Nephrol Dial Transplant (2020) 35: 544–546
doi: 10.1093/ndt/gfz244
Advance Access publication 5 December 2019

ndt
Nephrology Dialysis Transplantation

RESEARCH LETTER

Cardiovascular events associate with diabetes status rather than with early basal insulin treatment for the prevention of post-transplantation diabetes mellitus

David Topitz[1], Elisabeth Schwaiger[1,2], Florian Frommlet[3], Johannes Werzowa[4] and Manfred Hecking[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria, [2]Department of Internal Medicine II, Kepler University Hospital, Med Campus III, Linz, Austria, [3]Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria and [4]Ludwig, Boltzmann Institute of Osteology at the Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, Vienna, Austria

Correspondence to: Manfred Hecking; E-mail: manfred.hecking@meduniwien.ac.at

Post-transplantation diabetes mellitus (PTDM) is a common complication after solid organ transplantation, as well as a treatable and perhaps also a preventable disease [1]. The risk of developing PTDM depends on patient-specific risk factors such as age, genetic disposition and obesity and transplant-specific risk factors such as immunosuppressive treatment [1]. Moreover, the incidence of PTDM varies depending on the type of organ that the patient has received [2]. Although some results on the impact of PTDM on cardiovascular disease and its related mortality are not in full agreement [3, 4], most of the evidence is in favour of PTDM and impaired glucose tolerance (IGT) predicting mortality [5–7].

Recently, consensus statements for treatment of type 2 diabetics were released by the American Diabetes Association and the European Association for the Study of Diabetes [8], as well as by the European Renal and Cardiovascular Medicine and DIABESITY (http://www.era-edtaworkinggroups.org/en-US/group/diabesity#sthash.CL0bKBic.dpbs) (Diabetes and Obesity) working groups of the European Renal Association–European Dialysis and Transplant Association [9]. Therein the expert panel participants recommend certain antidiabetic drugs for selected type 2 diabetic patient populations, on the basis of the drugs' proven cardiovascular benefit [8]. Although treatment recommendations are also available for PTDM patients [10], these recommendations are not based on hard endpoints, because the available studies on antidiabetics in transplant patients are so far only powered for glycaemic control and safety.

In order to start filling this knowledge gap, we aimed at exploring the occurrence of cardiovascular events (CVEs) in (kidney) transplant patients who participated in the randomized, controlled Treat-to-target Trial of Basal Insulin in Posttransplant Hyperglycemia (TIP) from February 2009 to February 2011 [11]. Briefly, TIP participants randomized to the treatment group ($n = 25$) received isophane insulin immediately after kidney transplantation if their evening glucose was >140 mg/dL. After 1 year, none of them had required anti-hyperglycaemic treatment. The control patients ($n = 25$), however, had received the standard of care [short-acting insulin and/or oral antidiabetics for higher glucose levels (≥180–250 mg/dL)], and eight of them had required antidiabetic treatment after 1 year. All patients who were not on anti-hyperglycaemic therapy had undergone an oral glucose tolerance test (OGTT) at 3, 6 and 12 months.

The present analysis consisted of performing a follow-up study visit on all available TIP study participants from October 2015 to March 2016. During this visit, for which we obtained approval from the local ethics committee (EK no. 1909/2016), we recorded CVEs, specifically myocardial infarction, coronary angioplasty/artery bypass graft surgery, valve replacement, congestive heart failure, peripheral artery disease and stroke. We also obtained laboratory parameters, height and weight and re-evaluated patient demographics. We then divided our patients by the initial study group (basal insulin treatment versus standard-of-care control) and by glycaemic status during the study OGTTs [normal glucose tolerance (NGT; 2-h glucose <140 mg/dL) versus IGT (2-h glucose 140–199 mg/dL) plus diabetes (2-h glucose ≥200 mg/dL)]. Statistical methods comprised the log-rank test, unpaired two-tailed Student's *t*-test for continuous variables and unadjusted chi-square test for categorical variables.

We found that among the original 50 TIP study participants who were not lost to follow-up (3 previous treatment and 4 previous control patients), 3 participants had died of CVEs (2 treatment patients and 1 control patient) and 2 CVE-unrelated deaths had occurred (2 control patients). The average follow-up time, i.e. time since patient inclusion in the TIP study (as shown in Table 1 and Figure 1), was close to 77 months in the basal insulin treatment group as well as in the standard-of-care control group. During the three post-operative OGTTs, seven

Table 1. Demographics, anthropometrics, HbA1c and serum creatinine by patient category

