Original Investigation

Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality

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IMPORTANCE The established chronic kidney disease (CKD) progression end point of end-stage renal disease (ESRD) or a doubling of serum creatinine concentration (corresponding to a change in estimated glomerular filtration rate [GFR] of −57% or greater) is a late event.

OBJECTIVE To characterize the association of decline in estimated GFR with subsequent progression to ESRD with implications for using lesser declines in estimated GFR as potential alternative end points for CKD progression. Because most people with CKD die before reaching ESRD, mortality risk also was investigated.

DATA SOURCES AND STUDY SELECTION Individual meta-analysis of 1.7 million participants with 12 344 ESRD events and 223 944 deaths from 35 cohorts in the CKD Prognosis Consortium with a repeated measure of serum creatinine concentration over 1 to 3 years and outcome data.

DATA EXTRACTION AND SYNTHESIS Transfer of individual participant data or standardized analysis of outputs for random-effects meta-analysis conducted between July 2012 and September 2013, with baseline estimated GFR values collected from 1975 through 2012.

MAIN OUTCOMES AND MEASURES End-stage renal disease (initiation of dialysis or transplantation) or all-cause mortality risk related to percentage change in estimated GFR over 2 years, adjusted for potential confounders and first estimated GFR.

RESULTS The adjusted hazard ratios (HRs) of ESRD and mortality were higher with larger estimated GFR decline. Among participants with baseline estimated GFR of less than 60 mL/min/1.73 m^2, the adjusted HRs for ESRD were 32.1 (95% CI, 22.3-46.3) for changes of −57% in estimated GFR and 5.4 (95% CI, 4.5-6.4) for changes of −30%. However, changes of −30% or greater (6.9% [95% CI, 6.4%-7.4%] of the entire consortium) were more common than changes of −57% (0.79% [95% CI, 0.52%-1.06%]). This association was strong and consistent across the length of the baseline period (1 to 3 years), baseline estimated GFR, age, diabetes status, or albuminuria. Average adjusted 10-year risk of ESRD (in patients with a baseline estimated GFR of 35 mL/min/1.73 m^2) was 99% (95% CI, 95%-100%) for estimated GFR change of −57%, was 83% (95% CI, 71%-93%) for estimated GFR change of −40%, and was 64% (95% CI, 52%-77%) for estimated GFR change of −30% vs 18% (95% CI, 15%-22%) for estimated GFR change of 0%. Corresponding mortality risks were 77% (95% CI, 71%-82%), 60% (95% CI, 56%-63%), and 50% (95% CI, 47%-52%) vs 32% (95% CI, 31%-33%), showing a similar but weaker pattern.

CONCLUSIONS AND RELEVANCE Declines in estimated GFR smaller than a doubling of serum creatinine concentration occurred more commonly and were strongly and consistently associated with the risk of ESRD and mortality, supporting consideration of lesser declines in estimated GFR (such as a 30% reduction over 2 years) as an alternative end point for CKD progression.

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Chronic kidney disease (CKD) is a worldwide public health problem, with increasing prevalence, poor outcomes, and high treatment costs.[1] Yet despite the availability of simple laboratory tests to identify people with earlier stages of CKD, there are fewer clinical trials for kidney disease than for other common diseases.[2] One contributing reason may be that the established end point (ie, a doubling of serum creatinine concentration from baseline, corresponding to a 57% reduction in estimated glomerular filtration rate [GFR]) used to document CKD progression is a late event, requiring long follow-up periods and large sample sizes.[2-4] Improved methods for GFR estimation may allow for use of smaller reductions in estimated GFR (vs a doubling of serum creatinine concentration) as alternative end points to assess CKD progression.[4,5] Evaluation of such alternative end points should include their enumeration and quantification of their relationship with future progression to end-stage renal disease (ESRD) across a wide range of settings. Standardized definitions of CKD progression outcomes would also benefit observational studies and clinical practice.

One-year change in estimated GFR was strongly related to risk of ESRD in the Alberta Kidney Disease Network.[6] Other studies had focused on mortality and cardiovascular disease because these outcomes occur more commonly than ESRD and have shown a strong relationship with various definitions for CKD progression.[7-11] A systematic evaluation across studies using a uniform analytic approach is needed to provide a more rigorous basis for determining the prognosis associated with specific declines in estimated GFR. Clinical trials with a doubling of serum creatinine concentration or ESRD as an end point typically have follow-up periods of approximately 5 years. The goal for alternative kidney end points is to enable clinical trials of shorter duration (2 years is believed to be useful for observing a meaningful change in estimated GFR); however, the prognostic implications of shorter and longer periods for observing change in estimated GFR need to be quantified as well. A rigorous evaluation of estimates of CKD progression is also important to inform observational studies and clinical practice in which various measures of CKD progression have been used.[7]

We examined the association of change in estimated GFR over 1, 2, and 3 years with subsequent ESRD and mortality in a large, international consortium to test its strength and consistency across subgroups defined by baseline kidney function and comorbid conditions and provide the evidence base for evaluating the usefulness of potential alternative end points for CKD progression.

Methods

Study Selection Criteria

Details of the Chronic Kidney Disease Prognosis Consortium (CKD-PC) are described elsewhere[12-16] and in eAppendices 1 and 2 in the Supplement. Briefly, CKD-PC consists of 50 cohorts with at least 1000 participants (not applied to cohorts predominantly enrolling persons with CKD) with data on serum creatinine concentration and albuminuria and 50 or more outcome events of interest (either mortality or kidney outcomes).[12-16] All cohorts with appropriate data opted into this study. There were 22 cohorts (4 general population cohorts, 5 high-risk cohorts in terms of cardiovascular risk, and 13 CKD cohorts) with a repeated measure of serum creatinine concentration during an elapsed period of 6 months to 3.5 years to determine the relationship of change in estimated GFR on subsequent ESRD. There were 35 cohorts (15 general population cohorts, 7 high-risk cohorts in terms of cardiovascular risk, and 13 CKD cohorts) with mortality outcomes. Each meta-analysis for the present study was restricted to cohorts with at least 10 events and participants aged 18 years or older. Data transfer and analysis took place between July 2012 and September 2013, with subsequent updates. This study was approved by the institutional review board for use of deidentified data at the Johns Hopkins Bloomberg School of Public Health.

Procedures

Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation.[4,16] In cohorts in which the creatinine measurement was not standardized to isotope dilution mass spectrometry, creatinine concentrations were reduced by 5% (the established calibration factor) and drift over time was corrected when possible.[17]

We tested 2 indices of change in estimated GFR (percentage change and slope [annual change in estimated GFR]) during a baseline period. Percentage change in estimated GFR was calculated as: (last estimated GFR − first estimated GFR)/(first estimated GFR) × 100%. The slope was determined as an annual change estimated from a least-square regression model using all estimated GFR measurements obtained during the baseline period. Because the implications for the magnitude of change in estimated GFR may vary depending on the time for the change, we defined 3 baseline periods (1, 2, and 3 years) to determine the change in estimated GFR and repeated the analysis for each baseline period. The length of the baseline periods corresponds to the median length of follow-up in a trial that would use change in estimated GFR as an end point, and also corresponds to periods over which clinicians would want to determine if CKD has progressed. For each baseline period, a margin of 6 months before and after the end of the period was allowed for determining the last available estimated GFR to calculate the change (eg, estimated GFR between 6 months and 1.5 years after the first available estimated GFR could be used for the 1-year baseline period analysis). However, the estimated GFR closest to the end of the period of interest was selected for each participant. Given that a doubling of serum creatinine concentration (the established kidney end point) corresponds to a −57% change in estimated GFR using the CKD-EPI equation (for serum creatinine concentrations of ≥0.9 mg/dL in men and ≥0.7 mg/dL in women), our primary data presentation was based on percentage change in estimated GFR. All covariates were assessed at the time of first estimated GFR (eAppendix 2 in the Supplement provides details for specific cohorts).

