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ORIGINAL ARTICLE

Defining a minimal clinically meaningful difference in 12-month estimated glomerular filtration rate for clinical trials in deceased donor kidney transplantation

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Abstract

Background: A Minimal Clinically Meaningful Difference (MCMD) has not been defined for Estimated glomerular filtration rate (eGFR). Our goal was to define the MCMD for eGFR anchored to kidney graft failure.

Methods: A systematic review of studies with 12-month eGFR and subsequent renal graft failure was conducted. For observational studies, we calculated hazard ratio (HR) differences between adjacent eGFR intervals weighted by population distribution. Interventional trials yielded therapeutically induced changes in eGFR and failure risk. OPTN data analysis divided 12-month eGFR into bands for Cox regressions comparing adjacent eGFR bands with a death-censored graft survival outcome.

Results: Observational studies indicated that lower eGFR was associated with increased death-censored graft failure risk; each 5 ml/min/1.73 m^2 12-month eGFR band associated with a weighted incremental HR = 1.12 to 1.23. Clinical trial data found a 5 ml/min/1.73 m^2 difference was associated with incremental HR = 1.16 to 1.35. OPTN analyses showed weighted mean HRs across 10, 7, and 5 ml/min/1.73 m^2 bands of 1.47, 1.30, and 1.19.

Conclusions: A 5 ml/min/1.73 m^2 difference in 12-month eGFR was consistently associated with ~20% increase in death-censored graft failure risk. The magnitude of effect has been interpreted as clinically meaningful in other disease states and should be considered the MCMD in renal transplantation clinical trials.

KEYWORDS
clinical trial design, glomerular filtration rate, graft survival, kidney (allograft)

1 | INTRODUCTION

Glomerular filtration rate is a fundamental measure of renal function, and estimated glomerular filtration rate (eGFR), derived from serum creatinine, is the primary diagnostic test used to assess renal function in primary clinical care. In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines first used eGFR bands to define chronic kidney disease (CKD) stage.[1] Based on the associations between

eGFR and clinical outcomes (mortality, cardiovascular disease, renal-related laboratory abnormalities), differences of 15 ml/min/1.73 m^2 were used to define CKD stages, which were incorporated into the International Classification of Diseases, Tenth Revision diagnosis codes.[2] These eGFR-based stages were extensively revalidated in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[3] A difference of 15 ml/min/1.73 m^2 is clinically meaningful but is not a minimal clinically meaningful difference (MCMD), defined as "the smallest difference [in an outcome which is] beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."[4] For example, KDIGO Guideline recommendation 2.1.3 states that a decline in eGFR of >5 ml/min/1.73 m^2 per year is an indication of "rapid progression" of CKD, a clinically meaningful event that requires clinical intervention.

In 2019, the FDA released the Guidance for Industry on Delayed Graft Function (DGF) in Kidney Transplantation: Developing Drugs for Prevention.[5] In that guidance, the FDA allowed 12-month eGFR as a surrogate endpoint for drugs targeting the prevention of DGF, conditioned on a definition of what constitutes a MCMD in eGFR between treatment groups: "*If the goal of the clinical study is to demonstrate that the drug leads to an overall sustained improvement in renal function, compared to placebo, then renal function data need to be collected for all patients for a minimum of 12 months. A clinically meaningful difference in renal function (assessed using serum creatinine levels or glomerular filtration rate) should be justified.*"[5] There is a clearly a need to define an MCMD for eGFR in patients undergoing renal transplantation in the trial setting.

The goal of this analysis was to define a MCMD in 12-month eGFR as a predictor of subsequent death-censored graft failure in clinical trials in renal transplantation.

2 | MATERIALS AND METHODS

The development of an MCMD requires a "gold standard" clinical outcome to anchor differences in a surrogate measure. For kidney transplantation, the most relevant measure is renal graft failure, based upon its impact on morbidity, mortality, and healthcare cost.[6,7]

Two sources of data were used:

1. A systematic review of the literature on demonstrated relationships between eGFR and graft failure in both observational studies and randomized controlled trials in kidney transplantation among adult recipients
2. Analyses of the Organ Procurement and Transplantation Network (OPTN) database among adult recipients of single organ, deceased donor kidney transplant

2.1 | Systematic literature review of eGFR as a predictor of graft failure

The objective of this systematic literature review (SLR) was to summarize and synthesize the scientific literature, published between January 2000 and February 2020, to quantify the association between 12-month eGFR and graft failure in patients who have undergone kidney transplantation in the United States. This SLR was conducted in accordance with PRISMA guidance,[8] though the study was not submitted to an SLR registry. The protocol (Table S1), PRISMA Checklist (Table S2), and flow diagram (Figure S1) are included in the Supplemental Materials.

