1.28, 95% CI 1.01 to 1.62) but not cardiac or all-cause mortality.⁴⁵ With the new evidence, the TIDE study was stopped in 2010 after recruiting 1000 patients in 18 months.⁴⁶ In 2010, rosiglitazone was withdrawn from Europe on the recommendation of the EMEA because of its cardiovascular effects³⁷ but continues to have a restricted availability in the United States⁴⁷ and several other countries.

In similar meta-analyses, pioglitazone, the other approved thiazolidinedione, was not found to increase in adverse cardiovascular risk.^{48,49} A recent study by Juurlink et al found that pioglitazone treated patients had a lower risk for composite outcomes based on death or hospital admission for either acute myocardial infarction or heart failure (adjusted HR 0.83, 95% CI 0.76 to 0.90) and for outcomes like death (adjusted HR 0.86, 0.75 to 0.98) and heart failure (0.77, 0.69 to 0.87) compared to patients treated with rosiglitazone, but not the risk of acute

myocardial (adjusted HR 0.95, 95% CI 0.81 to 1.11).⁵⁰ Thus, unlike rosiglitazone, pioglitazone does not seem to be associated with increased cardiovascular risk. However, like rosiglitazone, pioglitazone does increase the risk of new-onset heart failure and worsen pre-existing heart failure (HR 1.27; 95% CI 1.18-1.37 with rosiglitazone and 1.25; 95% CI 1.16-1.34 with pioglitazone).⁵¹ This is believed to be a class effect of thiazolidinediones and these drugs should be avoided in patients with congestive heart failure.²

Do any Antidiabetic Drugs Reduce Cardiovascular Risk?

Unfortunately, there is limited evidence of a beneficial effect of any antidiabetic drug on atherosclerotic cardiovascular disease in T2DM. Even insulin has not been convincingly shown to reduce macrovascular complications of diabetes. Patients with T2DM have insulin resistance, hyperglycemia and hyperinsulinaemia. Whether hyperglycemia or hyperinsulinaemia is the cause of macrovascular disease in T2DM is debatable.⁵² Increased cardiovascular morbidity and mortality in individuals with the metabolic syndrome who have insulin resistance and hyperinsulinaemia but no hyperglycemia, suggests that hyperinsulinaemia may be the culprit. Animal studies have revealed that insulin is atherogenic probably due to its mitogenic properties; it also causes weight gain. Thus, although insulin achieves better glycaemic control and decreases microvascular complications in T2DM, it could theoretically increase cardiovascular morbidity and mortality.⁵³ Long-term follow-up of patients with T2DM in the UKPDS 34, showed a significant reduction in myocardial infarction and all-cause mortality in the intensive treatment group which included insulin.^{54,55} However, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial¹² and Veterans Affairs Diabetes Trial (VADT) showed no macrovascular benefit from intensive glucose control regimen that included insulin.⁵⁶ The ACCORD trial actually suggested an increase in all-cause and cardiovascular mortality.^{25,26} Recent meta-analyses of these trials have shown that intensive glycaemic control, often using multiple modalities including insulin, may be safe and actually reduces some macrovascular end points like acute myocardial infarction.^{28,57} In balance, the evidence of the beneficial effect of insulin on macrovascular complications is still inconclusive. However, these meta-analyses do show that treatment with insulin does not increase macrovascular complications.^{28,57}

The only antidiabetic agent which has frequently shown reduced cardiovascular morbidity and mortality is metformin. The UKPDS 34 study showed that metformin therapy was associated with significant reduction of 42% for diabetes-related death (95%CI, 9% to 63%) when compared to insulin or sulfonylureas (chlorpropamide or glibenclamide).¹¹ Importantly, this survival benefit persisted over the 10 years of post-trial follow-up with a risk reduction of 33% for metformin versus other modalities.⁵⁵ In a retrospective observational study of 16,417 Medicare beneficiaries with T2DM and congestive heart failure, Masoudi et al observed that all-cause mortality at 1 year was significantly lower in patients treated with metformin (HR 0.86; 95% CI, 0.78-0.97) as compared to patients receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin.⁵⁸ Other observational studies too have shown lower incidence of new onset heart failure and readmissions for heart failure with metformin.^{59,60}

More recently, pioglitazone too has been associated with favorable cardiovascular outcomes. In the PROactive (Prospective Pioglitazone Clinical Trial In Macrovascular Events) study, pioglitazone or placebo were added on to ongoing antidiabetic treatment. Patients who received pioglitazone showed a 16% reduction in the composite end point of death, MI, or stroke (HR 0.84, 95% CI 0.72–0.98) although reduction in the primary composite endpoint (coronary and peripheral vascular outcomes) was not significant.⁴⁹ Thus, unlike rosiglitazone, pioglitazone could actually decrease cardiovascular risk, presumably due to its beneficial effects on the lipid profile. While rosiglitazone increases levels of triglycerides and LDL cholesterol and the size of LDL particles, pioglitazone lowers triglyceride and LDL cholesterol in serum while increasing HDL cholesterol levels.⁴⁹ Moreover, pioglitazone also has a favorable effect on blood pressure and inflammatory markers.⁶¹

A major confounding factor in studying the cardiovascular effects of antidiabetic therapies has been the risk of hypoglycemia with most insulin-secretagogues or insulin itself, especially when lower levels of HbA1c are targeted in randomized studies.^{11,12,25,49} A recent meta-analysis shows that patients with long-standing diabetes are at greater risk of adverse cardiovascular effects and also increased risk of hypoglycemia.⁶² In fact, a direct correlation can be observed between incidence of severe hypoglycemia and cardiovascular mortality.⁶² Hypoglycemia may increase cardiovascular events by causing sympathetic over-activity, QT interval prolongation, cardiac arrhythmias, plaque inflammation and rupture,⁶³ thereby negating the benefits of better glucose control. Some authors therefore suggest that maximum cardiovascular benefit may be obtained with antidiabetic drugs that do not cause hypoglycemia (metformin, pioglitazone, alpha-glucosidase inhibitors) rather than insulin or its secretagogues like sulfonylureas.⁶³ However, most patients with long-standing or severe diabetes mellitus invariably require the addition of insulin or a secretagogue to achieve satisfactory glycaemic control.