We defined diabetes as having a fasting glucose level of 126 mg/dL or higher (≥7.0 mmol/L), a nonfasting glucose level of 200 mg/dL or higher (≥11.1 mmol/L), hemoglobin A_{1c} level of 6.5% or higher, use of glucose-lowering drugs, or self-reported diabetes. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of cardiovascular disease. Because albuminuria was not necessarily measured prior to the first available estimated GFR in several cohorts, adjustment for albuminuria when available was conducted only in sensitivity analyses. Even though the ratio of urine albumin to creatinine was our primary measure of albuminuria, we also included studies with urine albumin excretion rate, ratio of urine protein to creatinine, or quantitative dipstick protein.[18]

The primary outcome of interest was ESRD after the baseline period. We defined ESRD as initiation of renal replacement therapy or death due to kidney disease other than acute kidney injury. Cases of ESRD before the baseline period were excluded from the relevant analyses. Because the majority of patients with CKD die without reaching ESRD, we repeated the analysis for all-cause mortality as well as cardiovascular and noncardiovascular mortality. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death.

Statistical Analysis

We applied a 2-stage analytic approach, whereby each study was first analyzed separately, followed by a random-effects meta-analysis. The analysis overview and analytic notes for individual studies are described in eAppendix 2 in the Supplement. We imputed missing values of covariates but not change in estimated GFR (the main exposure) using cohort-specific mean values (details appear in eAppendix 2 in the Supplement). We quantified heterogeneity using the I^2 statistic and χ^2 test[12] and explored sources of heterogeneity with random-effects meta-regression analysis. Because the absolute risk of ESRD and the implication of change in estimated GFR vary substantially depending on baseline estimated GFR, analyses were stratified by first estimated GFR with lower estimated GFR defined as less than 60 mL/min/1.73 m^2 and higher estimated GFR defined as 60 mL/min/1.73 m^2 or greater. Analyses were performed using Stata/SE software version 12 (StataCorp). We considered 2-sided *P* values of less than .05 as statistically significant.

We modeled the adjusted hazard ratios (HRs) of ESRD and mortality after the end of the baseline period as a spline function of percentage change in estimated GFR with the aforementioned covariates. In each study, we fit piecewise linear splines for percentage change in estimated GFR (knots were placed at −57%, −25%, −10%, 10%, 25%) and used 0% change as a reference point. Cox models were adjusted for age, sex, race/ethnicity (blacks vs nonblacks), systolic blood pressure, total cholesterol, diabetes, history of cardiovascular disease, and first estimated GFR. Potential effect modifiers with change in estimated GFR were assessed by incorporating interaction terms.

We illustrate the opposite effects of decreasing risk and increasing prevalence of smaller percentage changes in estimated GFR using an approximation of the percentage population attributable risk (PAR; calculated from the prevalence of percentage change in estimated GFR, using the overall population distributions as a fixed standard, and its adjusted HR and 95% confidence interval). It is best to view the calculated percentage PAR as an approximation of the overall percentage of ESRD or mortality risk explained (rather than a truly preventable fraction) because change in estimated GFR is not fully reversible.[19] For the range of change in estimated GFR associated with lower risk, percentage PAR has a negative value corresponding to reduced (rather than excess) risk in the population compared with the reference point of 0% change.

The adjusted HRs from the meta-analysis were translated for percentage change in estimated GFR to absolute risk of ESRD or mortality at 1, 3, 5, and 10 years after the baseline period using the weighted average baseline risk. One-year baseline risk in each cohort was calculated for the following combination of covariates: age of 60 years, nonblack, male, no change in estimated GFR, a first estimated GFR of 50 mL/min/1.73 m^2, a systolic blood pressure of 130 mm Hg, a total cholesterol level of 5 mmol/L, and no history of diabetes or cardiovascular disease. Risk was scaled for longer follow-up and pooled across cohorts using a weighted average (implications of lower and higher baseline risk were also calculated and information appears in eAppendix 2 in the Supplement). We applied the adjusted sub-HRs from competing risk models accounting for death as a competing end point.[20]

Results

Study Characteristics

Twenty-two cohorts provided data on change in estimated GFR in 1 530 648 participants who had 12 344 subsequent ESRD events during a baseline period of 1 year and a mean follow-up period of 3.1 years. These studies included 1 341 193 participants with 8532 subsequent ESRD events for baseline periods of 2 years and 1 080 274 participants with 5159 subsequent ESRD events for baseline periods of 3 years (**Table 1**). Mortality analysis included 35 cohorts (1 757 886 participants with 223 944 deaths from 27 cohorts for baseline periods of 1 year, 1 589 257 participants with 158 603 deaths from 32 cohorts for 2 years, and 1 259 477 participants with 102 491 deaths from 34 cohorts for 3 years). Baseline assessments in each cohort took place from 1975 through 2012, with generally longer follow-up in older cohorts than newer cohorts. Participating cohorts spanned a wide spectrum of sample size and baseline characteristics (Table 1, **Table 2**, **Table 3**, and eTable 1 in the Supplement). The cohort averages for lower and higher estimated GFR strata were 48 and 92 mL/min/1.73 m^2, respectively, for first estimated GFR; 74 and 51 years for age; 20% and 51% for female sex; 7% and 1% for black race; 38% and 14% for diabetes; and 35% and 6% for history of cardiovascular disease.

Table 1. Participating Cohorts by Baseline Estimated Glomerular Filtration Rate (GFR)

	No. of Participants by Baseline Estimated GFR in mL/min/1.73 m^2		No. of Serum Creatinine Measurements, Median (IQR)	End-Stage Renal Disease[a]			All-Cause Mortality		
				No. of Events by Baseline Estimated GFR in mL/min/1.73 m^2		Mean (SD) Follow-up, y	No. of Events by Baseline Estimated GFR in mL/min/1.73 m^2		Mean (SD) Follow-up, y
	<60	≥60		<60	≥60		<60	≥60	
Meta-analysis by baseline period									
1 y	466 068	1 291 818	2 (2-3)	(n = 458 965) 11 214	(n = 1 071 683) 1130	3.1 (2.3)	144 558	79 386	4.4 (3.6)
2 y	363 143	1 226 114	3 (3-5)	(n = 356 813) 7523	(n = 984 380) 1009	2.4 (2.2)	97 795	60 808	3.7 (3.6)
3 y	235 560	1 023 917	5 (4-5)	(n = 230 178) 4058	(n = 850 096) 1101	2.0 (2.9)	55 135	47 356	3.2 (4.0)
Cohort data for 2-y baseline period[b]									
AASK	744	169	7 (6-7)	243	8	6 (3)	112	24	6 (3)
ADVANCE	1542	8457	4 (4-4)	16	21	3 (0.5)	150	407	3 (0.5)
Aichi	14	1798	2 (2-3)				1	15	7 (2)
AKDN	35 617	257 597	3 (3-4)	206	63	2 (1)	3878	5779	2 (1)
ARIC[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
BC CKD	7986	656	10 (8-14)	1178	53	2 (1)	1730	67	3 (1)
CARE	580	3101	3 (3-3)				62	150	3 (1)
CCF	17 102	31	6 (4-9)	290	1	1 (1)	1746	3	1 (1)
CHS[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
CIRCS	175	4286	3 (2-3)				53	564	17 (4)
CRIB	189	1	2 (2-2)	63	0	4 (2)	45	0	5 (2)
Framingham	46	652	2 (2-2)				17	54	6 (1)
Geisinger	14 850	20	6 (4-9)	257	0	3 (2)	2287	4	3 (2)
GLOMMS 1	645	2	11 (7-20)	58	0	3 (1)	274	1	3 (1)
IPHS	2147	60 319	3 (3-3)				983	10 019	12 (3)
KP Hawaii	5468	15 140	5 (4-8)	134	19	1 (0.7)	364	329	1 (1)
KPNW	320	202	7 (4-12)	21	10	4 (2)	167	73	5 (2)
KSHS	217	62 810	3 (3-5)				5	169	3 (1)
Maccabi	27 616	577 024	8 (7-9)	724	177	3 (1)	6199	14 042	4 (1)
MASTERPLAN	513	66	8 (7-9)	111	3	4 (1)	79	4	4 (1)
MDRD	591	27	8 (7-8)	431	13	7 (5)	270	5	13 (4)
MESA[c]	NA	NA	NA				NA	NA	NA
MRFIT	185	11 342	3 (3-3)	30	239	21 (6)	86	3900	23 (8)
NephroTest	465	88	3 (2-3)	92	3	3 (2)	61	1	4 (2)
NZDCS	1913	7093	3 (3-5)	152	100	6 (2)	728	1081	6 (2)
Ohasama	38	1039	3 (3-3)				6	59	7 (1)
Pima	12	1594	2 (2-2)	6	101	12 (8)	10	343	13 (8)
PREVEND	406	4334	2 (2-2)				34	98	4 (1)
Rancho Bernardo	33	174	2 (2-2)				9	17	7 (1)
RENAAL	1083	118	10 (9-10)	195	5	1 (1)	147	7	1 (1)
Severance	140	6105	2 (2-3)				6	119	12 (2)
Sunnybrook	1484	1173	7 (5-11)	168	18	3 (2)	437	90	5 (3)
Taiwan MJ	2247	96 533	2 (2-3)				362	1676	7 (4)
VA CKD	238 488	103 580	5 (4-7)	3148	175	3 (1)	77 337	21 552	3 (1)
ZODIAC	287	583	3 (3-3)				150	156	7 (3)

