Vascular Disease, ESRD, and Death: Interpreting Competing Risk Analyses

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Summary

Background and objectives Vascular disease, a common condition in CKD, is a risk factor for mortality and ESRD. Optimal patient care requires accurate estimation and ordering of these competing risks.

Design, setting, participants, & measurements This is a prospective cohort study of screened (n=885) and randomized participants (n=837) in the Modification of Diet in Renal Disease study (original study enrollment, 1989–1992), evaluating the association of vascular disease with ESRD and pre-ESRD mortality using standard survival analysis and competing risk regression.

Results The method of analysis resulted in markedly different estimates. Cumulative incidence by standard analysis (censoring at the competing event) implied that, with vascular disease, the 15-year incidence was 66% and 51% for ESRD and pre-ESRD death, respectively. A more accurate representation of absolute risk was estimated with competing risk regression: 15-year incidence was 54% and 29% for ESRD and pre-ESRD death, respectively. For the association of vascular disease with pre-ESRD death, estimates of relative risk by the two methods were similar (standard survival analysis adjusted hazard ratio, 1.63; 95% confidence interval, 1.20–2.20; competing risk regression adjusted subhazard ratio, 1.57; 95% confidence interval, 1.15–2.14). In contrast, the hazard and subhazard ratios differed substantially for other associations, such as GFR and pre-ESRD mortality.

Conclusions When competing events exist, absolute risk is better estimated using competing risk regression, but etiologic associations by this method must be carefully interpreted. The presence of vascular disease in CKD decreases the likelihood of survival to ESRD, independent of age and other risk factors.

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Introduction

Optimal care of CKD patients requires accurate estimation of the risk of two competing clinical outcomes: ESRD and death. Much has been published on characteristics that affect a patient's likelihood of surviving to ESRD (1–3). Age is the most intuitive: for a given level of kidney function, older patients are more likely to die before requiring renal replacement therapy compared with younger patients (2,4,5). Similarly, patients with diabetes and low levels of proteinuria have higher rates of pre-ESRD death (6–8), whereas patients with polycystic kidney disease tend to first develop ESRD (9). Identifying additional factors related to ESRD and pre-ESRD mortality may further distinguish high-risk phenotypes, perhaps meriting trials of more aggressive risk factor modification. However, estimating the risk of ESRD and pre-ESRD mortality requires a careful approach, and optimal analytic methods remain underutilized.

Competing events (those which preclude the endpoint of interest) are pervasive in nephrology. For example, in studies of ESRD risk, death before ESRD prevents ESRD from occurring. Most studies of ESRD use standard survival analysis methods, treating death before ESRD as a censored event (8,10–12). However, this violates a tenet of survival analysis, noninformative censoring, or the requirement that prognosis does not influence censorship (13). Clearly, death is strongly related to future prognosis. Competing risk regression methods, including estimates of instantaneous risk, acknowledge both the existence and possibly different rates of competing risks by level of a given variable, and they allow for an association between a competing event and prognosis (13,14). The use of competing risk methodology is particularly important when there are high rates of competing events, such as death during CKD progression.

One condition that may predispose to early death is vascular disease, common in CKD and a risk factor for both further renal decline and mortality (15–17). Vascular disease strongly associates with cardiovascular mortality among the general population and among dialysis patients (18,19). Cardiovascular risk increases with lower GFR (20–22), and distinguishing a CKD population with disproportionately higher cardiovascular risk might help improve patient management. For example, in the Study of Heart and Renal Protection, simvastatin/ezetimibe reduced the risk of major atherosclerotic events in CKD, and the authors suggest that the benefit may be greatest in high-risk patients

(23). Hypothesizing that patients with vascular disease have higher rates of death before ESRD than patients without vascular disease, we sought to determine the absolute and relative risks of the competing events of ESRD and pre-ESRD death among a population of patients with CKD. In addition, we demonstrate the differences in inference using methods of standard survival analysis and those of competing risk regression.

Materials and Methods

Study Design, Setting, Size, and Participants

This observational cohort study included randomized (n=837) and screened but not randomized participants (n=885) from the Modification of Diet in Renal Disease (MDRD) study (24). In brief, the MDRD study was a randomized controlled trial designed to measure the effects of diet and BP control on the progression of CKD. It ran from 1989 to 1993, and included participants aged 18–70 years. Initial serum creatinine was 1.2–7.0 mg/dl (1.4–7.0 in men). Exclusion criteria included insulin-dependent diabetes, renal artery stenosis, prior kidney transplant, mean arterial pressure >125 mmHg, proteinuria >10 g/d, glomerulopathies from autoimmune diseases, and pregnancy. In our study, we additionally excluded six individuals who lacked complete follow-up.

