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

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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

	Kidney transplant recipients				SPK transplant recipients	
	No disease (n = 1362)	Diabetes (n = 593)	Vascular disease (n = 663)	Diabetes and vascular disease (n = 852)	No disease (n = 84)	Vascular disease (n = 109)
Recipient characteristics						
Age at transplantation, yr						
Mean (SD)	47.1 (14.0)	54.2 (12.2)	54.3 (12.8)	58.9 (10.5)	42.3 (8.3)	44.9 (7.6)
Median (IQR)	47 (37–57)	56 (46–63)	56 (46–64)	61 (53–66)	42 (36–48)	45 (40–51)
≤44	581 (42.7)	132 (22.3)	149 (22.5)	84 (9.9)	52 (61.9)	52 (47.7)
45–65	648 (47.6)	346 (58.3)	379 (57.2)	518 (60.8)	32 (38.1)	57 (52.3)
≥66	133 (9.7)	115 (19.4)	135 (20.3)	250 (29.3)	0 (0.0)	0 (0.0)
Female	568 (41.7)	212 (35.8)	223 (33.6)	257 (30.2)	29 (34.5)	29 (26.6)
Race						
Caucasian	839 (61.6)	349 (58.9)	427 (64.4)	498 (58.5)	76 (90.5)	97 (89.0)
Asian	108 (7.9)	46 (7.8)	45 (6.8)	56 (6.6)	0 (0.0)	0 (0.0)
Black	70 (5.1)	47 (7.9)	61 (9.2)	91 (10.7)	0 (0.0)	0 (0.0)
Other	178 (13.1)	96 (16.2)	73 (11.0)	174 (20.4)	0 (0.0)	0 (0.0)
Unknown/missing	167 (12.3)	55 (9.2)	57 (8.6)	33 (3.8)	8 (9.5)[a]	12 (11.0)[a]
Body mass index						
Mean (SD)	25.3 (5.3)	28.0 (6.0)	25.9 (5.7)	28.2 (5.8)	24.4 (3.5)	25.2 (4.4)
Median (IQR)	25 (22–28)	27 (24–31)	25 (22–29)	27 (24–31)	24 (22–26)	24 (22–28)
<18.5 kg/m^2	56 (4.1)	10 (1.7)	31 (4.7)	12 (1.4)	0 (0.0)	0 (0.0
18.5–24.9 kg/m^2	526 (38.6)	164 (27.7)	248 (37.4)	236 (27.7)	51 (60.7)[b]	66 (60.6)[b]
25–29.9 kg/m^2	313 (23.0)	167 (28.2)	187 (28.2)	268 (31.5)	27 (32.2)	27 (24.8)
≥30 kg/m^2	174 (12.8)	157 (26.4)	104 (15.7)	263 (30.9)	6 (7.1)	16 (14.6)
Missing	293 (21.5)	95 (16.0)	93 (14.0)	73 (8.6)	—	—
Cause of kidney failure						
GN	519 (38.1)	134 (22.6)	249 (37.6)	140 (16.4)	[c]	[c]
Cystic	257 (18.9)	47 (7.9)	103 (15.6)	55 (6.5)		
Diabetes	0 (0.0)	237 (40.0)	0 (0.0)	446 (52.3)		
Vascular	132 (9.7)	42 (7.1)	101 (15.2)	90 (10.6)		
Others	454 (33.3)	133 (22.4)	210 (31.6)	121 (14.2)		
Dialysis vintage						
Mean (SD)	2.8 (2.9)	2.9 (2.6)	4.8 (3.7)	4.2 (2.7)	2.7 (1.8)	3.6 (2.1)
Median (IQR)	2 (1–4)	2 (1–4)	4 (2–7)	4 (2–6)	3 (2–3)	3 (2–5)
Preemptive	225 (16.5)	67 (11.2)	51 (7.7)	25 (2.9)	—	—
<1 yr	247 (18.1)	94 (15.9)	32 (4.8)	48 (5.6)	—	—
1 to <2 yr	231 (17.0)	97 (16.4)	82 (12.4)	116 (13.6)	32 (38.1)[d]	20 (18.4)[d]
2 to <3 yr	164 (12.0)	104 (17.5)	57 (8.6)	141 (16.5)	22 (26.2)	25 (22.9)
≥3 yr	495 (36.4)	231 (39.0)	441 (66.5)	522 (61.4)	30 (35.7)	64 (58.7)
Coronary artery disease	346 (25.4)	265 (44.7)	359 (54.1)	584 (68.5)	43 (51.2)	74 (67.9)
Peripheral vascular disease	0 (0.0)	0 (0.0)	129 (19.5)	132 (15.5)	0 (0.0)	20 (18.3)
Cancer	301 (22.1)	174 (29.3)	194 (29.3)	265 (31.1)	31 (36.9)	42 (38.5)
MACE	0 (0.0)	6 (1.0)	246 (37.1)	379 (44.5)	0 (0.0)	60 (55.0)
Donor characteristics						
Age, yr						
Mean (SD)	43.4 (14.3)	46.6 (15.3)	45.5 (15.0)	48.6 (14.8)	29.6 (11.5)	31.3 (11.0)
Median (IQR)	45 (34–53)	48 (36–58)	48 (37–55)	50 (39–59)	28 (20–42)	28 (22–42)
<40	478 (35.1)	182 (30.7)	193 (29.1)	212 (24.9)	61 (72.6)	74 (67.9)
≥40[b]	884 (64.9)	411 (69.3)	470 (70.9)	640 (75.1)	23 (27.4)	35 (32.1)
Type						
Living	718 (52.7)	262 (44.2)	211 (31.8)	250 (29.3)	0 (0.0)	0 (0.0)
Deceased	644 (47.3)	331 (55.8)	452 (68.2)	602 (70.7)	84 (100.0)	109 (100.0)
Sex						
Male	662 (48.6)	294 (49.6)	343 (51.7)	436 (51.2)	51 (60.7)	63 (57.8)
Female	691 (50.8)	293 (49.4)	314 (47.4)	404 (47.4)	33 (39.3)	46 (42.2)
Missing	9 (0.6)	6 (1.0)	6 (0.9)	12 (1.4)	0 (0.0.0)	0 (0.0)

