THE AMERICAN JOURNAL of MEDICINE®

The Reply

Numerous National Institutes of Health and industry-sponsored outcome trials, including FAVORIT, have considered diabetes as a checkbox diagnosis devoid of granularity, without defining type, duration, severity (therapeutic resistance or glycemic control), or diabetes-related comorbidity (retinopathy/blindness, neuropathy, nephropathy, or amputation). Assumptions that new onset diabetes after transplantation (NODAT) would have different outcomes than preexistent diabetes cannot be adequately explored from such retrospective database analyses. Our study included patients who had prior transplants, without recording of time of onset, duration, or relation between immunosuppressant therapy and diabetes.[1] We would suggest that more standardized data be utilized for future trials for both baseline data collection[2] and appropriate event adjudication.[3]

In response to the thoughtful questions raised by Drs. Wallia and Mollitch, we evaluated strategies for a glucose control trial assuming that NODAT patients might be less likely to receive complex insulin regimens. If this is accurate, then one could infer a similar increased hazard risk for NODAT to preexistent diabetes. This is the best that we can do in this database. This method has been used in other clinical outcome trials.[4] Table 1 depicts the increased hazards for mortality associated with these strategies for glycemic control. Demonstrated are the statistically significant increases in all-cause and noncardiovascular mortality associated with a diagnosis of diabetes, whether requiring medications or not. Also evident are further increases in mortality (especially from an infectious cause) associated with the use of insulin. Disputed suggestions that posttransplant diabetes may not carry the same risk as pretransplant diabetes are based upon relatively short-term observation of limited populations with inadequate adjudication, definition, and capture of events.[5-7] We caution those anticipating that NODAT not be associated with increased infection rates should carefully reexamine the data.

Funding: None

Conflict of Interest: None

Authorship: Each of the authors has fully participated and has approved the final manuscript. Each author has reviewed and is responsible for the content.

Table 1 Mortality Based on Absence or Presence of Diabetes, Glycemic Medication, and Insulin Groupings

	Number and Percentage of Participants with Event, and Incidence Rates (per 100 person-years)				
	No DM (n=2447)	DM, No Meds (n=465)	DM, Meds, No INS (n=292)	DM, with INS (n=720)	DM, Meds and INS (n=186)
All-Cause Mortality	199 (8.2%)	57 (12.3%)	40 (13.7%)	165 (22.9%)	32 (17.2%)
	2.2 per 100 pyr	3.0 per 100 pyr	3.4 per 100 pyr	5.9 per 100 pyr	4.2 per 100 pyr
Unadjusted model (hazard ratio), *P* value	ref	1.39 (1.04-1.87)	1.66 (1.18-2.33)	2.81 (2.28-3.45)	2.09 (1.44-3.04)
		.029	.003	<.001	<.001
Adjusted model* (hazard ratio), *P* value	ref	1.67 (1.21-2.32)	1.41 (0.96-2.08)	2.62 (2.08-3.31)	1.74 (1.14-2.67)
		.002	.08	<.001	.011
Cardiovascular Death	62 (2.6%)	19 (4.1%)	15 (5.2%)	82 (11.4%)	13 (7.1%)
	.6	1.0	1.3	3.0	1.7
Unadjusted	ref	1.48 (0.88-2.48)	1.96 (1.11-3.44)	4.51 (3.24-6.29)	2.71 (1.49-4.94)
		.14	.02	<.001	.001
Adjusted model*	ref	1.74 (1.01-3.00)	1.98 (1.09-3.60)	3.79 (2.62-5.47)	1.90 (0.93-3.89)
		.046	.025	<.001	.08
Noncardiovascular death	128 (5.2%)	37 (8.0%)	25 (8.6%)	77 (10.7%)	19 (10.2%)
	1.3	1.9	2.1	2.7	2.5
Unadjusted	ref	1.39 (0.96-2.01)	1.63 (1.06-2.50)	2.03 (1.52-2.69)	1.95 (1.20-3.16)
		.08	.026	<.001	.007
Adjusted model*	ref	1.82 (1.21-2.75)	1.25 (0.74-2.10)	2.06 (1.50-2.85)	1.80 (1.05-3.09)
		.004	.41	<.001	.031
Infection	42 (1.7%)	13 (2.8%)	11 (3.8%)	37 (5.1%)	10 (5.4%)
	0.4	.7	.9	1.3	1.3
Unadjusted	ref	1.45 (0.78-2.71)	2.17 (1.12-4.21)	2.93 (1.88-4.57)	3.11 (1.56-6.21)
		.24	.022	<.001	.001
Adjusted model*	ref	1.61 (0.76-3.41)	1.80 (0.82-3.93)	2.99 (1.79-5.00)	3.22 (1.53-6.96)
		.21	.14	<.001	.002
Malignancy	42 (1.7%)	11 (2.4%)	5 (1.7%)	11 (1.5%)	7 (3.8%)
	0.4	.6	.4	.4	.9
Unadjusted	ref	1.30 (0.67-2.55)	1.01 (0.40-2.56)	0.89 (0.46-1.73)	2.14 (0.96-4.76)
		.44	.98	.73	.06
Adjusted model*	ref	1.71 (0.83-3.52)	0.62 (0.19-2.03)	0.87 (0.43-1.78)	1.81 (0.74-4.38)
		.14	.43	.71	.19