2.2 | Estimating effects of incremental differences in eGFR

Three issues complicate defining a common MCMD in 12-month eGFR from the published literature:

1. The range of eGFR intervals varied by study
2. The eGFR reference category for the HRs differed by study
3. The relationship between 12-month eGFR and death-censored graft failure is non-linear, requiring population weighting to define a mean for each treatment group

While studies differed in eGFR intervals, the lowest common multiple was 5 ml/min/1.73 m^2 and this range was selected as the smallest eGFR interval for analysis. Four observational studies included in the SLR provided information allowing estimation of the increase in hazard due to 5 ml/min/1.73 m^2 changes in 12-month eGFR.[9–12] Survival-eGFR HRs (HR_x) are defined as the graft survival hazard rate at a given eGFR value, h_x, divided by the hazard rate for the reference eGFR value, h_{ref}:

$$HR_x = \frac{h_x}{h_{ref}}$$

For HRs sharing a common reference, the differences in hazard ratios may be estimated by simply subtracting HRs:

$$\Delta HR_{x-y} = HR_x - HR_y = \frac{h_x}{h_{ref}} - \frac{h_y}{h_{ref}} = \frac{h_x - h_y}{h_{ref}}$$

This operation yields a difference in hazard between two 12-month eGFR values, assuming risks are linear between eGFR bands. This appears to be a reasonable approximation for small, adjacent bands of 12-month eGFR based on results in Table 1 and Figure 1.

2.3 | OPTN analysis

We conducted analyses in the OPTN database, a comprehensive registry of transplant patients in the United States.

Included patients were adult (>18 years) recipients of a single organ, deceased donor kidney transplant between 01/01/2013 and 12/31/2018. Analyses were limited to deceased donors as half of the observational and clinical trial studies reviewed were exclusively deceased donor, and >70% of the patients in the all-comers studies

were deceased donor. Multiple organ transplants and non-incident transplants were excluded, as graft survival in these populations is known to be reduced.[13,14] Additional stratification or specification factors, such as extended criteria donor, were noted.

The aim of the regression analysis was to identify the impact of between-group differences in 12-month eGFR on long-term patient outcomes. Cox proportional hazards regression predicted death-censored graft failure after the first year of transplant as the predicted outcome. Follow-up was censored at 5 years post-transplantation. Predictor variables comprised recipient, donor, and transplantation variables (Table 2) and 12-month eGFR (CKD-EPI equation). Predictors were chosen based on existing literature of predictors of graft failure and previous analyses conducted by the authors.[9–12,15–17] Because 12-month eGFR was the predictor of interest, variables too highly correlated with 12-month eGFR (e.g., terminal serum creatinine) were excluded as predictors. To estimate the effect of between-group differences, eGFR at 12 months was coded into bands of 10, 7, and 5 ml/min/1.73 m^2. Regressions compared each band to the next sequential band. For example, the 15 to <20 ml/min/1.73 m^2 band was referenced to the 20 to <25 ml/min/1.73 m^2 band to predict death-censored graft failure, 20 to <25 versus 25 to <30 ml/min/1.73 m^2, and so on. This approach allows direct estimation of the change in graft failure risk due to small differences in 12-month eGFR. A weighted mean HR was calculated using the proportion of the patient population in each 12-month eGFR band from OPTN data. The 12-month eGFR bands are shown in Table 3. Due to sample size, the first band was always defined as eGFR <15 ml/min/1.73 m^2. The top band was defined by the value closest to 100 ml/min/1.73 m^2 to the highest eGFR value.

3 | RESULTS

3.1 | Systematic literature review: observational studies

Four studies assessed eGFR at 12 months and subsequent graft failure and had complete reporting of the relationship necessary for standardization (Table 4). Note, all studies assessed death-censored graft failure, although one also reported a composite graft failure plus mortality. We used death-censored graft failure for all subsequent analyses.

Schnitzler and colleagues published 2 studies using the same cohort from the USRDS dataset (Schnitzler A and Schnitzler B).[11,12] Schnitzler 2012A examined death-censored graft failure from 1 to 9 years post-transplantation, using five 12-month eGFR point estimates: 20, 30, 40, 50, and 60 ml/min/1.73 m^2. In Schnitzler 2012B, 12-month eGFR was divided into 5 ml/min/1.73 m^2 bands, predicting death-censored graft failure up to 9 years post-transplantation against an 80 ml/min/1.73 m^2 reference group. Prediction algorithms were validated using data from the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT Extended Criteria Donors (BENEFIT-EXT).[18] Given the differences in analytic approach, both studies were included.

Kasiske et al. retrospectively examined 12-month eGFR and graft failure in the Patient Outcomes in Renal Transplantation (PORT) Study.[10] eGFR values at 12 months post-transplant were divided into deciles, with additional sub-divisions at 15 ml/min/1.73 m^2 and 90 ml/min/1.73 m^2. Twelve-month eGFR was used to predict all-cause graft failure and death-censored graft failure in years 2 through 10

TABLE 1 Relationship between 12-month eGFR and all-cause graft failure: combined HR results from observational studies

