EDITORIAL (SEE VAN MELLE ET AL., P. 2084)

Diabetes and Heart Failure in Patients With Coronary Disease: Separating Markers From Mediators

Patients with type 2 diabetes compared with nondiabetic patients have two- to fivefold higher risk for developing heart failure (1–3) and have poorer outcomes once heart failure is present (4,5). These relationships have been identified in observational studies spanning the clinical spectrum of diabetes, including cohorts comprising patients with newly diagnosed type 2 diabetes (6), patients with or at high-risk for coronary heart disease (7,8), and those suffering acute coronary syndromes (9–11). In the study by van Melle et al. (12) published in this issue of *Diabetes Care*, the relationship between diabetes and heart failure risk among patients with stable coronary heart disease is again observed. In addition, the observation is made that higher A1C is linearly and independently associated with increased heart failure risk, independent of whether the patient has established diabetes, with the relationships qualitatively and quantitatively similar to prior reports (8,13). Before reviewing these observations in the context of the existing literature, a few comments with regard to the study design, analyses, and interpretations of van Melle et al. are warranted.

While the reported observations are consistent with much of the existing literature associating disordered glucose metabolism with incremental heart failure risk, it must be noted that this study identified only 77 incident heart failure events, including 30 among patients with diabetes (15.0%) and 47 in those without diabetes (7.4%). This small number of events limits the statistical power and precision of the analyses and calls for commensurate caution in the interpretation of the significance and magnitude of the reported associations. In addition, such a small number of observed outcome events limit the degrees of freedom in multivariable models. Standard convention would limit the testing of 8–10 covariates at the most in a population with 77 events (i.e., the number of observed events divided by 8–10) (14). In the final model presented, 18 covariates were included (including diabetes status and A1C measure), which runs the risk of overfitting the data and thereby potentially overestimating the magnitude and significance of observed associations. Finally, the failure to capture and analyze a number of clinical factors that may influence heart failure risk, especially those unique to patients with diabetes (e.g., concomitant therapy with insulin and thiazolidinediones, duration of diabetes, distinction of type 1 vs. type 2 diabetes, and concomitant microvascular disease, among others), further challenges the interpretation of the observations.

Beyond these methodological limitations, one must also exercise caution in interpreting the observed associations as evidence of a causal link, as van Melle et al. imply based on the association between increasing A1C and heart failure risk. The present observations (as do any observational analyses of association) fall well short of providing proof of causality. In fact, in the analyses limited to those patients with medically treated diabetes, no association was observed between A1C and heart failure, indirectly challenging the hypothesis that modifying A1C would alter the relationship along the continuum of the association. This issue has been recently demonstrated in the negative trial results of three large-scale randomized trials of intensive versus standard glucose control with regard to cardiovascular risk mitigation (15–17). Each of these trials was designed based on the anticipated treatment effect of such interventions derived from epidemiological modeling of the association between A1C and atherosclerotic event rates, a method that markedly overestimated the observed magnitude of the treatment effect observed (6). Thus, it remains entirely unclear whether poor glycemic control is a marker or a mediator (i.e., causative) of adverse cardiovascular events like heart failure.

Noting these limitations and assuming the observations of van Melle et al. are valid added to an extensive existing literature: what may we learn from such findings? While the high prevalence of concomitant morbidities known to contribute to heart failure among patients with diabetes—principal among them hypertension and coronary artery disease—undoubtedly contribute to increased risk, several studies have demonstrated that substantial heart failure risk associated with diabetes remains even after adjusting for these factors (8,18). Incremental information in this regard may be derived from the present study by van Melle et al. (12) where diabetes remained powerfully and independently associated with incident heart failure risk even after adjusting for interval ischemic events and the burden of ischemia derived from exercise stress testing, suggesting that other factors associated with diabetes likely contribute.

While the etiologic underpinnings of the observed associations between diabetes and heart failure risk beyond the excess burden of traditional risk factors remain poorly understood, the potential contributory role of a number of specific metabolic perturbations occurring in the setting of diabetes due to hyperglycemia, insulin resistance, dysregulation of lipid metabolism, perturbations of myocardial substrate metabolism, cardiac steatosis, aggregation of advanced glycation end products, or a combination of these and other metabolic insults continue to be the foci of many scientific investigations (19–21). Further understanding of these mechanistic links may serve to better inform clinical decision-making by refining risk prediction and providing the pathophysiological rationale for the use and further study of existing therapeutic options and may accelerate new drug development in pursuit of novel specific targets for pharmacological intervention.

The observed association between higher A1C and increasing heart failure risk, similar to previous published associations of both fasting glucose and A1C with incident heart failure risk (13,22,23), is intriguing and is compatible with the hypothesis that more intensive glucose control may mitigate such

risk. However, the accumulated evidence from trials strongly refute this hypothesis with no observed effect on heart failure incidence with more versus less intensive glucose control observed across the three recently reported cardiovascular outcome trials comprising an aggregate total of almost 1,000 incident heart failure events (15–17). Furthermore, some diabetes drugs may have deleterious effects independent of the degree of glucose control, such as the well-known increase in heart failure risk with thiazolidinediones (24), increased peripheral edema that may mimic heart failure with insulin use (25), and inhibition of ischemic preconditioning with sulfonylurea drugs (26,27). Conversely, other drugs have been hypothesized to have salutary effects on cardiac function and heart failure outcomes independent of glucose regulation and may yield favorable effects on heart failure incidence and outcomes (28–30). The clinical relevance of these observations, individually and in aggregate, remains poorly understood.