The Future of New Antidiabetic Therapies

The United States FDA in 2008⁶⁴ and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency in 2010, released draft guidelines on evaluation of new antidiabetic therapies before approval for marketing.⁶⁵ Lowering of HbA1c remains the preferred endpoint for demonstrating efficacy of new drugs.⁶⁴ However, a new antidiabetic agent should also be studied for effects on macrovascular complications including mortality.⁶⁵ To claim cardiovascular benefit, a new drug should be assessed in a large long-term clinical trial with at least 3 years of follow-up.⁶⁵ Since individual cardiovascular events may be few in number and may not reach statistical significance, the guidance recommends use of a composite endpoint termed MAJOR Cardiovascular Events (MACE), which includes cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, myocardial ischemia and hospitalization for acute coronary syndrome, coronary revascularization or worsening heart failure.⁶⁴⁻⁶⁶

Recognizing that demonstration of reduction of macrovascular complications will increase drug development costs and also delay the approval of potentially useful antidiabetic drugs, the draft guidance states that at the very least, the new drug must be shown to be devoid of adverse cardiovascular effects.⁶⁴ Phase II and III studies should involve longer follow-up (≥6

months for studies with monotherapy with the new drug and 2 years in confirmatory trials). It also recommends inclusion of patients with high risk of cardiovascular events (estimated annual risk >3%) in Phase II and III studies to ensure that the study population closely matches the target population in whom the new drug is likely to be used, and also to provide enough patients with cardiac events to permit meaningful estimation of cardiac safety.^{64,65} An independent cardiovascular endpoints committee must prospectively adjudicate cardiovascular events during Phase II and III trials in a blinded manner. Concomitant medications should be kept stable throughout the study to avoid masking of deleterious effects on co-morbidities like lipid profile or blood pressure. Other endpoints like cardiac function on echocardiography, brain natriuretic peptide levels and presence of cardiac arrhythmias could also be included.⁶⁵

The controversy around rosiglitazone arose due to differing interpretations of different meta-analyses.⁶⁷ Inclusion of studies with heterogeneous designs including non-uniform definitions of cardiac endpoints or short durations of follow-up in meta-analysis results in wider confidence intervals and may limit its ability to provide conclusive answers. The new regulatory guidance therefore recommends that Phase II and Phase III studies should be designed using consistent definitions of adverse cardiovascular events and have sufficiently long follow-up. Sponsors are also required to submit their own meta-analysis of all Phase II and III data including placebo-controlled, active-drug controlled and add-on trials to quantify cardiovascular risk of the new drug.¹ Finally, the US FDA guidance objectively defines the acceptable levels of cardiovascular risk.

- If the upper bound of the two-sided 95% CI of the estimated risk ratio from the meta-analysis of Phase II and III data is ≥ 1.8 , then a large safety trial should be conducted before approval is sought. This should be able to demonstrate that the upper bound is below 1.8, either by itself, or after pooling data with other pre-marketing studies. Even if the upper bound of estimated risk is < 1.8 , the point estimate of risk should be < 1.5 .
- If the upper bound of the 95% CI of estimated risk is between 1.3 and 1.8, a post-marketing study will be required to show that the upper bound of the 95% CI is < 1.3 .
- If the pre-approval data shows that the upper bound is < 1.3 , further cardiovascular safety trials may not be required.

Conclusion

While tight glycaemic control may decrease the development of microvascular complications in patients with T2DM, evidence that it decreases macrovascular complications is limited. In fact, a number of antidiabetic drugs may actually increase risk of myocardial infarction and cardiovascular mortality. Physicians should therefore weigh the cardiovascular risk against potential benefits when prescribing antidiabetic medications. Since cardiovascular adverse events are generally few in numbers, they may be missed in pre-marketing clinical trials which are not powered to detect these infrequent events. To overcome these concerns, regulatory agencies have proposed clear guidelines to ensure that new antidiabetic drugs are studied more intensively to prove that they are at least neutral in their cardiovascular effects. These measures will provide reasonable assurance to physicians and patients that new antidiabetic drugs are not only effective, but also safe. However, these measures will prolong the drug development cycle by 18 to 24 months and increase costs by an estimated US\$ 600 to 750 million⁶⁸ which could delay

the approval of useful drugs or even deter development of new antidiabetic therapies.

Conflict of Interest statement

Gopi Krishna Panicker, Vaibhav Salvi, and Snehal Kothari are employees of Quintiles Cardiac Safety Services, Mumbai. Dilip Karnad is a consultant to Quintiles Cardiac Safety Services and Bharat Serum and Vaccines Ltd and has been on the Advisory Board of Abbott Nutrition (India) and Glaxo SmithKline (India). Stock Ownership: None Honoraria: None Research Funding: None Expert Testimony: None Other Remuneration: None

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