Study	Loupy 2019	Kasiske 2011	Schnitzler 2012A		Schnitzler 2012B	
Population	All donors	All donors	Standard criteria deceased	Extended criteria deceased	Standard criteria deceased	Extended criteria deceased
12-month eGFR[a]	Hazard Ratio					
All values	0.96					
15		10.7			8.3	6.9
20		6.7	9.0	6.1	5.1	4.1
25		2.7	5.6	4.0	3.3	2.8
30		2.1	2.2	1.8	2.3	2.2
35		1.6	1.8	1.5	1.7	1.7
40		1.4	1.4	1.2	1.4	1.4
45		1.2	1.2	1.1	1.2	1.2
50		1.1	1.1	1.0	1.1	1.1
55		1.0	1.0	1.0	1.0	1.0
60		1.0	1.0	1.0	1.0	1.0
Weighted mean 5 ml/min/1.73 m^2 difference	0.20	0.20	0.23	0.15	0.15	0.12

[a]In ml/min/1.73 m^2

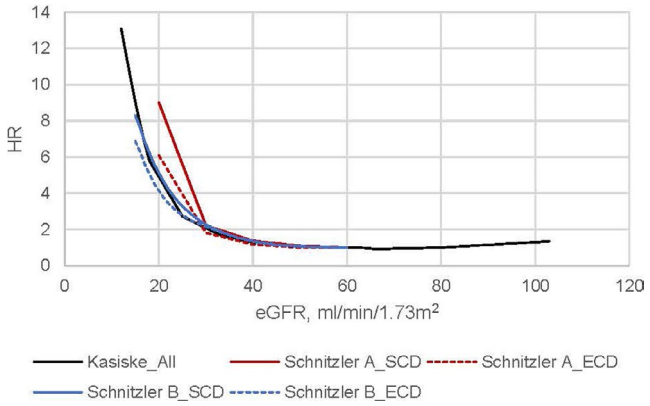


FIGURE 1 Combined figures from observational studies: relationship between 12-month eGFR and all-cause graft failure

post-transplantation using a multivariate Cox proportional hazard model. HRs were higher in the death-censored survival analysis.

The iBox initiative developed a death-censored graft failure prediction score.[9] The component survival analyses were structured with a large derivation sample and multiple validation samples from both observational studies and randomized controlled trials. In contrast to Schnitzler and Kasiske, the iBox analyses treated 12-month eGFR as a continuous linear variable. They reported a 4% relative risk reduction for each 1 ml/min/1.73 m^2 increase in eGFR.

To compare HRs at different 12-month eGFR levels, we extracted the curves of HRs versus eGFR levels presented by Kasiske 2011 and Schnitzler 2012B[19] while the HRs from Schnitzler 2012A were calculated from the reported predicted 9-year survival probabilities at 12-month eGFR values of 20, 30, 40, 50, and >60 ml/min/1.73 m^2. Figure 2A reproduces these data on a common set of axes. The independently derived relationships between eGFR and death-censored graft failure overlay each other. At 12-month eGFRs ≥40 ml/min/1.73 m^2, all curves represent HRs that are essentially equivalent. Below a value of 40 ml/min/1.73 m^2, all results demonstrate non-linear relationships that differ in terms of the degree of non-linearity. This likely reflects differences in patient populations and analytic methods (e.g., different eGFR reference values). The relationships between the studies treating the 12-month eGFR-graft survival relationship as non-linear, and the linearity assumptions in Loupy 2019 are further elucidated in Figure 2B, which plots the HRs on a $\log_{10}$ scale. This transformation clearly shows that the iBox HR, based on the assumed continuous linear relationship, is a population mean across all included eGFR values.

Table 1 replicates the data extracted from the relationships at specific 12-month eGFR levels for the four studies (shown graphically in Figure 1). HRs for eGFR <20 ml/min/1.73 m^2 are not available from Schnitzler 2012A, and HRs at eGFR >60 ml/min/1.73 m^2 were not included, for consistency. By evaluating the differences in HRs at adjacent 12-month eGFR values, we approximated the increase in hazard for 5 ml/min/1.73 m^2 increments in eGFR. HRs are similar between Kasiske and Schnitzler at 12-month eGFRs above 25 ml/min/1.73 m^2. The differences for 5 ml/min/1.73 m^2 at eGFRs below 25 are likely due to heterogeneity across studies and to the assumptions of linearity within bands required by our calculations. The estimate based on Loupy clearly differs at lower eGFR values, but this is an artifact of the linearity assumption in their model. However, evaluated near the central tendency of 12-month eGFRs

TABLE 2 Sample characteristics for OPTN analyses

RECIPIENT	Value	N	%
Gender	F	21 842	39.9
	M	32 943	60.1
Age	18–29	3192	5.8
	30–44	11 024	20.1
	45–59	20 616	37.6
	60–74	18 921	34.5
	>=75	1032	1.9
Race	Non-black	36 642	66.9
	Black	18 143	33.1
Diabetes	No	35 204	64.3
	Yes	19 525	35.6
	Missing	56	0.1
BMI	Mean (SD)	28.7	51.7
Most Recent PRA	Mean (SD)	25.0	37.4
DONOR	**Value**	***N***	**%**
Age	<=10	2346	4.3
	11–20	5497	10
	21–40	22 073	40.3
	41–60	21 649	39.5
	>60	3220	5.9
Diabetes	No	50 678	92.5
	Yes	3789	6.9
	Missing	318	0.6
HTN	No	39 746	72.5
	Yes	14 660	26.8
	Missing	379	0.7
Urine protein	No	28 920	52.8
	Yes	25 538	46.6
	Missing	327	0.6
TRANSPLANT	**Value**	***N***	**%**
CIT	≤40 h	53 453	97.6
	>40 h	1005	1.8
	Missing	327	0.6
Received on pump	No	28 983	52.9
	Yes	25 802	47.1
DR Locus mismatch	0	9728	17.8
	1	25 453	46.5
	2	19 306	35.2
	Missing	298	0.5
DGF	No	40 383	73.7
	Yes	14 399	26.3
	Missing	3	0