Variables, Data Sources and Measurement, and Bias

Vascular disease was defined as a baseline history (self-reported, augmented by medical record review) of coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Additional covariates included age at enrollment, baseline smoking status, measured BP, cholesterol levels, 24-hour urine protein excretion, and GFR, estimated both by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation—which has been shown to be more accurate in predicting clinical risk than the MDRD study equation (25,26)—and by direct measurement using iothalamate clearance. Proteinuria was log-transformed to achieve a more normal distribution. Treated ESRD (receiving peritoneal/hemodialysis, or a kidney transplant) was obtained by linkage with US Renal Data System, and all-cause mortality was obtained by linkage with the National Death Index. Participants free of either endpoint on December 31, 2007, were administratively censored.

Statistical Analyses

Baseline characteristics were compared by chi-squared tests and t tests as appropriate. Survival analyses were performed in two ways: (*1*) using standard survival analysis, with the complement of the Kaplan–Meier estimate for cumulative event rates and Cox proportional hazards regression for adjusted cause-specific hazard ratios; and (*2*) using the Fine and Gray method to incorporate rates of competing risks in the cumulative incidence function and subhazard ratios (Supplemental Material) (14). For Cox regression, participants were censored at ESRD in the model of pre-ESRD death, and pre-ESRD death in the model of ESRD. Analyses were stratified by categories of estimated GFR (eGFR) and age to determine event incidence within subgroups. The proportional hazards assumption was verified using time interaction terms and inspection of log negative log survival curves. In adjusted analysis, both methods used multivariable models containing sex and race for face validity as well as age, systolic BP, cause of kidney disease, diabetes, current smoking, cause of ESRD, presence of vascular disease, log 24-hour proteinuria, and eGFR. Cholesterol (LDL and HDL), diastolic BP, randomization status, and intervention group were all tested in multivariable models but lacked statistical significance (P>0.05) and made no meaningful difference in inference for the other variables. Thus, they were left out of the final model for the sake of parsimony.

Participants missing any covariate accounted for <4% of the sample; thus, data were examined by complete case analysis. In sensitivity analysis, mean imputation was used with no meaningful difference in results. Finally, analyses were rerun substituting iothalamate-measured GFR for CKD-EPI eGFR. All analyses were performed using multiprocessor Stata version 11.0/MP software for Windows (StataCorp, College Station, TX). All hypothesis tests were two sided, and statistical significance was defined as a P value <0.05.

Results

Baseline Characteristics

There were 1722 participants included in the analysis; 13% had vascular disease (Table 1). Those with vascular disease were older (60.2 years versus 49.4 years; P<0.001), less often female (21.4% versus 42.4%; P<0.001), and more often diabetic (14.3% versus 4.9%; P<0.001). They tended to have higher systolic BP, lower diastolic BP, and lower HDL cholesterol. There was no statistically significant difference in the proportion with advanced CKD (43.3% versus 38.6% with measured GFR<30 ml/min; P=0.20), but slightly more patients with vascular disease had macroalbuminuria (15.6% versus 11.1%; P=0.05). After a median of 7.2 years of follow-up (range, 6 days to 18.9 years; total, 14,963.6 years), 55.8% of patients with vascular disease reached ESRD and 30.8% died before ESRD, compared with 65.0% and 11.6% in those without baseline vascular disease. Administratively censored participants were followed for a median of 17.6 years (range, 16.4–18.9 years).

Cumulative Incidence of Endpoints

The 15-year cumulative incidence of ESRD using Kaplan–Meier techniques was 66% in both those with and without vascular disease (Figure 1A). Using competing risk methods, the 15-year cumulative incidence of ESRD differed, with an incidence of 54% among those with vascular disease and 62% among those without vascular disease (Figure 1B). Similarly, the 15-year cumulative incidence of pre-ESRD death by Kaplan–Meier was 51% and 19% among those with and without vascular disease, respectively (Figure 2A), and 29% and 10% by competing risk analysis (Figure 2B).