*Adjusted for country, age, race, sex, smoking status, systolic blood pressure, low-density lipoprotein, and chronic kidney disease status.
DM, diabetes; INS, insulin; med, medication.

Larry A. Weinrauch, MD[a,b,c,d]
John A. D'Elia, MD[b,c,d]
Matthew R. Weir, MD[e]
Suphamai Bunnapradist, MD[f]
Peter V. Finn, MD[a]
Jiankang Liu, MD, PhD[a]
Brian Claggett, PhD[a]
Anthony P. Monaco, MD[c,d,g]

[a]*Cardiovascular Division, Brigham and Women's Hospital, Boston, Mass*
[b]*Kidney and Hypertension Section, Joslin Diabetes Center, Boston, Mass*
[c]*Departments of Medicine and Surgery, Beth Israel Deaconess Medical Center, Boston, Mass*
[d]*Harvard Medical School, Boston, Mass*
[e]*Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore*
[f]*Division of Nephrology, Department of Medicine, University of California at Los Angeles, Los Angeles*
[g]*Division of Nephrology, New England Medical Center, Tufts University School of Medicine, Boston, Mass*

https://doi.org/10.1016/j.amjmed.2018.04.003

References

1. Weinrauch LA, D'Elia JA, Weir MR, et al. Infection and malignancy outweigh cardiovascular mortality in kidney transplant recipients: post hoc analysis of the FAVORIT Trial. *Am J Med.* 2018;131:165-172.

2. Arnold SV, Inzucchi SE, McGuire DK, et al. Evaluating the quality of comprehensive cardiometabolic care for patients with type 2 diabetes in the U.S.: the Diabetes Collaborative Registry. *Diabetes Care*. 2016;39 (7):e99-e101.
3. Hicks KA, Mahaffey KW, Mehran R, et al. on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. 2018;71:1021-1034 and *Circulation*. 2018;137:961-972 .
4. Weinrauch LA, D'Elia J, Finn PV, et al. Strategies for glucose control in a study population with diabetes, renal disease and anemia (TREAT study). *Diabetes Res Clin Pract*. 2016;13:143-151.
5. Gaynor JJ, Ciancio G, Guerra G, et al. Single-centre study of 628 adult primary kidney transplant recipients showing no unfavourable effect of new-onset diabetes after transplant. *Diabetologia*. 2015;58(2):334-345.
6. Cooper L, Oz N, Fishman G, et al. New onset diabetes after kidney transplantation is associated with increased mortality—a retrospective cohort study. *Diabetes Metab Res Rev*. 2017;33:e2920.
7. Ertelt K, Brener SJ, Mehran R, Ben-Yehuda O, McAndrew T, Stone GW. Comparison of outcomes and prognosis of patients with versus without newly diagnosed diabetes mellitus after primary percutaneous coronary intervention for ST-elevation myocardial infarction (the HORIZONS-AMI Study). *Am J Cardiol*. 2017;119:1917-1923.