	Insulin	Control	P-value*	Diabetes + IGT	NGT	P-value[a]
Patients, *n*	22	21		36	7	
Males, *n* (%)	14 (64)	14 (66)	1.0	24 (67)	4 (57)	0.68
Females, *n* (%)	8 (36)	7 (34)	1.0	12 (33)	3 (43)	0.68
Age (years), mean ± SD	54.0 ± 12.1	56.6 ± 13.3	0.55	**57.3 ± 12.1**	**45.6 ± 10.9**	**0.02**
Inclusion (months), mean ± SD	76.6 ± 15.1	76.6 ± 10.1	1.0	75.9 ± 13.8	80.1 ± 3.2	0.42
Height (cm), mean ± SD	168.7 ± 8	171.3 ± 3	0.33	170 ± 8.1	171.3 ± 10	0.67
Weight (kg), mean ± SD	74.8 ± 18.7	87.5 ± 14.2	0.1	77.2 ± 19.3	88.1 ± 11.1	0.18
BMI, (mean ± SD)	26.4 ± 6.9	30.3 ± 6.1	0.19	27.2 ± 7.3	30.2 ± 5.1	0.34
HbA1c (rel%), mean ± SD	6.0 ± 0.8	5.9 ± 0.8	0.51	6.0 ± 0.8	5.5 ± 0.4	0.21
Serum creatinine (mg/dL), mean ± SD	2.1 ± 1.8	1.6 ± 0.5	0.3	1.9 ± 1.5	1.8 ± 0.5	0.81

[a]P-values were determined using the unpaired two-tailed Student's *t*-test for continuous variables and the unadjusted chi-square test for categorical variables. Significant values are bold ($P<0.05$). HbA1c, haemoglobin A1c.

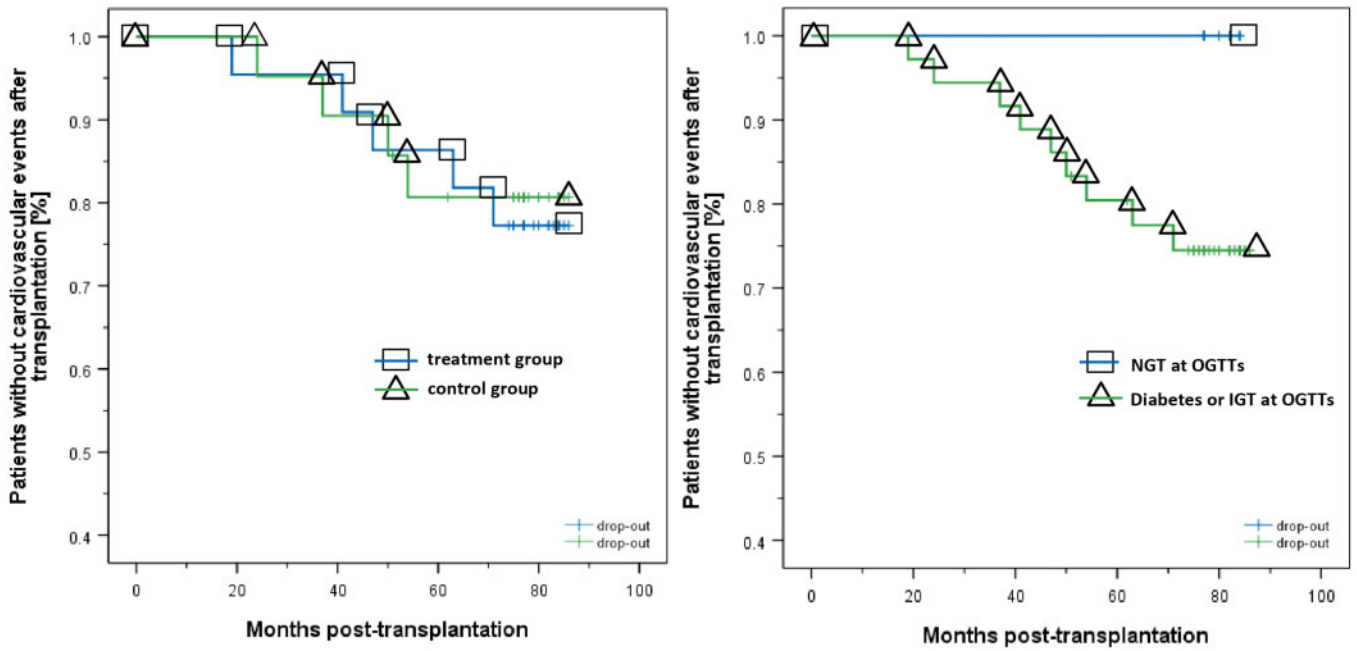

FIGURE 1: Cardiovascular events throughout 7 years of follow-up in kidney transplant recipients who received early basal insulin therapy versus standard of care (left panel) and in the same cohort of patients, but sorted by normal glucose tolerance (NGT) versus by impaired glucose tolerance (IGT) plus diabetes during three oral glucose tolerance tests performed in the first post-operative year (right panel). Cardiovascular events: myocardial infarction, coronary angioplasty/artery bypass graft surgery, valve replacement, congestive heart failure, peripheral artery disease and stroke. Log-rank test for the basal insulin treatment versus standard-of-care control group: P = 0.84. Log-rank test for non-diabetic versus diabetic plus pre-diabetic patients: P = 0.155.

participants had always had NGT (four treatment and three control patients). These participants were significantly younger (by 11.7 years on average), had lower glycated hemoglobin (HbA1c) at the study visit (P = 0.21) and had not experienced any CVEs (shown in Table 1 and Figure 1). In contrast, there was no meaningful difference between the treatment versus control group participants regarding CVE occurrence (shown in Figure 1). In a three-group comparison of diabetes versus IGT versus NGT, CVE occurrence in diabetics and patients with IGT was similarly worse than in patients with NGT (data not shown).