Because ESRD and pre-ESRD death are mutually exclusive and exhaustive—a participant must reach one or the other eventually—the sum of the cumulative incidence should approach 100% over time. However, in Kaplan–Meier analysis, the 15-year incidence of either endpoint in participants with vascular disease was 117%, a nonsensical result. A more

Table 1. Baseline characteristics by presence of vascular disease

	No Vascular Disease	Vascular Disease	*P* Value
Participants, *n* (%)	1498 (87)	224 (13)	
Age (yr), mean	49.4	60.2	<0.001
Female (%)	42.4	21.4	<0.001
African-American race (%)	12.9	8.5	0.10
Systolic BP (mmHg), mean	131.7	137.9	<0.001
Diastolic BP (mmHg), mean	81.8	78.7	<0.001
LDL cholesterol (mg/dl), mean	147.8	148.8	0.70
HDL cholesterol (mg/dl), mean	40.5	35.5	<0.001
Body mass index >30 (%)	24.1	29.5	0.10
Current smoking (%)	12.1	11.6	0.80
Diabetes (%)	4.9	14.3	<0.001
Cause of renal disease (%)			
GN	33.2	25.4	<0.001
Polycystic kidney disease	23.3	14.3	
Other	43.5	60.3	
Measured GFR (mean), ml/min per 1.73 m^2	39.7	35.4	0.01
CKD-EPI GFR (mean), ml/min per 1.73 m^2	38.8	33.9	<0.001
Estimated GFR (%)			
60–74	10.2	7.1	0.1
45–59	19.5	17.4	
30–44	27.2	26.3	
15–29	27.3	33.5	
0–14	10.6	14.2	
Proteinuria (mg/d), median (IQR)	29 (6–131)	24 (6–166)	0.10
Reached ESRD (%)	65.0	55.8	0.01
Died before ESRD (%)	11.6	30.8	<0.001
Died after ESRD onset (%)	26.4	47.3	<0.001

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IQR, interquartile range.

reasonable cumulative incidence, and more similar to the simple counting of events (Table 1), was estimated in competing risk analysis. At study end, 89% of patients with vascular disease were estimated to have reached a clinical endpoint (58% reached ESRD, and 31% died pre-ESRD).

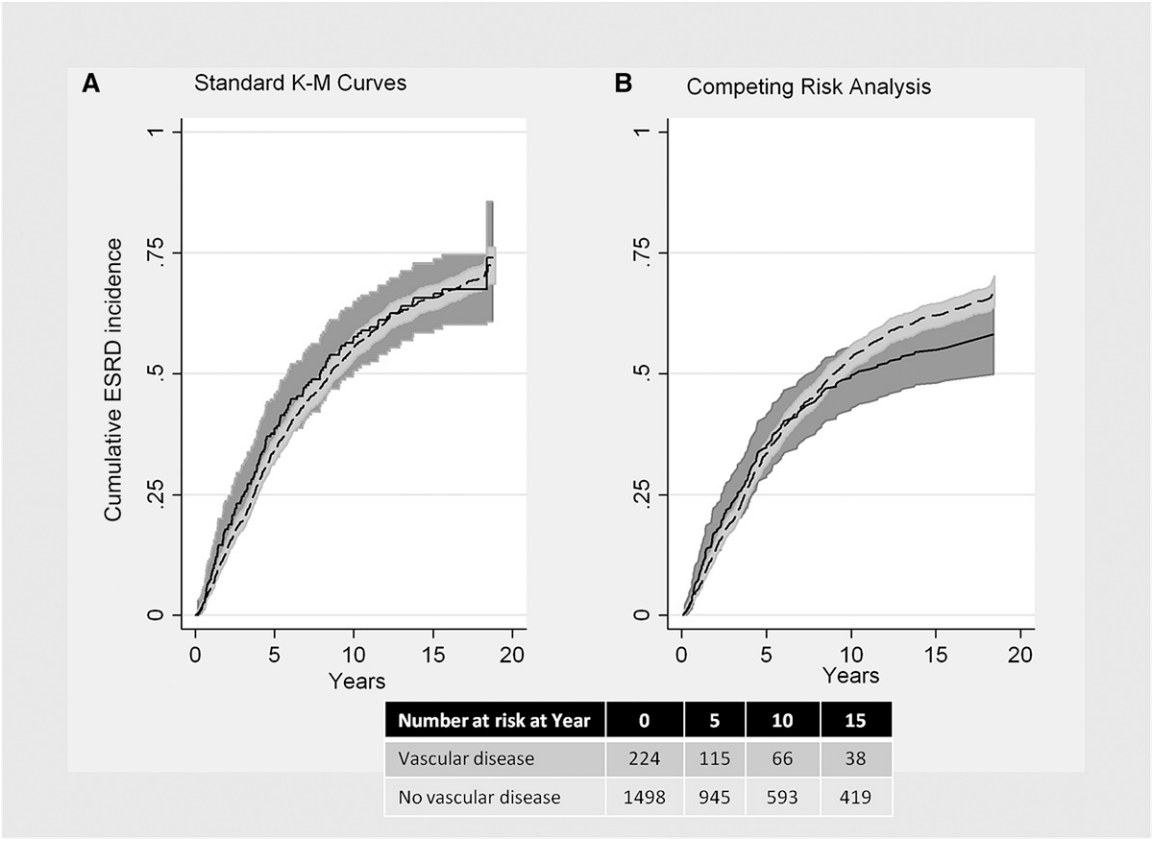
Cumulative Incidence of Pre-ESRD Death and Total Death, Stratified by eGFR and Age