TABLE 3 12-month eGFR bands at 10, 7, and 5 ml/min/1.73 m^2 from OPTN data

10 ml/min/1.73 m^2			7 ml/min/1.73 m^2			5 ml/min/1.73 m^2		
Band	***N***	**%**	**Band**	***N***	**%**	**Band**	***N***	**%**
<15	360	0.7	<15	360	0.7	<15	360	0.7
15 to <25	1430	2.6	15 to <22	832	1.5	15 to <20	510	0.9
25 to <35	3831	7.0	22 to <29	1734	3.2	20 to <25	920	1.7
35 to <45	7147	13.0	29 to <36	3281	6.0	25 to <30	1519	2.8
45 to <55	9555	17.4	36 to <43	4849	8.9	30 to <35	2312	4.2
55 to <65	9909	18.1	44 to <50	6305	11.5	35 to <40	3149	5.7
65 to <75	8253	15.1	50 to <57	6937	12.7	40 to <45	3998	7.3
75 to <85	5969	10.9	57 to <64	6973	12.7	45 to <50	4596	8.4
85 to <95	3992	7.3	64 to <71	6160	11.2	50 to <55	4959	9.1
95 to <105	2443	4.5	71 to <78	5102	9.3	55 to <60	5019	9.2
≥105	1896	3.5	78 to <85	3913	7.1	60 to <65	4890	8.9
			85 to <92	2954	5.4	65 to <70	4443	8.1
			92 to <99	2224	4.1	70 to <75	3810	7.0
			99 to <106	1417	2.6	75 to <80	3357	6.1
			≥106	1736	3.2	80 to <85	2612	4.8
						85 to <90	2113	3.9
						90 to <95	1879	3.4
						95 to <100	1410	2.6
						≥100	2929	5.3

TABLE 4 Summary of observational graft survival prediction studies

Study	Loupy 2019	Kasiske 2011	Schnitzler 2012A	Schnitzler 2012B
Donor type included	All donors (not specified)	All donors (not specified)	Living, Standard criteria deceased (SCD) and extended criteria deceased (ECD)	Standard criteria deceased (SCD) and extended criteria deceased (ECD
Source Data	Development: Four sites in France Validation: both observational studies and RCTs	Patient Outcomes in Renal Transplantation (PORT) Study	USRDS 1995–2003	Development: USRDS 1995–2004 Validation: BENEFIT and BENEFIT-EXT trials
Sample Size	Development: 4000 Validation: 3557	13 671	87 575	Development: 87 575 Validation: 589
Outcomes	Death-censored graft failure with median 7 years of follow-up	All-cause graft failure and death-censored graft failure in years 2 through 10 post-transplantation	Death-censored graft failure from 1 to 9 years post-transplantation	Death-censored graft failure up to 9 years post-transplantation

(Kasiske: median = 50; Schnitzler ECD: mean = 48.6), the results are comparable.

Using the population distribution of 12-month eGFRs by 5 ml/min/1.73 m^2 from the OPTN database (Table 3), each eGFR band HR difference was weighted by the proportion of the OPTN population represented by each band. Across studies, the weighted average incremental risk of death-censored graft failure for a 5 ml/min/1.73 m^2 difference in 12-month eGFR ranged from HR = 1.12 for extended criteria donors in Schnitzler 2012B; to HR = 1.15 for extended criteria donors in Schnitzler 2012A and standard criteria donors in Schnitzler 2012B; to HR = 1.20 for all donors in Loupy and Kasiske; to HR = 1.23 for standard criteria donors in Schnitzler 2012A.

3.2 | Systematic literature review: randomized controlled trials

The SLR identified 8 multisite, randomized controlled trials in renal transplantation that generated individual publications which assessed 12-month eGFR and graft outcomes (Table 5). These trials were studies of novel immunosuppressants compared with various

