Incidence of Major Adverse Cardiovascular Events and Cardiac Mortality in High-Risk Kidney-Only and Simultaneous Pancreas—Kidney Transplant Recipients

Wai H. Lim1,2, Charmaine Lok3,4, S. Joseph Kim3, Greg Knoll5,6, Baiju Shah7,8,9, Kyla Naylor9, Eric McArthur9, Bin Luo9, Stephanie N. Dixon9,10, Carmel Hawley11,12,13, Esther Ooi2,14, Andrea K. Viecelli11,12 and Germaine Wong15,16,17

1Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Australia; 2Medical School, University of Western Australia, Perth, Australia; 3Division of Nephrology, Department of Medicine, University Health Network—Toronto General Hospital, Toronto, Ontario, Canada; 4The University of Toronto, Toronto, Ontario, Canada; 5Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; 6Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada; 7Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 8Division of Endocrinology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; 9ICES, Toronto, Ontario, Canada; 10Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada; 11Princess Alexandra Hospital, Metro South and Integrated Nephrology and Transplant Services, Queensland, Australia; 12University of Queensland, Queensland, Australia; 13Translational Research Institute, Brisbane, Australia; 14School of Biomedical Sciences, University of Western Australia, Perth, Australia; 15University of Sydney, Sydney, Australia; 16Centre for Kidney Research, The Children’s Hospital at Westmead, Sydney, Australia; and 17Department of Renal Medicine and National Pancreas Transplant Unit, Westmead Hospital, Sydney, Australia

Correspondence: Wai H, Lim, Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia 6009. E-mail: wai.lim@health.wa.gov.au

Received 14 September 2020; revised 7 February 2021; accepted 8 February 2021; published online 23 February 2021

Kidney Int Rep (2021) 6, 1423–1428; https://doi.org/10.1016/j.ekir.2021.02.019
© 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Diabetes mellitus is the most common cause of chronic kidney disease (CKD) worldwide. In Canada, diabetes accounts for more than 30% of incident patients with kidney failure, with similar findings in Australia and other Western countries.1,2 Patients with diabetic kidney disease, regardless of stage or treatment, are at an increased risk for cardiovascular disease (CVD) and all-cause mortality, including those who have received kidney transplants.3 In patients with diabetes and advanced CKD or kidney failure, prevalent vascular disease often coexists with an excess of traditional CVD risk factors such as hyperlipidemia and hypertension.4,5 The presence of these comorbidities carries a substantially poorer prognosis, suggesting a likelihood of an additive adverse impact of diabetes and vascular disease on overall prognosis.6–8

The aim of this population cohort study is to establish the incidence rates of major adverse cardiovascular events (MACE), cardiac and all-cause mortality in kidney, and simultaneous pancreas—kidney (SPK) transplant recipients with functioning allografts at 12-months posttransplantation, stratified according to the presence and absence of diabetes and vascular disease using administrative healthcare databases (held at ICES, Toronto, Ontario, Canada). These datasets were linked using unique encoded identifiers and analyzed at ICES. The use of data in this project was authorized under section 45 of Ontario’s Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

RESULTS

The median (interquartile range [IQR]) follow-up time of the study cohort of 3663 recipients (3479 [95%] kidney-only and 193 [5%] SPK recipients) was 5.1 (3.2–7.4) years (Supplementary Figure S1). Among kidney transplant recipients, 1445 (41.6%) had diabetes and 1515 (43.6%) had vascular disease. Of the 193 SPK transplant recipients, 109 (56.5%) had vascular disease. Table 1 shows the baseline characteristics of the cohort, stratified according to transplant type, diabetes, and/or vascular disease.