The 15-year incidences of pre-ESRD death and total death (pre-ESRD and post-ESRD) were consistently higher among persons with vascular disease across stages of CKD and categories of age (Figure 3, A and B). The cumulative incidence estimate of pre-ESRD death from Kaplan–Meier analysis was greater in all subgroups than that from competing risk regression. The estimate of total death was the same: death has no competing event.

Independent Risk of ESRD and Pre-ESRD Death

The Cox proportional hazards model indicated that younger age, current smoking, polycystic kidney disease, diabetes, higher proteinuria, and lower eGFR were associated with higher risk of ESRD (Table 2, ESRD Cox model). Vascular disease was not significantly associated with ESRD in adjusted analysis (adjusted hazard ratio, 1.11; 95% confidence interval [95% CI], 0.91–1.36; *P*=0.30). Older age, African-American race, current smoking, diabetes, vascular disease, and lower eGFR were associated with death before ESRD; polycystic kidney disease was associated with a lower risk of pre-ESRD death (Table 2, pre-ESRD death Cox model). In other words, despite the tethering of the two events (a participant must eventually reach one of the two endpoints, and the majority did), certain patient characteristics were risk factors for both ESRD and pre-ESRD death in the Cox analysis.

Conversely, subhazard ratios estimated from competing risk regression necessarily discriminated between endpoints. Significant risk factors for ESRD included younger age, polycystic kidney disease, higher proteinuria, and lower eGFR (Table 2, ESRD competing risks model). Risk factors for pre-ESRD death included older age, diabetes, vascular disease, lower proteinuria, and higher GFR (Table 2, pre-ESRD death competing risks model). Similar coefficients for vascular disease were estimated by the Cox model (adjusted hazard ratio, 1.63; 95% CI, 1.20–2.20) and competing risk regression (adjusted subhazard ratio, 1.57; 95% CI, 1.63–2.14). In contrast, the coefficients for proteinuria, eGFR, and diabetes differed by method. Diabetes associated with ESRD in the Cox model but not in the competing risk model, reflecting the higher likelihood of pre-ESRD death among patients with diabetes. Lower eGFR and higher proteinuria were associated with a higher hazard but lower subhazard of pre-ESRD mortality: both were stronger risk factors for ESRD than mortality. Results were similar when using iothalamate-measured GFR (data not shown).



Number at risk at Year	0	5	10	15
Vascular disease	224	115	66	38
No vascular disease	1498	945	593	419

Figure 1. | **Absolute risk is overestimated by standard Kaplan–Meier analysis when competing events are common.** Cumulative incidence of ESRD by (A) standard Kaplan–Meier and (B) competing risk methods. No vascular disease (light gray shading and dotted line, 95% confidence intervals) versus vascular disease (dark gray shading and solid line, 95% confidence intervals). K–M, Kaplan–Meier.