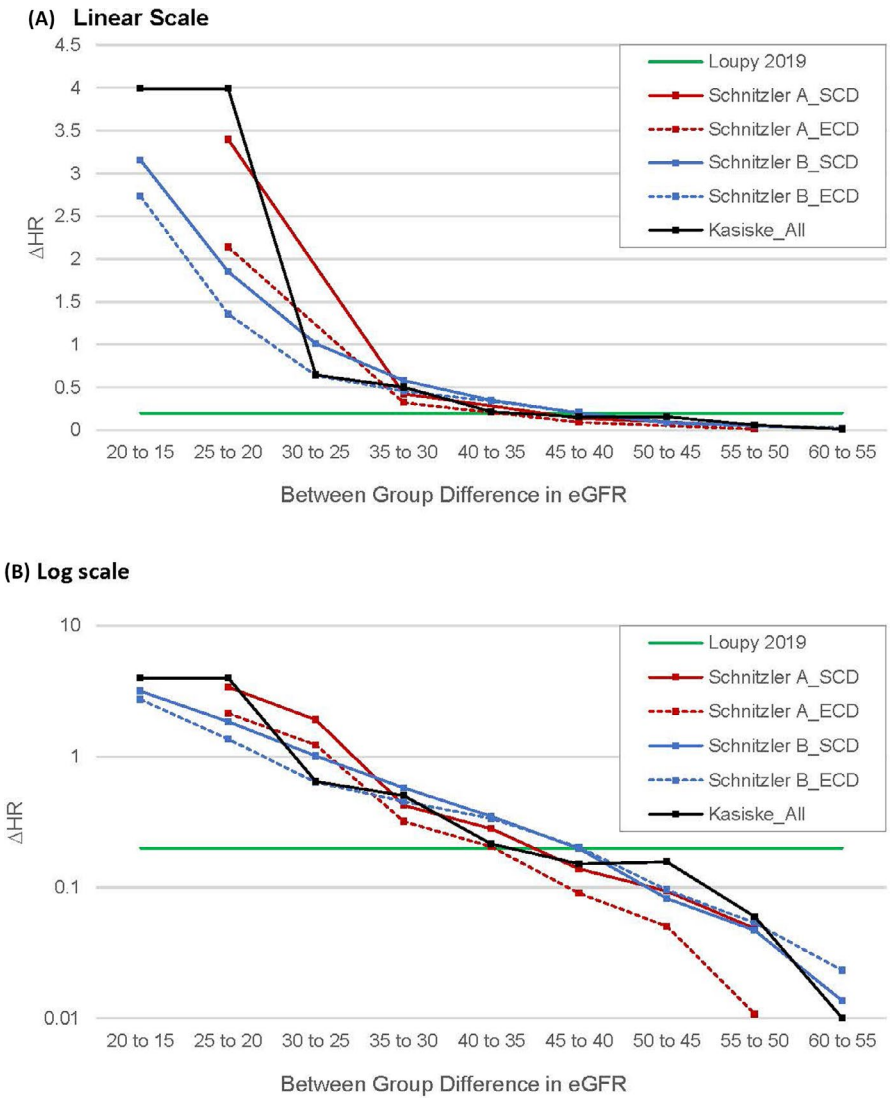


FIGURE 2 Change in all-cause graft failure hazard ratio by eGFR

standards of care, in addition to one trial for ANG-3777, a hepatocyte growth factor mimetic compared with placebo.[20] As shown in Table 5, only 4 trials demonstrated a significant and meaningful effect of treatment on eGFR at 12 months. Those studies were used to examine the relationship between 12-month eGFR and subsequent death-censored graft failure.

Two of the studies with significant eGFR treatment effects, BENEFIT by Vincenti et al and BENEFIT-EXT by Durrbach et al were belatacept Phase 3 trials with 12-month and 84-month follow-up, comparing more and less intensive belatacept regimens to cyclosporin.[18,21] The population in Durrbach 2010 was extended criteria kidney donors only. The third trial was a comparison of high- and low-dose cyclosporin and high- and low-dose tacrolimus or sirolimus maintenance therapy.[22] The fourth study was a Phase 2 trial comparing ANG-3777 to placebo in patients with signs of delayed graft function.[20] While the belatacept trials employed multiple composite endpoints, we used the results reported for death-censored graft failure, exclusive of mortality or other outcomes, in this assessment. Ekberg 2007 reported death-censored graft survival, and there were no deaths in the ANG-3777 study; thus, the outcome was stand-alone graft failure.

Ekberg, Durrbach, and Bromberg assessed both eGFR and graft failure simultaneously at 12 months. As the goal was to understand the association between 12-month eGFR and subsequent graft failure, the simultaneous measures are not by definition predictive. However, Durrbach and Bromberg also reported 6-month eGFR. As 6-month and 12-month post-transplantation eGFR have been shown to be stable and highly correlated in the OPTN data ($r = 0.84$)[17] and were clearly stable in these two trials, we also calculated the association between 6-month eGFR and 12-month death-censored graft failure in those two studies.