Incidence Rate and Cumulative Probability of MACE

Table 2 shows the incidence rates of MACE for kidney and SPK transplant recipients. For kidney transplant
## Table 1. Baseline characteristics of kidney and simultaneous pancreas–kidney transplant (SPK) recipients with functioning allografts at 12 months posttransplantation

| Recipient characteristics | Kidney transplant recipients | SPK transplant recipients |
|---------------------------|------------------------------|---------------------------|
| **No disease** (n = 1362) |                               |                           |
| **Diabetes** (n = 593)    |                               |                           |
| **Vascular disease** (n = 663) |                               |                           |
| **Diabetes and vascular disease** (n = 852) |                               |                           |
| **Age at transplantation, yr** |                               |                           |
| Mean (SD)                 | 47.1 (14.0)                  | 42.3 (8.3)                |
| Median (IQR)              | 47 (37–57)                   | 52 (38–48)                |
| ≤44                       | 581 (42.7)                   | 52 (61.9)                 |
| 45–65                     | 648 (47.6)                   | 32 (38.1)                 |
| ≥66                       | 133 (9.7)                    | 0 (0.0)                   |
| **Female**                | 568 (41.7)                   | 29 (34.5)                 |
| **Race**                  |                               |                           |
| Caucasian                 | 839 (61.6)                   | 76 (90.5)                 |
| Asian                     | 108 (7.9)                    | 0 (0.0)                   |
| Black                     | 70 (5.1)                     | 0 (0.0)                   |
| Other                     | 178 (13.1)                   | 0 (0.0)                   |
| Unknown/missing           | 167 (12.3)                   | 12 (11.0)                 |
| **Body mass index**       |                               |                           |
| Mean (SD)                 | 25.3 (5.3)                   | 24.4 (3.5)                |
| Median (IQR)              | 25 (23–28)                   | 24 (22–26)                |
| <18.5 kg/m²               | 526 (38.6)                   | 51 (80.7)                 |
| 18.5–24.9 kg/m²           | 313 (23.0)                   | 27 (32.2)                 |
| 25–29.9 kg/m²             | 174 (12.8)                   | 6 (7.1)                   |
| ≥30 kg/m²                 | 293 (21.5)                   | —                         |
| **Cause of kidney failure** |                               |                           |
| GN                        | 519 (38.1)                   | 140 (16.4)                |
| Cystic                    | 257 (18.9)                   | 55 (6.5)                  |
| Diabetes                  | 0 (0.0)                      | 446 (52.3)                |
| Vascular                  | 132 (9.7)                    | 90 (10.6)                 |
| Others                    | 454 (33.3)                   | 121 (14.2)                |
| **Diabetes vintage**      |                               |                           |
| Mean (SD)                 | 2.8 (2.9)                    | 2.7 (1.8)                 |
| Median (IQR)              | 2 (1–4)                      | 3 (2–3)                   |
| Preemptive                | 225 (16.5)                   | 3 (2–3)                   |
| ≤1 yr                     | 247 (18.1)                   | —                         |
| 1 to <2 yr                | 231 (17.0)                   | 32 (38.1)                 |
| 2 to <3 yr                | 184 (12.0)                   | 20 (18.4)                 |
| ≥3 yr                     | 495 (36.4)                   | 43 (51.2)                 |
| **Coronary artery disease** |                               | 74 (67.9)                |
| Peripheral vascular disease |                               |                           |
| Mean (SD)                 | 4.3 (3.7)                    | 4.2 (2.7)                 |
| Median (IQR)              | 2 (1–4)                      | 3 (2–3)                   |
| Preemptive                | 225 (16.5)                   | 3 (2–3)                   |
| ≤1 yr                     | 247 (18.1)                   | —                         |
| 1 to <2 yr                | 231 (17.0)                   | 32 (38.1)                 |
| 2 to <3 yr                | 184 (12.0)                   | 20 (18.4)                 |
| ≥3 yr                     | 495 (36.4)                   | 43 (51.2)                 |
| **Concor** | 301 (22.1) | 31 (36.9) | 42 (38.5) |
| **MACF**                  | 0 (0.0)                      | 60 (55.0)                 |