Abbreviation: IQR, interquartile range.

[a] Blank cells indicate the cohort did not have data on end-stage renal disease.

[b] The expanded cohort names appear in eAppendix 1 in the Supplement.

[c] The NAs indicate data were not available for the 2-year baseline period but those studies are included for other baseline periods.

Table 2. Baseline Characteristics for Participating Cohorts During the 2-Year Baseline Period Analysis for Estimated Glomerular Filtration Rate (GFR) of Less Than 60 mL/min/1.73 m^2

	Mean (SD)				Participants, %					
Cohort[a] by Estimated GFR <60 mL/min/1.73 m^2	Age, y	Baseline Estimated GFR, mL/min/1.73 m^2	Total Cholesterol, mmol/L	SBP, mm Hg	Female	Black	DM	History of CVD	Albuminuria[b]	Current Cigarette Smoking
AASK	54 (11)	42 (11)	5 (1)	150 (24)	39	100	0	53	64	44
ADVANCE	69 (6)	51 (8)	5 (1)	147 (23)	54	0	100	31	39	9
Aichi[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AKDN[c]	73 (11)	48 (10)	NA	NA	60	0	18	17	12	NA
BC CKD	70 (13)	33 (10)	5 (1)	134 (22)	46	0	42	4	69	6
CARE	66 (7)	52 (7)	5 (0)	134 (20)	21	2	18	100	19	8
CCF	72 (11)	47 (10)	5 (1)	131 (19)	55	12	26	22	27	8
CIRCS	63 (6)	54 (6)	5 (1)	135 (19)	70	0	6	4	7	14
CRIB	61 (15)	28 (9)	6 (1)	150 (23)	34	6	16	44	81	12
Framingham[c]	70 (6)	51 (8)	5 (1)	139 (16)	52	0	20	13	NA	13
Geisinger	70 (10)	52 (8)	5 (1)	131 (19)	59	1	31	15	44	7
GLOMMS 1[c]	70 (13)	33 (7)	NA	NA	50	0	61	48	72	11
IPHS	70 (6)	54 (6)	5 (1)	139 (17)	68	0	9	16	9	9
KP Hawaii	71 (11)	47 (10)	5 (1)	137 (22)	53	0	52	35	66	7
KPNW[c]	71 (10)	47 (11)	NA	142 (23)	48	2	40	24	8	13
KSHS[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Maccabi	72 (11)	50 (9)	5 (1)	134 (19)	58	0	30	9	40	1
MASTERPLAN	61 (12)	36 (11)	5 (1)	136 (20)	31	0	24	30	37	21
MDRD	52 (12)	35 (11)	6 (1)	132 (18)	38	7	4	13	83	10
MRFIT	52 (5)	55 (5)	6 (1)	130 (17)	0	5	10	3	13	34
NephroTest	60 (14)	37 (12)	5 (1)	137 (20)	32	10	24	19	96	15
NZDCS	71 (9)	48 (10)	5 (1)	142 (21)	57	0	100	2	14	8
Ohasama[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pima[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PREVEND	67 (9)	53 (7)	5 (1)	137 (21)	53	0	16	16	27	22
Rancho Bernardo[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RENAAL	61 (7)	40 (11)	6 (1)	152 (19)	38	13	100	44	100	18
Severance[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sunnybrook[c]	69 (14)	38 (12)	NA	NA	40	0	37	48	81	5
Taiwan	63 (10)	52 (8)	5 (1)	139 (24)	40	0	9	9	12	21
VA CKD[c]	75 (9)	48 (9)	4 (1)	NA	3	8	43	45	41	NA
ZODIAC	74 (8)	50 (8)	6 (1)	159 (24)	72	0	100	43	43	13
Total	74 (10)	48 (10)	4 (1)	135 (20)	20	7	38	35	38	6

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; SBP, systolic blood pressure.

SI conversion factor: To convert total cholesterol to mg/dL, divide by 0.0259.

[a] The expanded cohort names appear in eAppendix 1 in the Supplement. Appendices 1 and 2 in the Supplement provide further information regarding each cohort.

[b] Defined as a ratio of urine albumin to creatinine of 30 mg/g or greater, a ratio of urine protein to creatinine of 50 mg/g or greater, or a dipstick protein level of 1+ or greater.

[c] The NAs indicate data were not available.

Risk of ESRD According to Change in Estimated GFR

Overall, change in estimated GFR over 2 years had a median of −1% (5th-95th percentile, −26% to 26%), with a distribution skewed toward negative values, indicating more prevalent decline in estimated GFR (**Figure 1**). The prevalence of a change of −57% in estimated GFR was much lower than for lesser changes. Fifty-two percent of ESRD cases had a change of −30% in estimated GFR over 2 years, whereas only 16% of ESRD cases reached a change of −57% in estimated GFR during this time frame. Subsequent risk of ESRD showed higher adjusted HRs at greater negative percentage changes in estimated GFR and lower HRs at greater positive percentage changes in estimated GFR compared with no change in estimated GFR, with similar associations for lower and higher estimated GFR strata (Figure 1). A change of −57% in estimated GFR was associated with adjusted HRs for ESRD of 32.1 (95% CI, 22.3-46.3) at lower estimated GFR and 57.2 (95% CI, 21.9-149.1) at higher esti-

Table 3. Baseline Characteristics for Participating Cohorts During the 2-Year Baseline Period Analysis for Estimated Glomerular Filtration Rate (GFR) of 60 mL/min/1.73 m^2 or Greater