In conclusion, early basal insulin therapy after kidney transplantation had no beneficial effect on CVEs compared with previous standard of anti-hyperglycaemic care post-transplantation, despite clearly improved glycaemic control during the study period [11]. The fact that TIP study participants with NGT were significantly younger supports the hypothesis that PTDM is seen in older, sicker patients, which is not a novel finding [12]. However, the present analysis is the first to explore hard outcomes in solid organ transplant patients with PTDM by antidiabetic treatment. The findings are unexpected, and although the sample size is too small (by about one half) for the results to reach statistical significance when assuming the estimated hazard rates, they still generate the hypothesis that antidiabetic treatment in PTDM patients might not halt cardiovascular disease. While the PTDM community should have been aware that evidence on the association between treatment and hard outcomes is lacking, most transplant physicians

seem to assume that treatment of PTDM will be beneficial and treat PTDM anyway. This approach is understandable and may even be mandatory from a clinical standpoint—if anything, to at least prevent the direct consequences of hyperglycaemia. However, further clinical efforts into outcome studies are indispensable, especially in view of the recent consensus guidelines for type 2 diabetics [8, 9]. If knowledge from type 2 diabetics can be transferred to solid organ recipients with PTDM, which has a different pathophysiology than type 2 diabetes [12], then the most practical approach might be to enrol an adequate number of PTDM patients with various solid organ transplants into outcome studies testing inhibitors of sodium-glucose cotransporter-2 [13–15] and glucagon-like peptide 1 receptor agonists. Further results on PTDM prevention are also expected from a recently completed clinical trial [NCT03507829 (www.clinicaltrials.gov)] and will be analysed for hard outcomes.

FUNDING

This academic analysis was supported by the institutions of the respective co-authors and otherwise received no funding.

AUTHORS' CONTRIBUTIONS

D.T. collected the data, performed the analysis and wrote the article. M.H. collected the data and wrote the article. E.S. and J.W. revised the article. F.F. verified the results, reviewed the statistics and reviewed the article.

CONFLICT OF INTEREST STATEMENT

None declared. The data presented in this article have not been published previously, except in abstract form.

REFERENCES

1. Hecking M, Werzowa J, Haidinger M *et al.* Novel views on new-onset diabetes after transplantation: development, prevention and treatment. *Nephrol Dial Transplant* 2013; 28: 550–566
2. Jenssen T, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. *Nat Rev Endocrinol* 2019; 15: 172–188
3. 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: 334–345
4. Kuo HT, Sampaio MS, Vincenti F *et al.* Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. *Am J Kidney Dis* 2010; 56: 1127–1139
5. Cosio FG, Kudva Y, van der Velde M *et al.* New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; 67: 2415–2421
6. Eide IA, Halden TA, Hartmann A *et al.* Mortality risk in post-transplantation diabetes mellitus based on glucose and HbA1c diagnostic criteria. *Transpl Int* 2016; 29: 568–578
7. Valderhaug TG, Hjelmesæth J, Hartmann A *et al.* The association of early post-transplant glucose levels with long-term mortality. *Diabetologia* 2011; 54: 1341–1349
8. Davies MJ, D'Alessio DA, Fradkin J *et al.* Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41: 2669–2701
9. Sarafidis P, Ferro CJ, Morales E *et al.* SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant* 2019; 34: 208–230
10. Sharif A, Hecking M, de Vries AP *et al.* Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014; 14: 1992–2000
11. Hecking M, Haidinger M, Doller D *et al.* Early basal insulin therapy decreases new-onset diabetes after renal transplantation. *J Am Soc Nephrol* 2012; 23: 739–749
12. Hecking M, Kainz A, Werzowa J *et al.* Glucose metabolism after renal transplantation. *Diabetes Care* 2013; 36: 2763–2771
13. Hecking M, Jenssen T. Considerations for SGLT2 inhibitor use in post-transplantation diabetes. *Nat Rev Nephrol* 2019; 15: 525
14. Halden TAS, Kvitne KE, Midtvedt K *et al.* Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. *Diabetes Care* 2019; 42: 1067
15. Schwaiger E, Burghart L, Signorini L *et al.* Empagliflozin in posttransplantation diabetes mellitus: a prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *Am J Transplant* 2019; 19: 907–919

Received: 21.7.2019; Editorial decision: 15.10.2019