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Table 1. (Continued)

	Kidney transplant recipients				SPK transplant recipients	
	No disease (n = 1362)	Diabetes (n = 593)	Vascular disease (n = 663)	Diabetes and vascular disease (n = 852)	No disease (n = 84)	Vascular disease (n = 109)
Transplant factor						
Year						
2005–2008	384 (28.2)	140 (23.6)	221 (33.3)	224 (26.3)	22 (26.2)	39 (35.8)
2009–2012	617 (45.3)	283 (47.7)	306 (46.2)	362 (42.5)	39 (46.4)	39 (35.8)
2013–2016	361 (36.5)	170 (28.7)	136 (20.5)	266 (31.2)	23 (27.4)	31 (28.4)

Data are expressed as mean (standard deviation [SD]), median (interquartile range [IQR]), or as number (proportion [%]). GN, glomerulonephritis; MACE, major adverse cardiovascular events; SPK, simultaneous pancreas–kidney.
[a]Cells include missing data or other non-Caucasian racial groups.
[b]In accordance with ICES privacy policies, cell sizes ≤5 cannot be reported; therefore, cells include missing data.
[c]Predominantly the cause of ESKD is attributed to diabetes, but a small number of cases with kidney failure are attributable to diseases other than diabetes and therefore data are not shown for SPK recipients.
[d]Numbers may include recipients with waiting time of <1 year.

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% confidence interval [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 post-transplantation, 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 pre-transplantation 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 pre-transplantation vascular disease and those with both pretransplantation diabetes and vascular disease. For SPK transplant recipients with functioning allografts at

Table 2. Incidence rate for MACE, cardiovascular mortality, all-cause mortality, and the composite outcome of mortality and MACE in kidney and SPK transplant recipients with functioning allografts at 12 months posttransplantation

