JACC: CARDIOVASCULAR IMAGING
VOL. 4, NO. 10, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.09.003

iVIEW

EDITOR'S PAGE

Imaging of Pharmacologic Intervention

Decoding Therapeutic Mechanism or Defining Effectiveness?

Thomas H. Marwick, MBBS, PhD,* Jagat Narula, MD, PhD†

Thiazolidinediones (TZD) have a variety of cardiovascular effects (1), and despite the expectation of cardiovascular benefits from improved glycemic control, some members of the group appear to have an adverse effect on mortality (2). These paradoxical findings reflect the complexities of the pathophysiological processes linking diabetes to adverse cardiovascular outcomes, including effects on atheroma burden, plaque vulnerability (including necrosis and inflammation), and platelet activity. In this issue of *iJACC*, 2 papers use imaging techniques to address the role of TZDs in plaque inflammation in animals and humans (3,4). Both studies show this agent to reduce plaque inflammation, as evidenced by fluorodeoxyglucose uptake relative to controls; 1 of the manuscripts also showed histologically-verified reduction of neovascularization. These findings, which suggest a role for pioglitazone in reducing plaque vulnerability, supplement previous studies that demonstrate reduced plaque burden with TZDs (5,6).

These studies provide mechanistic information about the effects of TZDs on the cardiovascular system, but it would not be appropriate to conclude from these findings that the concern about the cardiovascular sequelae of TZDs was ill-placed or that we should feel reassured about the cardiovascular safety of these agents. Despite these reassuring findings, we need to recognize that the effects of these agents are complex and inconsistent (7,8), and more importantly, the limitations of using surrogate endpoints and a reminder for us to focus on the "bigger picture" (9).

Nearly 20 years ago, the U.S. Food and Drug Administration defined a surrogate endpoint as a laboratory measurement that can be used as a substitute for a clinically meaningful endpoint (e.g., health status, functional status, or survival) and that is expected to predict the effect of the therapy (10). In situations where achievement of adequate statistical power with clinical outcomes would require large numbers of patients to be followed over long periods, their substitution with surrogates can control the size, duration, and cost of studies. The Prentice criteria (11) broadly stipulate that the marker (in this case, plaque burden or inflammation) should be associated with clinical outcome, but they also require that the marker fully capture the net effect of treatment on outcome. Both components of this definition are potential sources of problems. For example, while clinicians use blood pressure, glycosylated hemoglobin, and intraocular pressure as valid markers of the risks of hypertensive complications, diabetic microvascular complications, and visual loss from glaucoma, arrhythmia suppression is not a good surrogate for long-term survival (12). Nonetheless, the greater barrier is posed by the second component of these criteria. Perhaps the best example is that of torcetrapib, which documented a beneficial effect on high-density lipoprotein, but was associated with an increase in adverse cardiovascular events (13). Generally, the association of surrogate endpoints with outcome seems to be dependent on the complexity of the process involved. The TZD agents are involved in many pathways, such that a favorable response in one part maybe counterbalanced by an unfavorable response in another.

Fleming and DeMets (14) described 4 pathways through which surrogates may fail as markers of hard endpoints, which may be applied to the specific topic of TZD evaluation:

1. Absence of the surrogate from the causal pathway of disease. This might apply to studies

From the *Cleveland Clinic, Cleveland, Ohio; and †Mount Sinai Hospital, New York, New York.

where improved glycemic control is used as a surrogate of macrovascular disease endpoints.

2. Presence of multiple causal pathways. Several studies have documented an association of TZD with a reduction of atherosclerotic burden, for example, based on reduced carotid intima-medial thickness (3,4). There is a risk in overstating the importance of this finding; few patients die from increasing atherosclerotic burden, in comparison with the numbers developing acute complications due to plaque rupture and thrombosis. Indeed, while composite analyses of studies linking the regression of coronary plaque burden to reduced coronary events have shown them to be associated (15), the clinical outcome that dominates this link is revascularization rather than mortality.
3. Involvement of the surrogate in the pathway, without the surrogate being influenced by the drug, even if it is effective. This might apply to other indexes of plaque instability, such as necrosis and apoptosis (7).
4. The effect of the drug has disease-independent effects that may not influence the surrogate. The TZDs have multiple pleiotropic effects, including on hypertension, angiotensin-2, and renal protection (16), that may benefit outcome and yet not influence imaging surrogates.

The limitation of imaging surrogates for agents such as TZDs is that they influence a huge variety of pathways, extending even to associations with neoplasia (17). Imaging markers teach valuable lessons about biological activity. They supplement but may not necessarily replace the need for clinical outcomes studies defining the long-term risks and benefits of pharmacological interventions (18).

REFERENCES

1. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 2011;342:d1309.
2. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
3. Vucic E, Dickson SD, Calcagno C, et al. Pioglitazone modulates vascular inflammation in atherosclerotic rabbits: noninvasive assessment with FDG-PET-CT and dynamic contrast-enhanced MR imaging. J Am Coll Cardiol Img 2011;4:1100–9.
4. Mizoguchi M, Tahara N, Tahara A, et al. Pioglitazone attenuates atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetes: a prospective, randomized, comparator-controlled study using serial FDG PET/CT imaging study of carotid artery and ascending aorta imaging. J Am Coll Cardiol Img 2011;4:1110–8.
5. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–73.
6. Webb DR, Davies MJ, Gray LJ, et al. Searching for the right outcome? A systematic review and meta-analysis of controlled trials using carotid intima-media thickness or pulse-wave velocity to infer anti-atherogenic properties of TZDs. Diab Obes Metab 2010;12:124–32.
7. Thorp E, Kuriakose G, Shah YM, Gonzalez FJ, Tabas I. Pioglitazone increases macrophage apoptosis and plaque necrosis in advanced atherosclerotic lesions of nondiabetic low-density lipoprotein receptor-null mice. Circulation 2007;116:2182–90.
8. Gerstein HC, Ratner RE, Cannon CP, et al. Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. Circulation 2010;121:1176–87.
9. Finn AV, Chandrashekhar Y, Narula J. Seeking alternatives to hard end points: is imaging the best APPROACH? Circulation 2010;121:1165–8.
10. Department of Health and Human Services. Food and Drug Administration. New drug, antibiotic, and biological drug product regulations: accelerated approval. Federal Register 1992;57:13234–42.
11. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8:431–40.
12. Pratt CM, Moye LA. The Cardiac Arrhythmia Suppression Trial: background, interim results and implications. Am J Cardiol 1990;65:20B–29B.
13. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109–22.
14. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.
15. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399–407.
16. Sugawara A, Uruno A, Kudo M, Matsuda K, Yang CW, Ito S. PPARγ agonist beyond glucose lowering effect. Korean J Intern Med 2011;26:19–24.
17. Stephenson J. Diabetes drug may be associated with increase in risk of bladder cancer. JAMA 2011;306:143.
18. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.