	Mean (SD)				Participants, %					
Cohort[a] by Estimated GFR ≥60 mL/min/1.73 m^2	Age, y	Baseline Estimated GFR, mL/min/1.73 m^2	Total Cholesterol, mmol/L	SBP, mm Hg	Female	Black	DM	History of CVD	Albuminuria[b]	Current Cigarette Smoking
AASK	55 (10)	67 (6)	5 (1)	150 (24)	38	100	0	45	38	41
ADVANCE	66 (6)	83 (13)	5 (1)	144 (21)	40	0	100	24	28	16
Aichi	49 (6)	92 (14)	5 (1)	126 (15)	18	0	0.3	0.06	4.2	31
AKDN[c]	54 (15)	89 (16)	NA	NA	59	0	7	4	4	NA
BC CKD	56 (15)	78 (16)	5 (2)	136 (23)	45	1	52	1	67	6
CARE	58 (9)	80 (13)	5 (0)	128 (18)	12	3	13	100	11	17
CCF[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CIRCS	54 (9)	84 (12)	5 (1)	130 (17)	66	0	5	1	2	23
CRIB[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Framingham	59 (9)	89 (18)	5 (1)	127 (18)	50	0	9	5	12	15
Geisinger[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GLOMMS 1[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPHS	59 (10)	87 (12)	5 (1)	133 (18)	68	0	5	5	2	7
KP Hawaii	58 (13)	86 (16)	5 (1)	135 (20)	49	0	67	16	41	13
KPNW[c]	67 (10)	73 (10)	NA	142 (22)	55	5	46	20	11	11
KSHS	37 (7)	91 (11)	5 (1)	114 (14)	34	0	2	1	1	30
Maccabi	47 (15)	94 (19)	5 (1)	124 (17)	59	0	11	1	17	2
MASTERPLAN[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MDRD[c]	47 (12)	65 (4)	6 (1)	129 (20)	63	11	7	7	NA	NA
MRFIT	47 (6)	89 (13)	6 (1)	128 (14)	0	7	5	1	3	58
NephroTest[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NZDCS	59 (13)	86 (16)	5 (1)	138 (19)	49	0	100	1	7	16
Ohasama	63 (8)	84 (11)	5 (1)	129 (17)	67	0	8	2	5	16
Pima[c]	32 (14)	122 (15)	4 (1)	118 (17)	63	0	27	NA	18	28
PREVEND	52 (11)	83 (13)	5 (1)	125 (18)	49	1	8	5	8	32
Rancho Bernardo	69 (5)	78 (11)	5 (1)	132 (17)	52	0	16	10	8	8
RENAAL[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Severance	44 (9)	90 (15)	5 (1)	120 (18)	38	0	1	0.4	4	32
Sunnybrook[c]	52 (16)	91 (20)	NA	NA	46	0	26	23	79	5
Taiwan	40 (12)	96 (15)	5 (1)	119 (18)	50	0	2	2	1	22
VA CKD[c]	69 (10)	71 (13)	4 (1)	NA	3	11	52	38	72	NA
ZODIAC	64 (11)	77 (12)	6 (1)	155 (25)	49	0	100	28	32	23
Total	51 (16)	92 (18)	5 (1)	125 (18)	51	1	14	6	17	8

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; SBP, systolic blood pressure.

SI conversion factor: To convert total cholesterol to mg/dL, divide by 0.0259.

[a] The expanded cohort names appear in eAppendix 1 in the Supplement. Appendices 1 and 2 in the Supplement provide further information regarding each cohort.

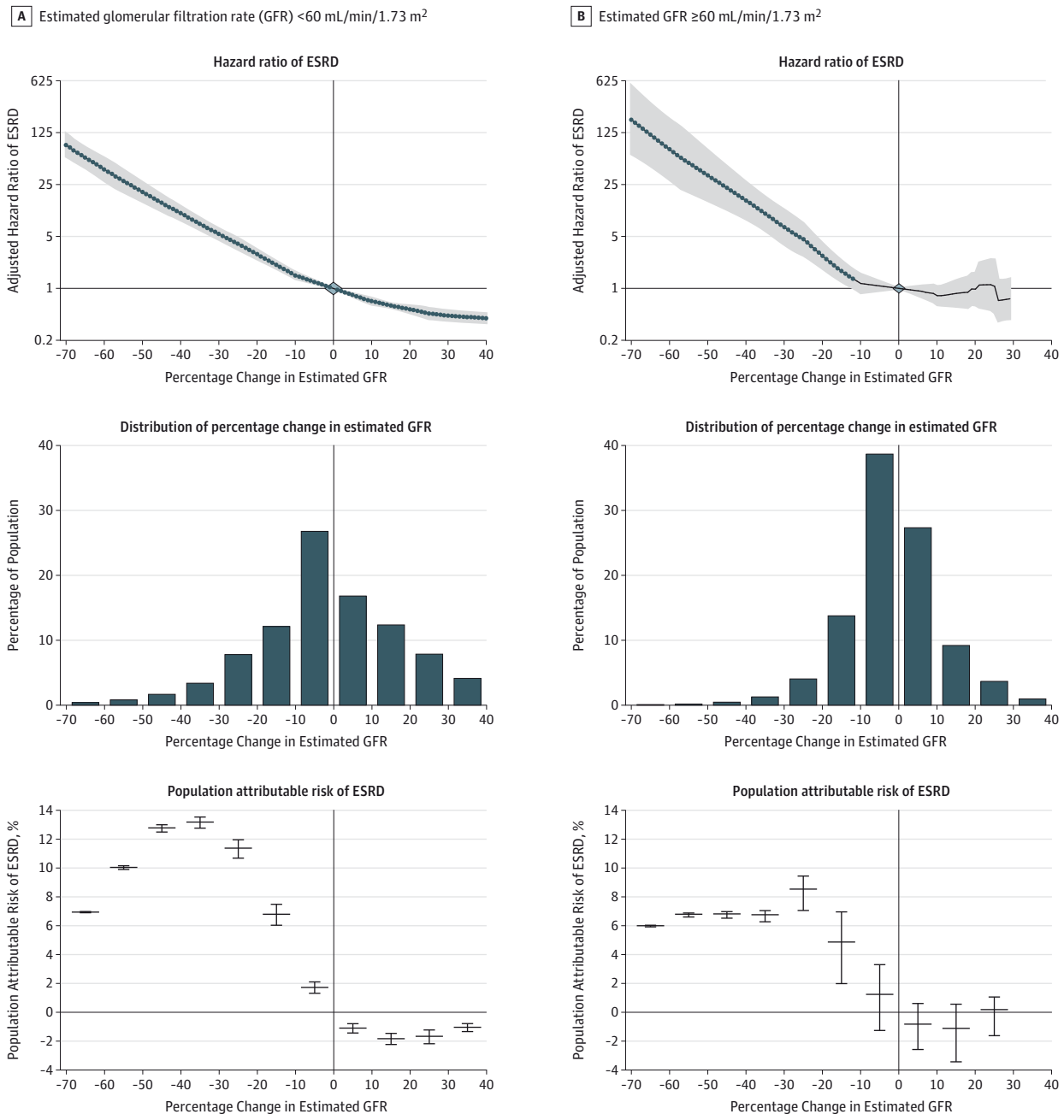
[b] Defined as a ratio of urine albumin to creatinine of 30 mg/g or greater, a ratio of urine protein to creatinine of 50 mg/g or greater, or a dipstick protein level of 1+ or greater.

[c] The NAs indicate data were not available.

mated GFR. A change of −30% in estimated GFR was associated with adjusted HRs of ESRD of 5.4 (95% CI, 4.5-6.4) at lower and 6.7 (95% CI, 3.9-11.5) at higher estimated GFR. Sensitivity analyses assessing the percentage change in estimated GFR over shorter (1 year) and longer (3 years) baseline periods yielded similar associations with ESRD in both the lower and higher estimated GFR strata (**Table 4** and eFigures 1 and 2 in the Supplement). Further adjustment for albuminuria yielded similar results (eFigure 3 in the Supplement), as did multiple imputation of missing data (eAppendix 2 in the Supplement).