| **Other characteristics** | Kidney transplant recipients | SPK transplant recipients |
|---------------------------|------------------------------|---------------------------|
| **Age, yr**               |                               |                           |
| Mean (SD)                 | 43.4 (14.3)                  | 29.6 (11.5)               |
| Median (IQR)              | 45 (34–53)                   | 28 (20–42)                |
| ≤40                       | 478 (35.1)                   | 61 (72.6)                 |
| ≥40                      | 884 (64.9)                   | 74 (67.9)                 |
| **Type**                  |                               |                           |
| Living                    | 718 (52.7)                   | 0 (0.0)                   |
| Deceased                  | 644 (47.3)                   | 84 (100.0)                |
| **Sex**                   |                               |                           |
| Male                      | 662 (48.6)                   | 51 (80.7)                 |
| Female                    | 691 (50.8)                   | 63 (57.8)                 |
| Missing                   | 9 (0.6)                      | 0 (0.0)                   |

(Continued on following page)
recipients, the overall incidence rate of MACE was up to 3 times higher in recipients with diabetes or vascular disease compared to those without disease throughout the follow-up period. Recipients with both diabetes and vascular disease experienced the highest incidence of MACE, with an overall rate of 69.6 (95% CI 61.5–78.5) events per 1000 person-years, 7 times higher compared to those without disease (9.0 [95% CI 7.1–11.3] events per 1000 person-years). For SPK transplant recipients, the incidence rate of MACE was consistently higher in recipients with vascular disease compared to those without vascular disease, with overall incidence rates of 56.0 (95% CI = 38.9–78.0) and 24.5 (95% CI = 12.9–42.7) events per 1000 person-years, respectively. The Kaplan–Meier MACE-free survival curves stratified by kidney and SPK transplant recipients are shown in Supplementary Figure S2A and S2B, respectively.

Incidence Rates of Cardiac and All-Cause Mortality

For kidney transplant recipients, recipients with vascular disease experienced a higher incidence of cardiac mortality compared to those without vascular disease (Table 2). At 5 years posttransplantation, recipients with both diabetes and vascular disease exhibited the highest incidence of cardiac mortality (10.5 [95% CI = 7.4–14.4] events per 1000 person-years), compared to those with only vascular disease (5.2 [95% CI = 3.0–8.4] events per 1000 person-years) or with diabetes (2.5 [95% CI = 1.0–5.1] events per 1000 person-years). The 5-year incidence rate for recipients without disease was 1.2 (95% CI = 0.5–2.4) events per 1000 person-years. For all-cause mortality, kidney transplant recipients with both diabetes and vascular disease exhibited the highest incidence of all-cause mortality, with 3- and 7-year incidence rates of 41.6 (95% CI = 33.9–50.4) and 51.1 (95% CI = 44.4–58.4) events per 1000 person-years, respectively.

This compared with respective rates of 7.6 (95% CI = 5.2–10.7) and 8.3 (95% CI = 6.4–10.6) events per 1000 person-years for recipients without disease.

For SPK transplant recipients, the incidence rates of cardiac or all-cause mortality were consistently higher in recipients with vascular disease compared to those without across all time periods. At 7-years posttransplantation, the incidence rates for cardiac and all-cause mortality were 5.2 (95% CI = 1.3–14.2) and 15.3 (95% CI = 7.5–28.1) events per 1000 person-years for recipients with vascular disease, compared with 2.3 (95% CI = 0.1–11.4) and 13.5 (95% CI = 5.5–28.1) events per 1000 person-years in those without vascular disease.

Incidence Rates of the Composite Outcome of MACE and Mortality

For kidney transplant recipients, the incidence rates for both composite outcomes were highest for recipients with both diabetes and vascular disease, which were between 5 and 8 times higher compared to those for recipients without disease (Supplementary Figure S3). For SPK transplant recipients, the incidence rates for both composite outcomes were consistently up to 2.5 times higher compared to those without across all time points (Supplementary Figure S4).