The inverse relationship between 12-month eGFR and death-censored graft failure is readily observable for these 4 studies (Figure 3): the higher the 12-month eGFR, the lower the percent death-censored graft failure. In Vincenti, a 13.5 and 14.5 ml/min/1.73 m^2 between-group difference in 12-month eGFR was associated with a 44% to 41% relative risk reduction in graft failure at 84 months. Proportionately, this would be a 16% and 14% relative risk reduction at 5 ml/min/1.73 m^2. In Durrbach, a 6.8 and 7.6 ml/min/1.73 m^2 between-group difference in 12-month eGFR was associated with a 27% and 26% relative risk reduction in death-censored graft failure at 12 months. Proportionately, this would be a 20% and 17% relative

TABLE 5 Mean 12-month eGFR and graft failure by treatment arm[a]

Study	Groups	12-month eGFR	6-month eGFR	Between-group difference
Vincenti et al., 2016[21]	Belatacept-More Intensive	67.0		14.5
	Belatacept -Less Intensive	66.0		13.5
	Cyclosporin	52.5		Ref
Eckberg et al., 2007[22]	Standard-dose cyclosporin	57.1		0.4
	Low dose cyclosporin	59.4		2.7
	Standard-dose tacrolimus	65.4		8.7
	Low dose tacrolimus	56.7		Ref
Durrbach et al., 2010[18]	Belatacept -More Intensive	50.1	48.9	7.6
	Belatacept -Less Intensive	49.3	47.6	6.8
	Cyclosporin	42.5	41.0	Ref
Bromberg et al., 2020[20]	ANG-3777	50.0	49.9	10.8[b]
	Placebo	37.4	39.1	
	Tacrolimus	54.8		

[a]Shaded area indicates studies in which interventions did not produce a significant or meaningful difference in 12-month eGFR.

[b]Difference utilized 6-month data.

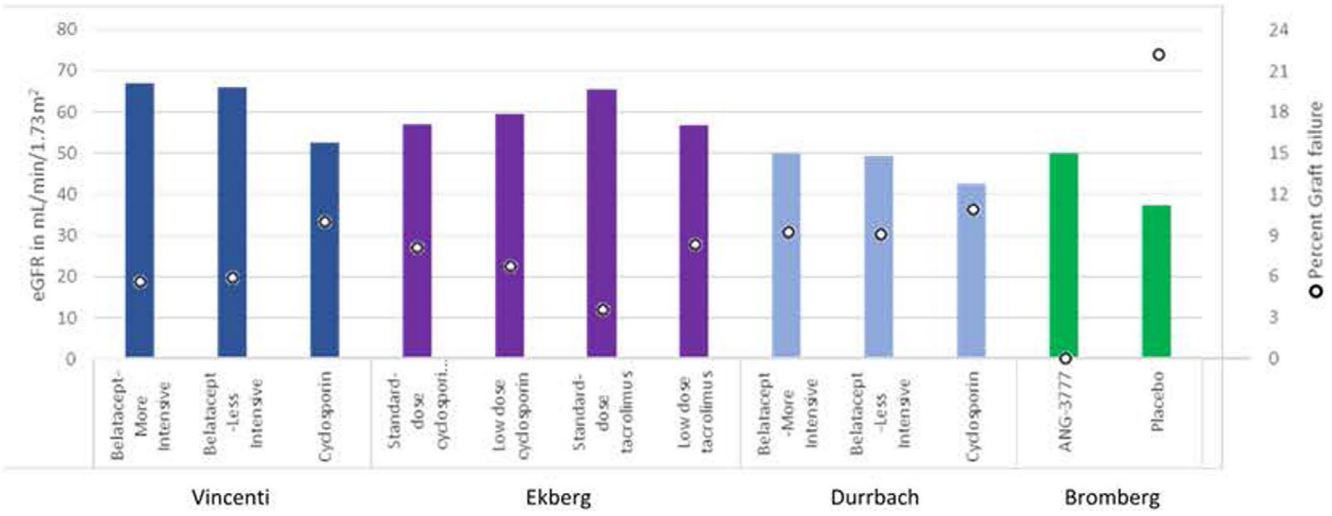


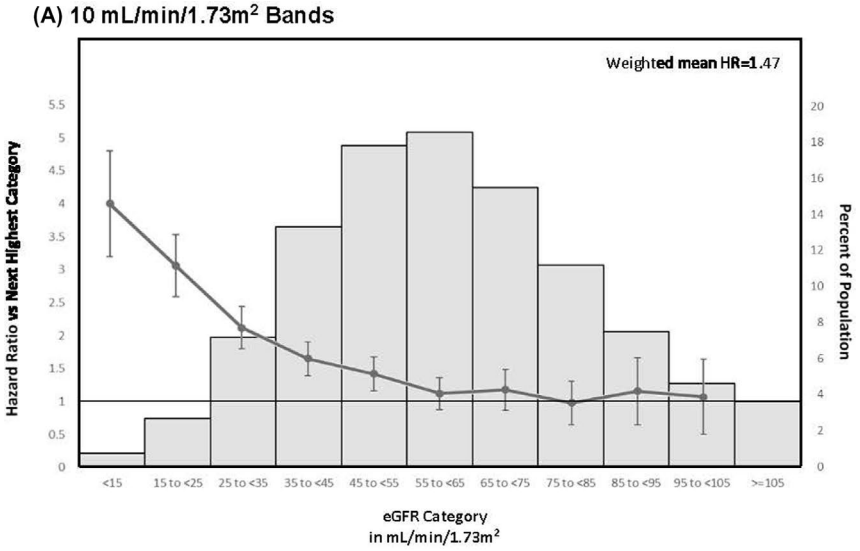
FIGURE 3 12-month eGFR plotted against graft failure in 3 randomized controlled trials