The percentage PAR of ESRD was positive for those with a decrease in estimated GFR and negative for those with an increase in estimated GFR compared with those with a stable estimated GFR (Figure 1). The percentage PAR showed that the lower levels of risk associated with smaller

Figure 1. End-Stage Renal Disease (ESRD) Associated With Percentage Change in Estimated GFR During a 2-Year Baseline Period



Values trimmed at less than −70% change (0.22% and 0.055% of the study population for estimated GFR <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2, respectively) and greater than 40% change (5.9% and 0.51% of the population for estimated GFR <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2, respectively). In the top 2 panels, the diamonds indicate the reference point of 0% change in estimated GFR.

reductions in estimated GFR were offset by a higher prevalence, leading the percentage PAR to peak around −40% to −30% for the lower estimated GFR stratum and −30% to −20% for the higher stratum. In the lower estimated GFR stratum with a 2-year baseline, the cumulative prevalence of ESRD was 0.79% (95% CI, 0.52%-1.06%) for estimated GFR changes of −57% or greater vs 6.9% (95% CI, 6.4%-7.4%) for changes of −30% or greater (Table 4). As a result, the cumulative percentage PAR increased markedly from 10% to 44%, respectively. Thus, of the 63% of ESRD cases attributable to estimated GFR decline (below 0%), 16% can be attributed to the participants with a change of −57% or greater in estimated GFR compared with 70% with a change of −30% or greater in estimated GFR. Similar results were observed in the higher estimated GFR stratum. As expected, the cumulative prevalence of any given decline in estimated

Table 4. End-Stage Renal Disease Associated With Change in Estimated Glomerular Filtration Rate (GFR) During Baseline Periods of 1 to 3 Years' Duration by Level of Kidney Function

	Change in Estimated GFR During the 2-Year Baseline Period					
	−57%	−40%	−30%	−25%	−20%	0% (Stable)
Estimated GFR <60 mL/min/1.73 m^2						
1-y Baseline period						
Adjusted HR (95% CI)	21.5 (16.1-28.8)	7.4 (6.1-8.9)	4.0 (3.4-4.6)	3.0 (2.6-3.4)	2.4 (2.2-2.7)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.43 (0.30-0.57)	1.7 (1.4-1.9)	4.2 (3.9-4.6)	6.4 (6.1-6.8)	10 (10-11)	54 (54-55)
Cumulative PAR (95% CI), %[a]	4.3 (4.2-4.3)	15 (14-15)	25 (24-25)	30 (29-31)	35 (33-36)	46 (43-48)
2-y Baseline period						
Adjusted HR (95% CI)	32.1 (22.3-46.3)	10.2 (8.2-12.7)	5.4 (4.5-6.4)	4.0 (3.3-4.8)	2.9 (2.5-3.3)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.79 (0.52-1.06)	3.2 (2.8-3.7)	6.9 (6.4-7.4)	10 (10-11)	15 (14-15)	54 (53-54)
Cumulative PAR (95% CI), %[a]	10 (10-10)	31 (31-32)	44 (43-45)	51 (49-52)	55 (54-57)	63 (60-65)
3-y Baseline period						
Adjusted HR (95% CI)	36.8 (27.3-49.7)	10.4 (8.0-13.4)	5.0 (3.9-6.4)	3.2 (2.4-4.2)	2.5 (2.1-3.1)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	1.3 (0.9-1.7)	4.8 (4.3-5.4)	9.5 (8.9-10.2)	13 (13-14)	18 (18-19)	53 (52-54)
Cumulative PAR (95% CI), %[a]	17 (17-17)	40 (40-41)	52 (51-53)	56 (55-57)	60 (58-61)	65 (62-67)
Estimated GFR ≥60 mL/min/1.73 m^2						
1-y Baseline period						
Adjusted HR (95% CI)	48.4 (19.0-123.0)	13.1 (7.9-21.6)	5.5 (3.6-8.4)	3.7 (2.5-5.5)	2.5 (1.8-3.3)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.13 (0.05-0.21)	0.56 (0.42-0.70)	1.8 (1.6-2.0)	3.4 (3.2-3.7)	6.8 (6.5-7.0)	64 (63-64)
Cumulative PAR (95% CI), %[a]	4.9 (4.7-4.9)	13 (12-13)	20 (19-21)	25 (23-26)	30 (27-31)	37 (31-42)
2-y Baseline period						
Adjusted HR (95% CI)	57.2 (21.9-149.1)	15.3 (8.5-27.2)	6.7 (3.9-11.5)	4.6 (2.8-7.6)	2.7 (1.8-4.1)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.18 (0.07-0.29)	0.85 (0.62-1.09)	2.2 (2.0-2.5)	4.0 (3.7-4.3)	6.8 (6.5-7.1)	62 (62-62)
Cumulative PAR (95% CI), %[a]	8.5 (8.4-8.6)	21 (20-21)	28 (27-29)	32 (30-34)	35 (33-37)	41 (33-47)
3-y Baseline period						
Adjusted HR (95% CI)	60.6 (19.0-193.0)	15.7 (7.4-33.4)	7.0 (3.9-12.7)	4.6 (2.6-7.9)	2.9 (2.0-4.2)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.24 (0.07-0.41)	1.1 (0.8-1.4)	2.7 (2.4-3.0)	4.6 (4.3-4.9)	8.5 (8.1-8.8)	67 (66-67)
Cumulative PAR (95% CI), %[a]	6.3 (6.2-6.3)	13 (13-14)	20 (19-21)	23 (22-24)	27 (25-29)	34 (28-38)

Abbreviations: HR, hazard ratio; PAR, population attributable risk.

[a] Cumulative indicates a change in estimated GFR of this level or greater. The 95% CIs are based on the whole eligible study sample in the Chronic Kidney Disease Prognosis Consortium as a standard population.

GFR and the cumulative percentage PAR were lower during shorter baseline periods and higher during longer baseline periods.

The strength of associations of percentage estimated GFR decline with ESRD was largely consistent across studies at lower estimated GFR (19 studies) and at higher estimated GFR (9 studies) (eFigure 4 in the Supplement). Variation in HRs across studies was not related to variation in study characteristics. For example, the adjusted HR of ESRD associated with a −30% change in estimated GFR during 2 years was unrelated to baseline estimated GFR, prevalence of diabetes, and median albuminuria (eFigures 5 and 6 in the Supplement), despite each being a strong risk factor for ESRD. Meta-regression of these factors as well as mean follow-up time and age across 3 different baseline periods and 2 estimated GFR strata showed no pattern (only 4 of 30 combinations with *P* values of <.05; eFigures 5-10 in the Supplement).

The average absolute risk of ESRD was strongly related to the first estimated GFR as well as to the length of follow-up and the change in estimated GFR (**Figure 2** and eTables 2 and 3 in the Supplement). For example, at a baseline estimated GFR of 35 mL/min/1.73 m^2, the average 10-year risks of ESRD (adjusted for covariates and competing mortality risk) were 99% (95% CI, 95%-100%), 64% (95% CI, 52%-77%), and 18% (95% CI, 15%-22%) after a 2-year baseline period during which estimated GFR changed by −57%, −30% and 0%, respectively. Even though greater decline in estimated GFR was always associated with a higher subsequent risk of ESRD, the absolute and attributable risk varied markedly across patient characteristics, as well as across cohorts even after adjustment for covariates (eFigures 11-12 and eTables 2 and 3 in the Supplement).

Analysis of change in estimated GFR using slope rather than percentage change showed a strong association with ESRD risk as well (eFigures 13-15 in the Supplement). In addition, longer baseline period narrowed the distribution of slopes and strengthened the association with ESRD.