Sensitivity Analysis

For kidney transplant recipients with functioning allografts at 12-months posttransplantation, the overall incidence rate of MACE within the first 12 months posttransplantation for recipients with pretransplantation diabetes was 24.6 (95% CI = 14.0–43.3) events per 1000 person-years. This compared with respective rates of 25.7 (95% CI = 16.0–41.3) and 62.8 (95% CI = 45.5–86.7) events per 1000 person-years for recipients with pretransplantation vascular disease and those with both pretransplantation diabetes and vascular disease. For SPK transplant recipients with functioning allografts at
In this contemporaneous cohort of kidney and SPK transplant recipients with functioning allografts at 12 months posttransplantation, the overall incidence rate of MACE within the first 12 months post-transplantation for recipients with pretransplantation vascular disease was 75.6 (95% CI = 36.1–158.7) events per 1000 person-years.

**DISCUSSION**

In this contemporaneous cohort of kidney and SPK transplant recipients with functioning allografts at 12 months posttransplantation spanning a decade, we have shown that the incidences of MACE, cardiac mortality, and all-cause mortality early post-transplantation were higher in recipients with diabetes or vascular disease. There were 3 noteworthy findings. First, our study showed that the highest incidence rates of MACE and cardiac mortality occurred between 1 and 3 years posttransplantation, suggesting that this early time frame posttransplantation may represent the most
susceptible period for developing cardiac complications. Second, the incidence rate of MACE was similar between the highest-risk kidney transplant recipients (i.e., those with diabetes and vascular disease) and SPK transplant recipients with vascular disease. The incidence rates of cardiac and all-cause mortality were more than 50% higher in the former group, suggesting the likelihood that kidney transplant recipients (with type 2 diabetes) were of different clinical and prognostic phenotype compared to SPK transplant recipients (with treated type 1 diabetes). Third, there is a comparable high incidence of MACE within the first 12 months posttransplantation in kidney and SPK transplant recipients with pretransplantation diabetes and/or vascular disease, further emphasizing the importance of careful monitoring for CVD risk factors and events in these high-risk recipients.

The relationship between diabetes and vascular disease status on posttransplantation outcomes has been examined previously in several population cohort studies. In a Brazilian cohort of 288 high-risk potential kidney transplant candidates on the waiting list, the presence of either diabetes or coronary artery disease was associated with an increased incidence of MACE during follow-up. In patients without diabetes, the presence of coronary artery disease was associated with a higher cumulative incidence of either fatal or nonfatal MACE at 5 years compared to the incidence in patients without coronary artery disease (46% vs. 11%, \( P < 0.01 \)), but this was not apparent for patients with diabetes. In a population cohort study of 7128 deceased-donor kidney transplant recipients from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry, the presence of vascular disease increased the mortality rate, which was most marked in patients without type 2 diabetes. Similar to these studies, we have shown that the incidence rates of MACE, cardiac mortality, and all-cause mortality in kidney transplant recipients were influenced by the presence of either diabetes or vascular disease status. However, in contrast, we have shown a possible additive effect between diabetes and vascular disease for MACE and mortality. The incidence rate of MACE and mortality after 12 months posttransplantation was more than 8 times higher in recipients with both diabetes and vascular disease compared to those without disease, and was more than 2 times higher than in patients with either risk factor alone. However, it remains unclear whether the early risk of cardiac complications was attributed to inadequate treatment or monitoring of vascular risk factors posttransplantation, contributing events relating to the management of the allograft and associated complications, or whether it represents an acceleration of atherosclerotic disease progression posttransplantation.

Two cohort studies from Canada and the United Kingdom have provided more recent estimates of the incidence rates of MACE in kidney and SPK transplant recipients, but neither of these studies explicitly evaluated differences in the incidence rates of MACE by diabetes or vascular disease status. Our study findings add to the existing literature by providing up-to-date estimates of MACE and mortality in kidney and SPK transplant recipients with functioning allografts at 12 months posttransplantation, stratified by diabetes or vascular disease status.