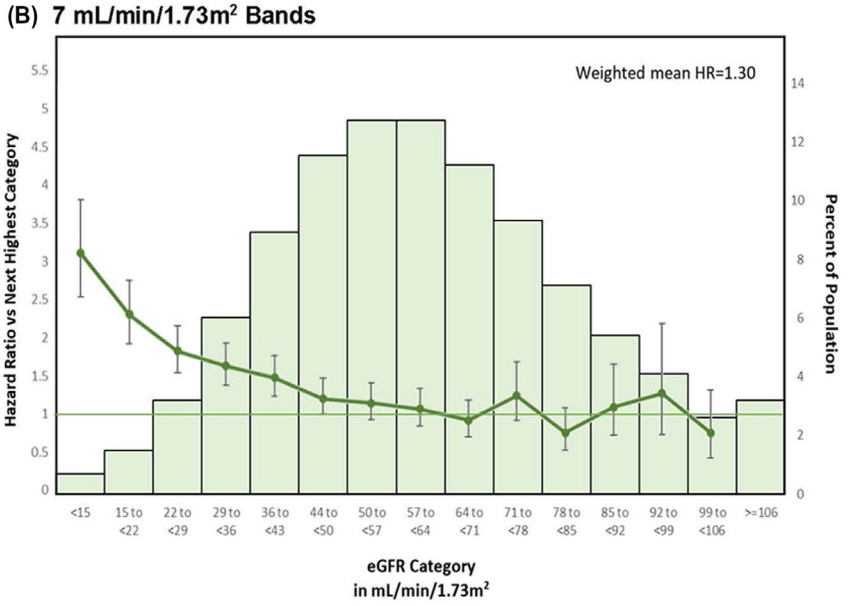
risk reduction at 5 ml/min/1.73 m^2. The 6-month eGFR value also produced a 20% and 17% relative risk reduction at 5 ml/min/1.73 m^2 as well.

In Ekberg, a 0.4, 2.7, and 8.7 ml/min/1.73 m^2 between-group difference in 12-month eGFR was associated with a 2%, 19%, and 57% relative risk reduction in death graft failure at 12 months. Proportionately, this would be a 25%, 35%, and 33% relative risk reduction at 5 ml/min/1.73m^2. In Bromberg, a 12.6 ml/min/1.73 m^2 between-group difference in 12-month eGFR was associated with a 100% relative risk reduction in graft failure at 12 months. Proportionately, this would be a 40% relative risk reduction at 5 ml/min/1.73 m^2, and 46% if 6-month eGFR is used.

3.3 | OPTN analyses

There were 54 785 adult kidney transplantation patients who met all inclusion criteria, including provision of a valid 12-month serum creatinine, of which 2419 experienced a graft failure after 12 months (2.8%). Table 2 shows the characteristics of the analytic sample.





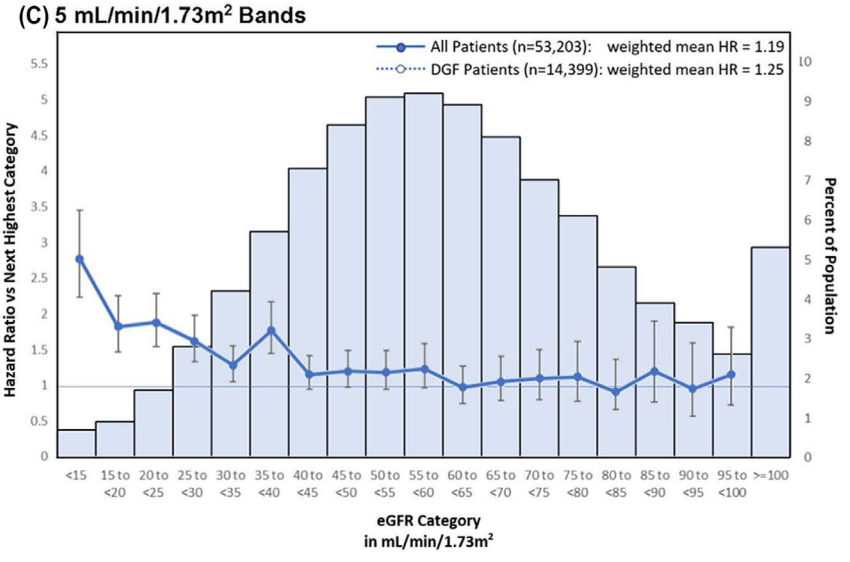


FIGURE 4 Hazard ratio for death-censored graft failure by eGFR band by percent of population within each eGFR band

There were no notable differences between this sample and the OPTN adult kidney transplant recipient overall population.

Figure 4A shows the HR of each 10 ml/min/1.73 m^2 12-month eGFR band versus the next highest band, with the higher band as reference, that is, HRs reflect incremental death-censored graft failure risk for the lower eGFR band. As shown, all but one band had a HR > 1.0, indicating the lower eGFR band had increased risk of death-censored graft failure. The incremental risk is highest (HR = 1.42 to 4.0) in 12-month eGFR bands below 55 ml/min/1.73 m^2, and stabilizes at a weighted average HR of 1.11 at bands ≥55 ml/min/1.73 m^2. The weighted mean HR across all 10 ml/min/1.73 m^2 bands was 1.47.