Mortality Risk According to Change in Estimated GFR

In cohorts with mortality data, approximately 7-fold more individuals had an estimated GFR change of −30% or greater (cumulative prevalence of 7.1%; 95% CI, 6.6%-7.7%) compared with a change of −57% or greater (cumulative prevalence of 0.97%;

Figure 2. Risk of End-Stage Renal Disease by Change in Estimated Glomerular Filtration Rate (GFR) During a 2-Year Baseline Period, First Estimated GFR, and Subsequent Follow-up

First Estimated GFR During a 2-Year Baseline Period	Follow-up After Last Estimated GFR, y	Change in Estimated GFR During 2-Year Baseline Period, %					
		−57	−40	−30	−25	−20	0 (Stable)
20	1	63	31	19	15	11	3.9
	3	97	72	52	43	34	13
	5	100	94	80	71	60	26
	10	100	100	99	97	92	57
35	1	20	8.1	4.8	3.7	2.7	0.95
	3	54	25	16	12	9.2	3.3
	5	82	47	31	25	19	7.0
	10	99	83	64	55	44	18
50	1	5.0	1.9	1.1	0.86	0.63	0.23
	3	16	6.4	3.8	3.0	2.2	0.80
	5	32	14	8.1	6.4	4.7	1.7
	10	66	33	21	17	12	4.8
65	1	0.71	0.20	0.090	0.061	0.037	0.014
	3	3.9	1.1	0.49	0.34	0.21	0.079
	5	12	3.5	1.6	1.1	0.68	0.26
	10	37	12	5.5	3.9	2.4	0.90
80	1	0.45	0.12	0.054	0.038	0.023	0.0090
	3	2.5	0.70	0.31	0.21	0.13	0.050
	5	7.9	2.2	1.0	0.69	0.42	0.16
	10	25	7.7	3.4	2.4	1.5	0.58

Colors indicating absolute risk gradient, % (based on percentiles of the cells in the table):

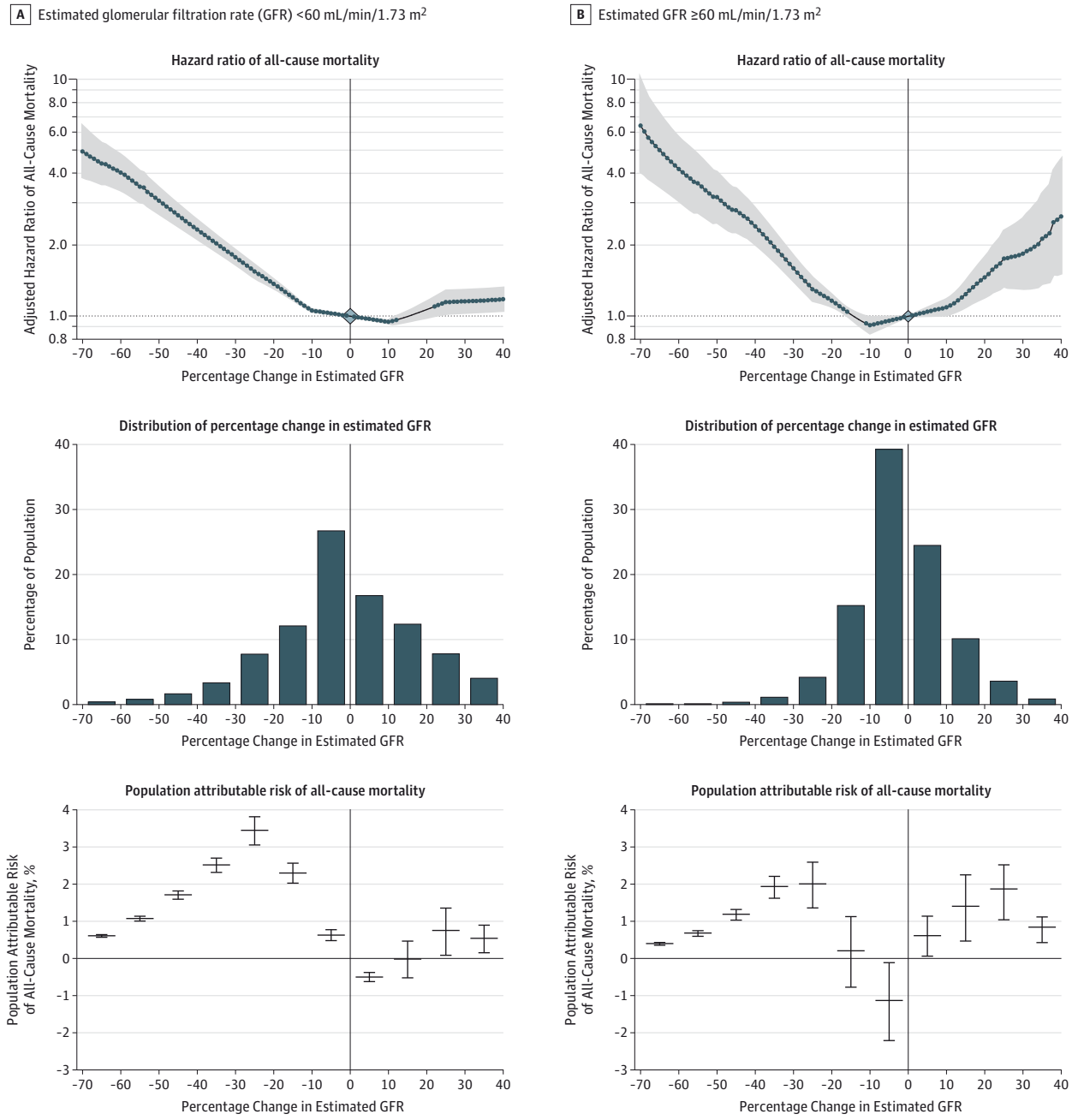
100	73	43	20	12	5.2	3.1	1.1	0.62	0.16	0.01

Baseline risk is calculated for participants with 0% change in estimated GFR, estimated GFR of 50 mL/min/1.73 m^2, age of 60 years, male sex, nonblack race, systolic blood pressure of 130 mm Hg, total cholesterol level of 5 mmol/L, and without diabetes or a history of cardiovascular disease.

95% CI, 0.70%-1.25%) during a 2-year baseline period (**Figure 3**A and **Table 5**). Compared with those with stable estimated GFR (estimated GFR change of 0%), the adjusted HR of all-cause mortality was higher with greater estimated GFR decline but was largely flat in the range of minimal decline (change of −10% or less) or increase (Figure 3A). For example, the adjusted HR was 1.8 (95% CI, 1.6-1.9) for a change of −30% in estimated GFR, 2.3 (95% CI, 2.1-2.5) for a change of −40%, and 3.7 (95% CI, 3.2-4.4) for a change of −57%. In terms of percentage PAR, a higher prevalence of smaller changes in estimated GFR surpassed the corresponding lower relative risk, with a peak of percentage PAR around change in estimated GFR of −30% to −20% (Figure 3A). Largely similar associations were observed among individuals with higher baseline estimated GFR, but a higher risk associated with an increase in estimated GFR (positive change in estimated GFR) was evident (Figure 3B). Of note, the prevalence of decline in estimated GFR was consistently less in those with higher baseline estimated GFR, and a change of −57% in estimated GFR was rare (occurred in approximately 0.2% of individuals). A decline of 30% in estimated GFR was consistently associated with higher subsequent all-cause mortality risk across cohorts for both lower and higher baseline estimated GFR (eFigure 16 in the Supplement), although the absolute mortality risk varied markedly across cohorts even after accounting for covariates (eFigures 17 and 18 in the Supplement). We observed consistent results for cardiovascular and noncardiovascular mortality (eFigures 19 and 20 in the Supplement).