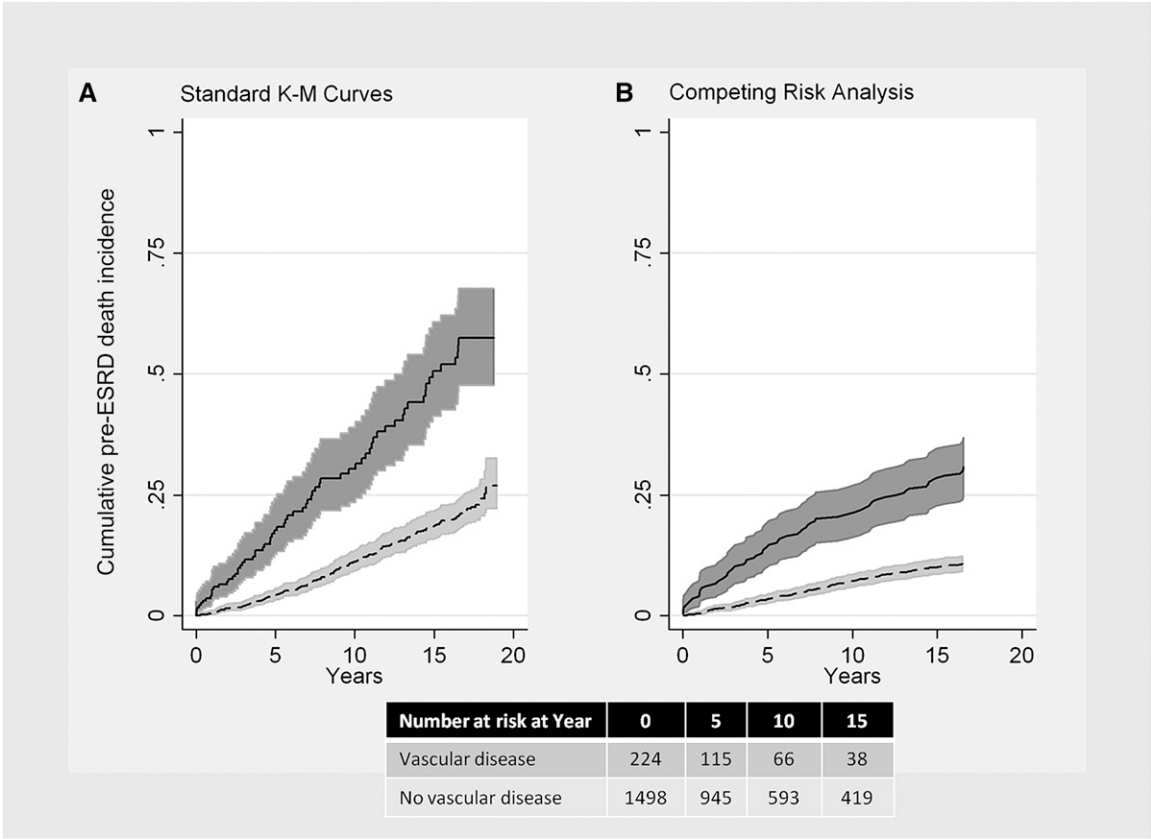
Discussion

In this study, we demonstrate that vascular disease is an independent risk factor for death before ESRD. In absolute terms, estimated by competing risk methods, patients with vascular disease experienced 19% more death before ESRD at 15 years than patients without vascular disease—an estimate very similar to simple incidence calculation. In contrast, cumulative incidence was grossly overestimated by standard survival analysis. The increased risk for pre-ESRD death among patients with vascular disease persisted after stratification by age and kidney function and multivariable adjustment. The adjusted instantaneous risk of pre-ESRD death was 63% greater among those with vascular disease, assuming that ESRD onset was not informative (the cause-specific hazard ratio). Taking into account the true (minimal) difference in rates of ESRD by presence of vascular disease only slightly attenuated the association (*i.e.*, the subhazard and hazard ratios were similar at 1.57 versus 1.63, respectively).

These results extend the association between vascular disease and premature death to those with CKD. Previous studies have demonstrated a strong association between vascular disease and death in the general population (27,28), as well as between vascular disease and death in hemodialysis patients (19,29). Vascular disease can be a cause or consequence of CKD, and our results suggest that either preventing the development of vascular disease or more aggressively managing prevalent cases may be a reasonable initial goal in reducing CKD mortality.