Transplant type	Overall incidence rate (95% CI)[a]	3-yr Incidence rate (95% CI)[a]	5-yr Incidence rate (95% CI)[a]	7-yr Incidence rate (95% CI)[a]
Outcome: MACE				
Kidney				
No disease	9.0 (7.1–11.3)	6.9 (4.6–9.9)	8.8 (6.7–11.5)	8.9 (6.9–11.3)
Vascular disease	28.2 (23.2–34.0)	25.9 (19.3–34.0)	26.0 (20.5–32.6)	27.1 (22.0–33.2)
Diabetes	28.6 (23.1–35.0)	19.9 (13.9–27.6)	23.6 (18.0–30.3)	28.0 (22.4–34.7)
Diabetes and vascular disease	69.6 (61.5–78.5)	64.6 (54.5–76.0)	66.7 (58.0–76.5)	67.6 (59.3–76.7)
Simultaneous pancreas kidney				
No vascular disease	24.5 (12.9–42.7)	25.6 (10.4–53.3)	26.1 (12.7–47.9)	24.5 (12.4–43.6)
Vascular disease	56.0 (38.9–78.0)	63.7 (38.9–98.7)	55.8 (36.3–82.5)	60.7 (41.7–85.5)
Outcome: cardiac mortality				
Kidney				
No disease	1.4 (0.7–2.4)	0.8 (0.2–2.1)	1.2 (0.5–2.4)	1.1 (0.5–2.1)
Vascular disease	6.1 (4.0–8.9)	4.2 (2.0–8.0)	5.2 (3.0–8.4)	6.6 (4.3–9.7)
Diabetes	3.8 (2.0–6.4)	2.4 (0.8–5.8)	2.5 (1.0–5.1)	2.4 (1.1–4.8)
Diabetes and vascular disease	12.2 (9.2–15.9)	9.4 (6.1–14.1)	10.5 (7.4–14.4)	12.0 (8.9–15.8)
Simultaneous pancreas–kidney				
No vascular disease	2.1 (0.1–10.2)	0.0 (–)	0.0 (–)	2.3 (0.1–11.4)
Vascular disease	7.5 (2.8–16.6)	6.4 (1.1–21.2)	6.5 (1.6–17.6)	5.2 (1.3–14.2)
Outcome: all-cause mortality				
Kidney only				
No disease	9.9 (7.9–12.2)	7.6 (5.2–10.7)	8.2 (6.1–10.7)	8.3 (6.4–10.6)
Vascular disease	26.5 (21.9–31.9)	16.1 (11.2–22.6)	19.9 (15.2–25.5)	25.3 (20.5–31.0)
Diabetes	30.9 (25.3–37.3)	17.7 (12.2–25.0)	23.6 (18.1–30.2)	28.0 (22.5–34.6)
Diabetes and vascular disease	55.7 (49.1–63.0)	41.6 (33.9–50.4)	44.2 (37.6–51.7)	51.1 (44.4–58.4)
Simultaneous pancreas–kidney				
No vascular disease	12.0 (4.9–24.9)	8.2 (1.4–27.2)	8.2 (2.1–22.3)	13.5 (5.5–28.1)
Vascular disease	21.8 (12.7–35.1)	12.7 (4.0–30.6)	14.8 (6.5–29.3)	15.3 (7.5–28.1)
Outcome: Composite cardiovascular mortality or first MACE				
Kidney only				
No disease	10.5 (8.4–13.0)	7.5 (5.1–10.6)	10.0 (7.7–12.9)	10.0 (7.8–12.5)
Vascular disease	32.2 (26.7–38.4)	29.3 (22.3–38.0)	29.8 (23.8–36.8)	31.1 (25.5–37.6)
Diabetes	31.2 (25.4–38.1)	21.3 (15.1–29.3)	25.8 (19.9–32.9)	30.2 (24.3–37.2)
Diabetes and vascular disease	79.4 (70.5–89.0)	72.3 (61.6–84.4)	75.3 (65.8–85.7)	77.1 (68.2–87.0)
Simultaneous pancreas–kidney				
No vascular disease	27.8 (15.1–47.3)	25.9 (10.5–54.0)	26.7 (13.0–49.0)	27.7 (14.6–48.2)
Vascular disease	64.8 (46.1–88.7)	71.3 (44.8–108.2)	64.2 (42.8–92.8)	68.0 (47.6–94.4)
Outcome: composite all-cause mortality or first MACE				
Kidney only				
No disease	17.5 (14.8–20.6)	12.8 (9.6–16.7)	15.8 (12.8–19.2)	16.0 (13.2–19.1)
Vascular disease	46.8 (40.3–54.2)	39.3 (31.1–49.2)	42.3 (35.1–50.5)	44.8 (38.0–52.4)
Diabetes	50.7 (43.3–59.1)	34.3 (26.2–44.1)	43.0 (35.3–51.9)	49.4 (41.7–58.1)
Diabetes and vascular disease	105.5 (95.4–116.4)	97.5 (85.0–111.4)	99.1 (88.3–110.9)	103.0 (92.7–114.2)
Simultaneous pancreas–kidney				
No vascular disease	35.7 (21.1–56.7)	34.1 (15.9–64.8)	31.9 (16.8–35.5)	36.7 (21.3–59.2)
Vascular disease	75.2 (55.1–100.3)	77.8 (50.0–116.0)	70.4 (48.1–99.8)	76.8 (55.2–104.4)

CI, confidence interval; MACE, major adverse cardiovascular events; SPK, simultaneous pancreas–kidney.
[a]Denotes data expressed as incidence rates of events per 1000 person-time years and 95% confidence interval occurring after 12 months posttransplantation.

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.[9] 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.[S1] 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[S2] and the United Kingdom[S3] 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.

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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.

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