With the larger declines in estimated GFR, absolute all-cause mortality risk was consistently higher for all the levels of baseline estimated GFR across different subsequent follow-up times (**Figure 4** and eTables 4 and 5 in the Supple-

Figure 3. All-Cause Mortality Associated With Percentage Change in Estimated GFR During a 2-Year Baseline Period



Values trimmed at less than −70% change (0.30% and 0.050% of the study population for estimated GFR <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2, respectively) and greater than 40% change (5.8% and 0.46% of the population for estimated GFR <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2, respectively). In the top 2 panels, the diamonds indicate the reference point of 0% change in estimated GFR.

ment). For a baseline estimated GFR of 35 mL/min/1.73 m^2, the absolute all-cause mortality risk during 10 years of follow-up was 32% (95% CI, 31%-33%) if estimated GFR was stable, whereas the mortality risk was 50% (95% CI, 47%-52%) for an estimated GFR change of −30%, 60% (95% CI, 56%-63%) for a change of −40%, and 77% (95% CI, 71%-82%) for a change of −57%. Similar patterns were observed for cardiovascular and noncardiovascular disease mortality risk (eTables 6 and 7 in the Supplement).

Further adjustment for smoking and albuminuria, when available, did not alter the results substantially (eFigures 21 and 22 in the Supplement). Greater mortality risk at a greater percentage decline in estimated GFR was observed consistently for analyses using a baseline period of 1 year or 3 years (eFig-

Table 5. All-Cause Mortality Associated With Change in Estimated Glomerular Filtration Rate (GFR) During Baseline Periods of 1 to 3 Years' Duration by Level of Kidney Function

	Change in Estimated GFR During the 2-Year Baseline Period					
	−57%	−40%	−30%	−25%	−20%	0% (Stable)
Estimated GFR <60 ml/min/1.73 m^2						
1-y Baseline period						
Adjusted HR (95% CI)	3.8 (3.3-4.4)	2.4 (2.2-2.6)	1.9 (1.7-2.0)	1.6 (1.5-1.8)	1.4 (1.4-1.5)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.48 (0.34-0.62)	1.8 (1.5-2.0)	4.3 (4.0-4.7)	6.5 (6.1-6.9)	11 (10-11)	54 (54-55)
Cumulative PAR (95% CI), %[a]	0.48 (0.45-0.50)	1.8 (1.7-1.9)	3.7 (3.4-3.9)	4.9 (4.5-5.2)	6.5 (5.9-7.1)	9.8 (8.6-11.0)
2-y Baseline period						
Adjusted HR (95% CI)	3.7 (3.2-4.4)	2.3 (2.1-2.5)	1.8 (1.6-1.9)	1.5 (1.4-1.6)	1.4 (1.3-1.4)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.97 (0.70-1.25)	3.5 (3.1-3.9)	7.1 (6.6-7.7)	11 (10-11)	15 (14-16)	54 (53-55)
Cumulative PAR (95% CI), %[a]	0.96 (0.89-1.01)	3.7 (3.4-3.9)	6.2 (5.8-6.6)	7.9 (7.3-8.5)	9.6 (8.7-10.4)	12 (11-14)
3-y Baseline period						
Adjusted HR (95% CI)	3.3 (2.7-3.9)	2.2 (2.0-2.4)	1.8 (1.6-1.9)	1.5 (1.4-1.7)	1.4 (1.3-1.4)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	1.7 (1.3-2.1)	5.3 (4.7-5.9)	10 (9-11)	14 (13-15)	19 (18-20)	54 (53-55)
Cumulative PAR (95% CI), %[a]	1.5 (1.4-1.6)	5.1 (4.7-5.5)	8.2 (7.5-8.9)	10 (9-11)	12 (11-13)	14 (13-16)
Estimated GFR ≥60 mL/min/1.73 m^2						
1-y Baseline period						
Adjusted HR (95% CI)	3.6 (2.5-5.0)	2.1 (1.8-2.5)	1.6 (1.4-1.7)	1.3 (1.2-1.4)	1.2 (1.1-1.2)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.12 (0.04-0.19)	0.48 (0.36-0.61)	1.6 (1.4-1.8)	3.1 (2.9-3.4)	6.5 (6.2-6.8)	64 (64-65)
Cumulative PAR (95% CI), %[a]	0.38 (0.33-0.42)	1.4 (1.2-1.6)	2.9 (2.5-3.3)	3.7 (3.1-4.3)	4.6 (3.8-5.4)	4.8 (2.5-6.9)
2-y Baseline period						
Adjusted HR (95% CI)	3.8 (2.8-5.2)	2.4 (2.0-2.9)	1.6 (1.4-1.8)	1.3 (1.2-1.5)	1.2 (1.1-1.2)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.16 (0.06-0.26)	0.73 (0.51-0.94)	2.0 (1.7-2.2)	3.7 (3.4-4.0)	6.7 (6.4-7.0)	64 (63-64)
Cumulative PAR (95% CI), %[a]	0.63 (0.56-0.68)	2.6 (2.2-2.8)	4.5 (3.8-5.0)	5.7 (4.6-6.5)	6.4 (5.1-7.5)	5.3 (2.0-8.3)
3-y Baseline period						
Adjusted HR (95% CI)	4.8 (3.7-6.1)	2.3 (2.0-2.6)	1.5 (1.3-1.6)	1.2 (1.1-1.3)	1.1 (1.1-1.1)	1 [Reference]
Cumulative prevalence (95% CI), %[a]	0.22 (0.06-0.38)	0.98 (0.71-1.26)	2.6 (2.3-2.9)	4.7 (4.3-5.0)	8.8 (8.4-9.2)	68 (67-68)
Cumulative PAR (95% CI), %[a]	0.89 (0.83-0.93)	3.3 (3.0-3.5)	5.1 (4.5-5.6)	6.0 (5.0-6.8)	6.7 (5.4-7.8)	5.7 (2.0-9.1)

Abbreviations: HR, hazard ratio; PAR, population attributable risk.

[a] Cumulative indicates a change in estimated GFR of this level or greater. The 95% CIs are based on the whole eligible study sample in the Chronic Kidney Disease Prognosis Consortium as a standard population.

ures 23-28 in the Supplement and Table 5). Results were similar for the analysis using the 2-year slope of change in estimated GFR, although as anticipated, a given absolute decline in estimated GFR contributed to higher relative risk among those with lower vs higher baseline estimated GFR (eFigures 29-31 in the Supplement).

Discussion

In this international meta-analysis of more than 1.7 million participants with 12 344 ESRD events and 223 944 deaths, we documented that reductions in estimated GFR from baseline smaller than a doubling of serum creatinine concentration were strongly and consistently associated with subsequent risk of ESRD and captured a much higher proportion of the subsequent ESRD risk, providing a basis for their use as alternative outcomes for CKD progression. The HR of ESRD adjusted for first estimated GFR and other covariates was substantially higher with greater declines in estimated GFR across a wide range of cohorts, GFR levels, and other patient characteristics. Estimated GFR changes of −57% and −30% were associated with greater than 30- and 5-fold adjusted HRs of ESRD, respectively, but the prevalence of the latter was nearly 10-fold higher than the former and consequently had a much higher percentage PAR (44% vs 10%). Although weaker than ESRD risk, associations with mortality were qualitatively similar. These data provide a basis for understanding the trade-off between higher risk and lower prevalence in choosing a larger or smaller percentage change in estimated GFR as an outcome when studying CKD progression. Even though the HRs were consistent across studies, absolute risks varied dramatically by baseline estimated GFR, participant characteristics, and different cohorts, and were substantially higher than the lifetime risk for comparably aged unselected populations.[21]