In contrast to previous work linking vascular disease and CKD progression (17,30), we did not find a significant association between vascular disease and ESRD. Certain methodological issues explain these differences. First, ESRD is a narrower outcome than a serum creatinine increase of 0.4 mg/dl (17) or eGFR decrease of 3 ml/min per 1.73 m^2 per year (30). Second, the definition of vascular disease differed slightly between studies. Third, study eligibility differed. In previous studies, participants had to survive until the subsequent study visit (and measure of kidney function), effectively excluding participants who died in the interim. This exclusion, common in literature investigating factors related to CKD progression, can result in overestimated risk. In contrast, our study maintains people who die before ESRD as part of the risk set. In fact, were we to exclude participants dying before ESRD, the association between vascular disease and ESRD approaches significance (adjusted hazard ratio, 1.21; 95% CI, 0.99–1.48; P=0.06).

A strength of our study is the rigorous exploration of competing risks. In standard survival analysis, participants who experience a competing event are treated similarly to those lost to follow-up: by censoring. Censoring competing events artificially supposes that those who experience a competing event (*e.g.*, death) remain at the same risk of the



Number at risk at Year	0	5	10	15
Vascular disease	224	115	66	38
No vascular disease	1498	945	593	419

Figure 2. | Competing risk analysis estimates absolute risk more accurately than standard Kaplan–Meier techniques when competing events are common. Cumulative incidence of pre-ESRD death by (A) standard Kaplan–Meier and (B) competing risk methods. No vascular disease (light gray shading and dotted line, 95% confidence intervals) versus vascular disease (dark gray shading and solid line, 95% confidence intervals). K–M, Kaplan–Meier.

event of interest (*e.g.*, ESRD) as the remaining participants, conditioned on adjustment variables. The cumulative incidence estimated from Kaplan–Meier analysis is a function of only one cause-specific hazard (*e.g.*, the instantaneous risk of either ESRD or pre-ESRD death), and therefore it applies only to people who did not experience the competing endpoint. Hence, standard survival analysis is flawed and often grossly overestimates absolute risk in the presence of an informative competing event (31,32). In contrast, in competing risk regression, the competing event is considered informative by default. Cumulative incidence calculations separate the hazard into subhazards; the cumulative incidence of ESRD or death is simply the cumulative incidence of one added to the cumulative incidence of the other. Thus, when absolute risk estimates are desired, competing risk regression is the method of choice (31). Another way to evaluate competing events is through the use of composite outcomes; however, there are fundamental limitations to this method. Composite endpoints assume a degree of equivalency between component outcomes, which may not be realistic. For example, a patient with polycystic kidney disease may have similar composite risk to a patient with the same eGFR and vascular disease, in which the risk is driven by the likelihood of ESRD in the former and death in the latter.

Instantaneous risk estimates from Cox proportional hazard regression and competing risk regression serve different purposes. A cause-specific hazard ratio estimates risk for a given event, presupposing that the rates of competing events are nil or the same by level of the characteristic. In etiological research, a hazard ratio is appropriate, accurate, and easy to interpret (33). However, in forecasting event rates, relating the hazard ratio to the cumulative incidence is difficult. For instance, in our analysis, despite a significant association between lower eGFR and pre-ESRD death in the Cox model, a lower mean eGFR would not translate into higher pre-ESRD mortality, because participants with low eGFR disproportionately reach ESRD before death. The subhazard ratio, on the other hand, allows direct calculation of the cumulative incidence function:

$$\mathrm{CIF}_1(t) = 1 - e^{-H_1(t)}$$

where $\mathrm{CIF}_1(t)$ is the cumulative incidence function and $H_1(t)$ the cumulative subhazard for event 1 at time t.

The estimation and interpretation of the subhazard diverges from that of the hazard in two important ways. First, the risk set is different. In calculating cause-specific hazards, persons experiencing the competing event are censored at the time of event. In calculating subhazards, persons experiencing the competing event are maintained in the risk set to account for the (zero) probability of their reaching the event of interest. Second, the partial likelihood function is weighted by whether and when a participant experienced the competing event. The subhazard ratio of pre-ESRD death for vascular disease thus