As readers of *Diabetes Care* are certainly aware, the regulatory landscape for the development of diabetes drugs has undergone a major transformation over the past 2 years (26,31). Approval of all diabetes drugs will now require testing in cohorts at high cardiovascular risk and, at a minimum, the demonstration of cardiovascular safety; whether existing drugs will have to undergo similar assessments remains uncertain. Although the focus of such regulatory guidance has been on the effects of therapies on atherosclerotic vascular disease risk, heart failure is a common comorbidity in these populations. On this regulatory backdrop—and with continuing advances in both clinical and translational research—we are likely to continue to evolve our understanding with regard to the mechanistic links between diabetes, measures of glucose control, and heart failure; gain insight and evidence with regard to the effects of glucose control on heart failure risk; and derive further information with regard to specific diabetes therapies that may influence cardiac performance and heart failure risk independent of glucose modulation. These possibilities underpin certain optimism for patients with diabetes who must live with the substantial threat of developing heart failure and for the clinicians who care for them.

Darren K. McGuire, md, mhsc[1,2]
M. Odette Gore, md[2]
Frederick A. Masoudi, md, msph[3]

From the [1]Division of Cardiology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; the [2]Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; and the [3]Division of Cardiology, Department of Medicine, Denver Health Medical Center, Denver, Colorado.

Corresponding author: Darren K. McGuire, darren.mcguire@utsouthwestern.edu.

DOI: 10.2337/dc10-1123

Acknowledgments— D.K.M. reports consultancy relationships with Tethys Bioscience, F. Hoffmann-La Roche, and Daiichi-Sankyo. No other potential conflicts of interest relevant to this article were reported.

References

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34(1):29–34
2. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care 2004;27:1879–1884
3. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. Circulation 1991;83:356–362
4. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. Circulation 2005;111:583–590
5. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102:1014–1019
6. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
7. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259
8. Lewis EF, Solomon SD, Jablonski KA, Rice MM, Clemenza F, Hsia J, Maggioni AP, Zabalgoitia M, Huynh T, Cuddy TE, Gersh BJ, Rouleau J, Braunwald E, Pfeffer MA, PEACE Investigators. Predictors of heart failure in patients with stable coronary artery disease: a PEACE study. Circ Heart Fail 2009;2:209–216
9. Jaffe AS, Spadaro JJ, Schechtman K, Roberts R, Geltman EM, Sobel BE. Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus. Am Heart J 1984;108:31–37
10. McGuire DK, Newby LK, Bhapkar MV, Moliterno DJ, Hochman JS, Klein WW, Weaver WD, Pfisterer M, Corbalán R, Dellborg M, Granger CB, Van De Werf F, Topol EJ, Califf RM, SYMPHONY and 2nd SYMPHONY Investigators. Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. Am Heart J 2004;147:246–252
11. McGuire DK, Emanuelsson H, Granger CB, Magnus Ohman E, Moliterno DJ, White HD, Ardissino D, Box JW, Califf RM, Topol EJ. Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes: findings from the GUSTO-IIb study. GUSTO IIb Investigators. Eur Heart J 2000;21:1750–1758
12. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the Heart and Soul Study. Diabetes Care 2010;33:2084–2089
13. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103:2668–2673
14. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–1379
15. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
16. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572

17. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360: 129–139
18. Aguilar D, Solomon SD, Køber L, Rouleau JL, Skali H, McMurray JJ, Francis GS, Henis M, O'Connor CM, Diaz R, Belenkov YN, Varshavsky S, Leimberger JD, Velazquez EJ, Califf RM, Pfeffer MA. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. Circulation 2004; 110:1572–1578
19. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005; 294:334–341
20. Saunders J, Mathewkutty S, Drazner MH, McGuire DK. Cardiomyopathy in type 2 diabetes: update on pathophysiological mechanisms. Herz 2008;33:184190
21. Masoudi FA, Inzucchi SE. Epidemiology, mechanisms, and pharmacotherapy. Am J Cardiol 2007;99:113B–132B
22. Held C, Gerstein HC, Yusuf S, Zhao F, Hilbrich L, Anderson C, Sleight P, Teo K, ONTARGET/TRANSCEND Investigators. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 2007; 115:1371–1375
23. Barzilay JI, Kronmal RA, Gottdiener JS, Smith NL, Burke GL, Tracy R, Savage PJ, Carlson M. The association of fasting glucose levels with congestive heart failure in diabetic adults < or =65 years: the Cardiovascular Health Study. J Am Coll Cardiol 2004;43:2236–2241
24. McGuire DK, Inzucchi SE. New drugs for the treatment of diabetes mellitus: part I: thiazolidinediones and their evolving cardiovascular implications. Circulation 2008;117:440–449
25. Chelliah A, Burge MR. Insulin edema in the twenty-first century: review of the existing literature. J Investig Med 2004;52: 104–108
26. Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II: incretin-based therapy and beyond. Circulation 2008;117:574–584
27. Yellon DM, Hausenloy DJ. Realizing the clinical potential of ischemic preconditioning and postconditioning. Nat Clin Pract Cardiovasc Med 2005;2:568–575
28. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 2005;28:2345–2351
29. Nikolaidis LA, Elahi D, Shen YT, Shannon RP. Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. Am J Physiol Heart Circ Physiol 2005;289: H2401–H2408
30. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. Diabetes 2005; 54:146–151
31. Gore MO, McGuire DK. Cardiovascular disease and type 2 diabetes mellitus: regulating glucose and regulating drugs. Curr Cardiol Rep 2009;11:258–263