A doubling of serum creatinine concentration has been accepted by the US Food and Drug Administration as a surrogate end point for CKD progression in clinical trials since 1993.[3] Adoption of a lesser decline in estimated GFR as an alternative end point for CKD progression has the potential to shorten duration of follow-up, reduce costs, and increase efficiency of clinical trials. Consistency of effects over time suggests applicability for shorter as well as for longer trials, which is relevant for diseases that are progressing more rapidly or slowly,

Figure 4. Risk of All-Cause Mortality by Change in Estimated Glomerular Filtration Rate (GFR) During a 2-Year Baseline Period, First Estimated GFR, and Subsequent Follow-up

First Estimated GFR During a 2-Year Baseline Period	Follow-up After Last Estimated GFR, y	Change in Estimated GFR During 2-Year Baseline Period, %					
		-57	-40	-30	-25	-20	0 (Stable)
20	1	11	6.9	5.3	4.6	4.0	3.0
	3	31	21	16	14	12	9.4
	5	52	37	29	26	23	17
	10	87	72	62	57	52	42
35	1	7.8	4.9	3.8	3.3	2.9	2.1
	3	23	15	12	10	9.1	6.8
	5	40	27	22	19	17	13
	10	77	60	50	45	41	32
50	1	5.6	3.5	2.7	2.4	2.1	1.5
	3	17	11	8.5	7.5	6.6	4.9
	5	31	20	16	14	13	9.4
	10	64	47	39	35	32	24
65	1	2.3	1.4	1.0	0.78	0.70	0.60
	3	7.9	5.0	3.4	2.8	2.5	2.1
	5	15	10	6.4	5.3	4.7	4.1
	10	37	25	18	15	13	11
80	1	2.5	1.6	1.1	0.86	0.77	0.66
	3	8.7	5.5	3.7	3.0	2.7	2.3
	5	16	10	7.1	5.8	5.2	4.5
	10	40	28	19	16	14	13

Colors indicating absolute risk gradient, % (based on percentiles of the cells in the table):

87	42	29	19	15	11	7.0	4.9	3.0	2.1	0.6

Baseline risk is calculated for participants with 0% change in estimated GFR, estimated GFR of 50 mL/min/1.73 m^2, age of 60 years, male sex, nonblack race, systolic blood pressure of 130 mm Hg, total cholesterol level of 5 mmol/L, and without diabetes or a history of cardiovascular disease.

respectively. The strong and consistent ESRD risk associations that we demonstrated herein are a necessary, but not sufficient condition for a surrogate end point in clinical trials. Several other types of data are useful, and preliminary results support our suggestion of a 30% to 40% decline in estimated GFR as an outcome for clinical trials in CKD.[22-24]

First, evaluation of outcomes other than ESRD (such as cardiovascular disease and death) is important because they often occur more frequently and may precede ESRD. Our analyses show a 50% mortality risk in 10 years with a change of −30% in estimated GFR compared with a 32% mortality risk with stable estimated GFR, similar demographic and clinical characteristics, and if baseline estimated GFR is 35 mL/min/1.73 m^2. Second, evaluation of clinical trials is necessary to assess whether the effect of the treatment on the surrogate end point is consistently associated with the effect of treatment on the clinical end point. Attenuation of the HR of the treatment effect for lesser declines in estimated GFR compared with the HR for the clinical end point can outweigh the benefit of an increased number of end point events.[11,22] Third, because the number and type of trials in CKD are limited, particularly with respect to length of follow-up and number of ESRD events reached, simulation studies are necessary to assess a wide range of potential scenarios to evaluate the utility, robustness, and power of lesser estimated GFR declines.[23] In particular, simulation studies can address the association of short-term (acute) effects on kidney function in the same or opposite direction from the long-term effect of a treatment, such as lower blood pressure or renin-angiotensin system inhibition.

In principle, acute treatment effects on estimated GFR will be more important for end points defined by smaller percentage declines in estimated GFR. An understanding of acute treat-

ment effects on estimated GFR should be a part of any clinical trial that relies on a change in estimated GFR as an alternative to ESRD. Difficulty in ruling out small acute treatment effects provides a rationale for favoring a larger decline in estimated GFR in clinical trials (eg, change of −30% to −40%) than in observational studies and clinical practice in which guidelines define a certain decline in estimated GFR as a decrease in GFR category accompanied by a 25% or greater decrease in estimated GFR from baseline.[7] Last, absolute risk of ESRD is important to consider. Our results indicate that a decline in estimated GFR starting at severely reduced estimated GFR was associated with high rates of ESRD during the subsequent 1 to 5 years. However, estimated GFR decline starting at moderately reduced or normal estimated GFR was associated with a markedly lower risk of ESRD even after 10 or more years. There was also marked variation across studies suggesting caution in the translation of the level of estimated GFR decline to exact risk of ESRD.

To our knowledge, only one study investigated the association of estimated GFR change with ESRD risk,[6] but our results regarding change in kidney function and mortality risk are consistent with several previous reports.[8-10,25-28] Most of them investigated annualized rate of change,[9,26-28] but a few reported that an approximately 20% to 25% decline in estimated GFR over 1 to 3 years conferred mortality risk.[8,10,25] A time-to-event end point based on percentage change in estimated GFR calculated from only 2 measurements of serum creatinine at baseline and follow-up is simpler and easier to implement in clinical trials than an end point defined on the rate of decline in estimated GFR. Similarly, percentage change may be used as a clinical outcome in cohort studies, clinical care, or both. We comprehensively studied both percentage and absolute change in estimated GFR over 3 different baseline periods and adjusted for baseline estimated GFR and covariates uniformly across cohorts. The consistent results across a wide range of cohorts in various settings and regions support the generalizability of our findings.

As previously reported,[25,27,29,30] we observed an increase in mortality risk with an increase in estimated GFR, particularly among individuals with higher first estimated GFR. We expanded the previous literature to include cause-specific death (cardiovascular vs noncardiovascular disease) and confirmed a similar relationship for both outcomes. This association may be a consequence of loss of muscle mass associated with chronic illness, resulting in a decline in creatinine generation.[28,31] It may also be a consequence of acute illness associated with resolving acute kidney injury. The role of hyperfiltration within a poor prognosis among those with higher estimated GFR has yet to be elucidated.[32]

Despite its large size, broad scope, and robustness of the findings across a large number of sensitivity analyses, this study has a number of limitations. Standardization of serum creatinine values may have varied across time and studies. Percentage change in estimated GFR based on a single first and single last estimated GFR is less precise than alternative designs in which multiple measures are available at each time point. Variation in design across cohorts introduces heterogeneity; however, consistency across cohorts (despite dramatic variation in design and populations) increases our confidence in the results. Furthermore, we did not conduct a formal quality appraisal of the studies included in the meta-analysis.

Adjustment for the first estimated GFR means that the groups being compared have already diverged markedly at the end of the baseline period when follow-up for ESRD begins. For example, with a first estimated GFR of 30 mL/min/1.73 m^2, percentage changes of 57%, 30%, and 0% over a 2-year baseline period correspond to a last estimated GFR during this period of 13, 21, and 30 mL/min/1.73 m^2, which provides insight as to why greater estimated GFR declines are associated with greater subsequent ESRD and mortality risk. However, it also points out the distinction from clinical practice in which the last estimated GFR is known and the question of interest is often different (ie, whether previous progression adds information about risk above and beyond the last measurement).[8,30] For clinical practice, the present analysis is useful for defining what level of change in the future can be considered important and what its consequences would be. However, once the change has occurred, the relative importance of the change vs the last estimated GFR measure requires further analysis, and is beyond the scope of this study.

Conclusions

Declines in estimated GFR smaller than a doubling of serum creatinine concentration occurred more commonly and were strongly and consistently associated with the risk of ESRD and mortality, supporting consideration of lesser declines in estimated GFR (such as a 30% reduction over 2 years) as an alternative end point for CKD progression.

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