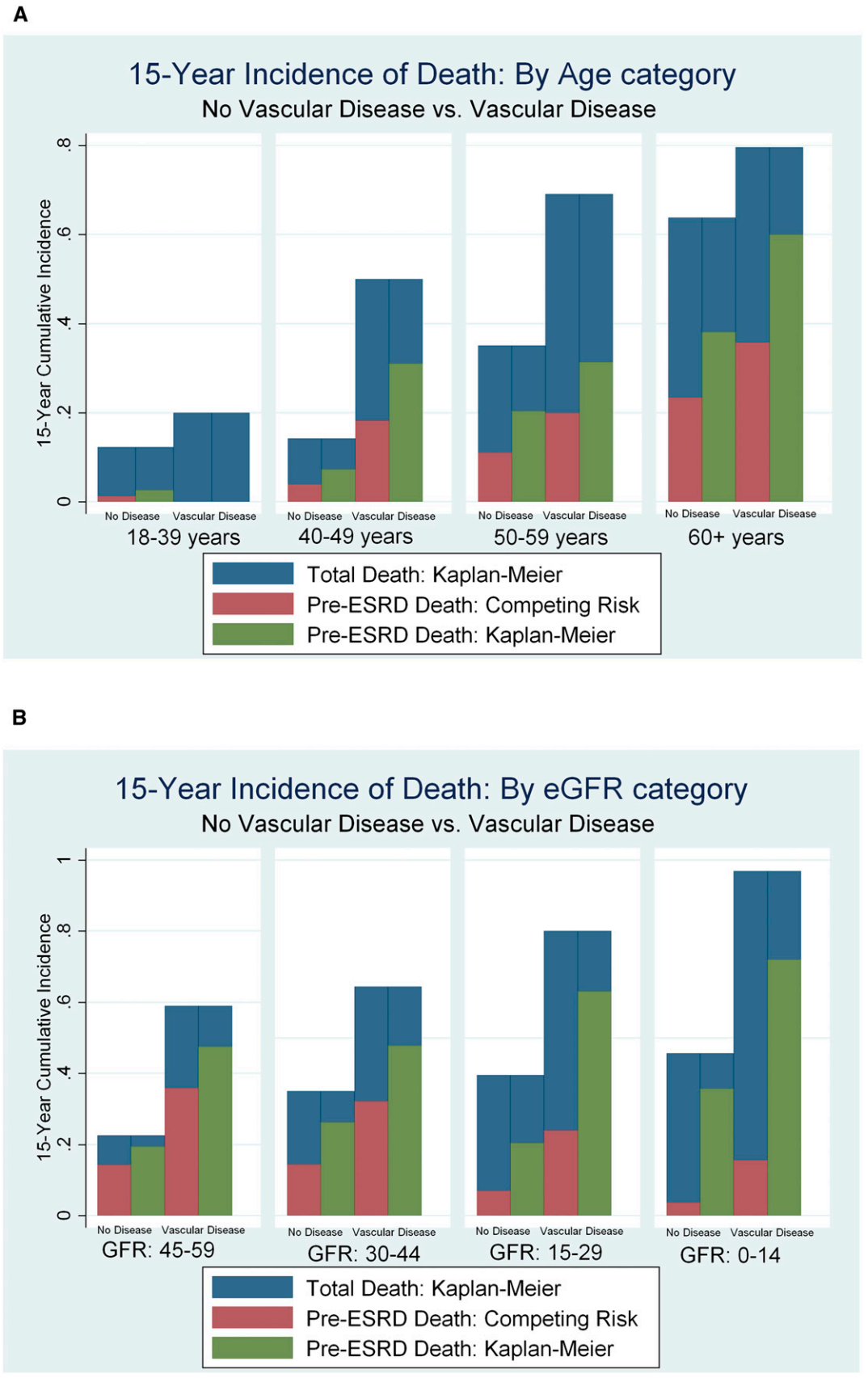


Figure 3. | **Mortality is higher in those with vascular disease, independent of age or estimated GFR.** Pre-ESRD and total mortality rates by category of (A) estimated GFR (ml/min per 1.73 m^2) and (B) age, by presence of vascular disease.

Table 2. Independent associations between baseline characteristics, ESRD, and pre-ESRD death