The strengths of this study are the completeness of the data and the likely accurate ascertainment of those with diabetes or vascular disease in a contemporaneous cohort of kidney and SPK transplant recipients within a single-payer healthcare system. Therefore, the estimates of MACE and mortality generated from this study will be directly applicable to current real-world clinical practice. The interpretations of these findings must be carefully considered against the notable limitations, including the lack of granular data on the differences in the management and severity of these vascular risk factors. Our cohort comprises of predominantly a Caucasian/White population, and therefore the estimates of MACE and mortality may not be reliably extrapolated to other transplant cohorts with differing healthcare systems and organ allocation algorithms.

In this large retrospective study, we have provided important estimates for the incidence of MACE, cardiac mortality, and all-cause mortality in kidney and SPK transplant recipients, and we have highlighted that the incidences of these complications differed according to the presence or absence of diabetes or vascular disease.

**DISCLOSURE**

All the authors declared no competing interests.

**ACKNOWLEDGMENTS**

The authors gratefully acknowledge the substantial contributions of the data analysts at ICES. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The study was completed at the ICES Western site, where core funding is provided by the Academic Medical Organization of Southwestern Ontario, the Schulich School of Medicine and Dentistry, Western University, and the Lawson Health Research Institute. Parts of this material are based on data and information compiled and
SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods
Supplementary References

Figure S1. Flow diagram of the study cohort of kidney and simultaneous pancreas kidney (SPK) transplant recipients with functioning allografts at 12-months post-transplant in Ontario between 2005 and 2014.

Figure S2. Kaplan Meier major adverse cardiovascular event (MACE)-free survival curves for kidney (Figure 2A) and simultaneous pancreas kidney (SPK) transplant recipients (Figure 2B) up to 10-years post-transplantation, stratified by diabetes and vascular disease status. Corresponding number at risk tables shown below each graph.

Figure S3. Bar graph showing the incidence rates (per 1000 person-years) of the composite of first MACE or cardiac mortality in kidney transplant recipients at 3, 5 and 7-years post-transplantation, stratified by diabetes and vascular disease status.

Figure S4. Bar graph showing the incidence rates (per 1000 person-years) of the composite of first MACE or cardiac mortality in simultaneous pancreas kidney (SPK) transplant recipients at 3, 5 and 7-years post-transplantation, stratified by vascular disease status.

Table S1. The Reporting of studies conducted using observational routinely-collected data (RECORD) statement – checklist of items, extended from The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Table S2. Coding definitions for demographic and comorbid conditions.

REFERENCES

1. United States Renal Data System. Chapter 11: International Comparisons. Volume 2: End-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.

2. Australia and New Zealand Dialysis and Transplant Registry. Chapter 1: Incidence of Renal Replacement Therapy for End Stage Kidney Disease. Adelaide, Australia: Australia and New Zealand Dialysis and Transplant Registry; 2019.

3. Lim WH, Wong G, Pilmore HL, et al. Long-term outcomes of kidney transplantation in people with type 2 diabetes: a population cohort study. Lancet Diabetes Endocrinol. 2017;5:26–33.

4. Wattanakit K, Folsom AR, Selvin E, et al. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007;18:629–636.

5. Rajagopalan S, Dellegrottaglie S, Furniss AL, et al. Peripheral arterial disease in patients with end-stage renal disease: observations from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Circulation. 2006;114:1914–1922.

6. Norman PE, Davis WA, Bruce DG, Davis TM. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care. 2006;29:575–580.

7. Badjatiya A, Merrill P, Buse JB, et al. Clinical outcomes in patients with type 2 diabetes mellitus and peripheral artery disease: results from the EXSCEL Trial. Circ Cardiovasc Interv. 2019;12, e008018.

8. Giannopoulos S, Armstrong EJ. Diabetes mellitus: an important risk factor for peripheral vascular disease. Expert Rev Cardiovasc Ther. 2020;18:131–137.

9. Gowdak LH, de Paula FJ, Cesar LA, et al. Diabetes and coronary artery disease impose similar cardiovascular morbidity and mortality on renal transplant candidates. Nephrol Dial Transplant. 2007;22:1456–1461.