	ESRD				Pre-ESRD Mortality			
	Cox Model		Competing Risks Model		Cox Model		Competing Risks Model	
	Hazard Ratio (95% CI)	*P* Value	Subhazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Subhazard Ratio (95% CI)	*P* Value
Vascular disease	1.11 (0.91–1.36)	0.30	0.82 (0.60–1.13)	0.20	1.63 (1.20–2.20)	0.002	1.57 (1.15–2.14)	0.004
Age[a]	0.86 (0.81–0.91)	<0.001	0.80 (0.75–0.86)	<0.001	2.15 (1.81–2.56)	<0.001	2.13 (1.81–2.51)	<0.001
Female sex	0.92 (0.81–1.04)	0.20	0.94 (0.81–1.09)	0.40	0.79 (0.60–1.04)	0.10	0.87 (0.66–1.14)	0.30
African-American race	1.08 (0.90–1.31)	0.40	0.92 (0.70–1.20)	0.50	1.48 (1.01–2.16)	0.04	1.31 (0.89–1.93)	0.20
Current smoker	1.30 (1.09–1.55)	0.004	1.14 (0.93–1.41)	0.20	1.50 (1.01–2.23)	0.04	1.37 (0.92–2.03)	0.10
Systolic BP[b]	1.04 (1.00–1.08)	0.06	1.02 (0.98–1.08)	0.90	1.09 (1.02–1.17)	0.01	1.05 (0.98–1.13)	0.20
Diabetes status	1.47 (1.12–1.93)	0.01	0.97 (0.64–1.46)	0.90	2.13 (1.42–3.19)	<0.001	1.54 (1.03–2.32)	0.04
PKD[c]	3.04 (2.60–3.54)	<0.001	3.07 (2.49–3.77)	<0.001	0.52 (0.30–0.91)	0.02	0.30 (0.17–0.52)	<0.001
Glomerular disease[c]	0.98 (0.84–1.14)	0.80	1.09 (0.91–1.31)	0.30	0.96 (0.69–1.34)	0.80	1.01 (0.72–1.41)	0.90
Log-proteinuria	2.00 (1.81–2.21)	<0.001	1.77 (1.59–1.98)	<0.001	1.19 (0.97–1.46)	0.10	0.71 (0.57–0.88)	0.002
Estimated GFR[d]	1.62 (1.56–1.70)	<0.001	1.55 (1.47–1.64)	<0.001	1.18 (1.08–1.29)	<0.001	0.92 (0.86–0.99)	0.03

95% CI, 95% confidence interval; PKD, polycystic kidney disease;
[a]Per decade increase.
[b]Per 10 mmHg increase.
[c]Reference: Other cause of kidney disease.
[d]Per 10 ml/min per 1.73 m^2 lower.

signifies that vascular disease is associated with an increased probability of pre-ESRD death, even after taking into account variable rates of ESRD. This may be clinically useful in developing preventative protocols, for instance, or predicting the results of more aggressive cardiovascular risk factor management. In contrast to the hazard ratio, however, this result is not easily generalizable: it may only be applied to a population with similar rates of competing events (33). In addition, subhazards can be confusing because apparent "protection" for one event may merely reflect a dramatically increased risk for a competing event (*e.g.*, lower subhazard of pre-ESRD mortality with lower eGFR in our study).

This study has certain limitations. Participants in the MDRD study may receive more intensive nephrologic care than other populations, potentially prolonging survival. Whereas ESRD rates were higher than previous studies (but similar to a CKD population receiving nephrology care; ref. 34), the mortality rate and associations between pre-ESRD death, age, and eGFR were similar to previous studies of CKD progression in the general population (1,4). Our ESRD definition includes only treated ESRD; however, this is common in observational studies, and the number of ESRD patients in the United States who completely forgo dialysis is thought to be low (35). MDRD study enrollment took place over 20 years ago. Vascular disease management may have improved since that time, affecting the relative risk of ESRD and pre-ESRD death. However, precisely because enrollment was so remote, this study incorporates 18 years of follow-up. Most participants (78%) experienced either ESRD or pre-ESRD death, enabling more accurate estimates of the survival experience. Next, our definition of vascular disease incorporates peripheral vascular, cardiovascular, and cerebrovascular disease; however, similar definitions have been used in previous studies (17). Whereas sensitivity of self-reported vascular disease may be as low (54%–81%) (36), the definition of vascular disease was augmented by medical record review in the MDRD study. Provided that misclassification is random, results would be conservatively biased, attenuating our ability to detect associations. Finally, standard survival analysis generalizes only to similar populations as the MDRD study—a healthier population (due to exclusion criteria) with nondiabetic CKD. Competing risks analyses generalize only to populations with similar characteristics, rates of ESRD, and pre-ESRD death. In a general population of CKD patients, pre-ESRD death may be more common.

In summary, we conclude that competing risk analyses are important in obtaining valid estimates of absolute risk but must be interpreted with caution when studying associations. In our CKD population, vascular disease independently associated with pre-ESRD death, with nearly three times the incidence as participants without vascular disease. Additional attention to cardiovascular risk factor reduction in patients with vascular disease may be warranted.

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Disclosures

None.

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