Figure 4B shows the HR of each 7 ml/min/1.73 m^2 12-month eGFR band versus the next highest band. As shown, all but two bands have a HR > 1.0. The incremental risk is highest (HR = 1.22 to 3.23) in eGFR bands below 64 ml/min/1.73 m^2. Estimates are somewhat less stable at eGFR ≥64 ml/min/1.73 m^2, with a weighted average HR of 1.10 at bands ≥64 ml/min/1.73 m^2. The weighted mean HR across all 7 ml/min/1.73 m^2 bands was 1.30.

Figure 4C shows the HR of each 5 ml/min/1.73 m^2 12-month eGFR band versus the next highest band. As shown, all but two bands have a HR>1.0. The incremental risk is highest (HR = 1.23 to 2.77) in eGFR bands below 60 ml/min/1.73 m^2. The weighted average HR at bands ≥60 ml/min/1.73 m^2 was 1.06. The weighted mean HR across all 5 ml/min/1.73 m^2 bands was 1.19.

4 | DISCUSSION

The goal of this analysis was to define a minimal clinically meaningful difference in 12-month eGFR anchored to its ability to predict subsequent death-censored graft failure in adult patients who have undergone deceased donor kidney transplantation. We evaluated this relationship based on a review of observational studies and clinical trials and conducted an analysis of the OPTN database. The evidence converges that a 5 ml/min/1.73 m^2 difference in 12-month eGFR is associated with an approximate 20% increase in relative risk for subsequent death-censored graft failure.

Across observational studies, a 5 ml/min/1.73 m^2 difference in 12-month eGFR demonstrated a 12% to 23% increase in risk of death-censored graft failure. Analyses from the OPTN database demonstrated that a 5 ml/min/1.73 m^2 difference in 12-month eGFR was associated with a 19% increase risk of death-censored graft failure. Across clinical trials, a 5 ml/min/1.73 m^2 between-group difference produced a relative risk reduction ranging from 16% to 40%, though the graft failure rate in the placebo arm of the ANG-3777 study was high at 20%, driving that highest estimate. It is important that the randomized controlled trials demonstrated that an experimentally induced difference between groups in 12-month eGFR was associated with a reduction in death-censored graft failure similar to that seen in observational studies. For example, epidemiological studies show a strong relationship between high levels of high-density lipids (HDL) and reduced cardiovascular events,[23–25] yet multiple trials of cholesteryl ester transfer protein (CETP) drugs demonstrated that, while effective at increasing HDL, they did not reduce cardiovascular events.[26] The concordance between the observational and experimental literature in this case demonstrates that it is the achieved eGFR at 12 months that is associated with graft failure.

Having defined what between-group differences in 12-month eGFR mean in terms of incremental death-censored graft failure risk, the definition of an MCMD is determined by what degree of risk reduction is clinically meaningful, that is, is a ~20% average risk reduction clinically meaningful? Seminal studies with angiotensin blockers in patients with kidney disease utilizing a composite CKD endpoint (doubling of serum creatinine, renal replacement therapy, and death) showed a 20% to 25% reduction versus placebo[27,28] which was sufficient for labeling. The benefits of statins in reducing cardiovascular events are well-accepted, with a recent meta-analysis by the Cholesterol Treatment Trialists' Collaboration finding that lowering LDL cholesterol 1.0 mmol/L with a statin lowered risk for cardiovascular events by 21% (RR = 0.79), and were considered a "significant reduction."[29] There are other examples of drugs being approved across a range of indications in which a 20% risk reduction in a seminal endpoint was sufficient evidence of a clinically meaningful effect.[30,31]

There are limitations and caveats of the present study that help place our results in context. First, the non-linear relationship between eGFR and death-censored graft failure highlights the tension in applying between-treatment group clinical trial outcomes to decision-making for individual patients. Designed for clinical trial settings, the proposed MCMD in 12-month eGFR is necessarily a population-based measure that allows assessment of differences in mean outcomes for treatment arms in a trial. Our analysis shows that an MCMD for 12-month eGFR in a trial setting is 5 ml/min/1.73 m^2, for kidney transplant patients that are similar to those in the OPTN database. For a clinical trial in a different population, say recipients of high KDPI organs with lower expected 12-month eGFR levels, an appropriate MCMD may be lower than our estimate. And, as a tool for evaluating results of clinical trials, an MCMD will require interpretation to assess failure risks for individual patients in clinical practice. Clearly, the risk associated with a 5 ml/min/1.73 m^2 differs by eGFR value, but this issue is not unique to eGFR, as nearly all biomarkers have non-linear relationships with outcomes, for example, LDL, blood pressure, BMI, and cardiovascular outcomes; and serum phosphorus, potassium, hemoglobin, and CKD mortality.[32–37] Further, CKD stages from 3a to 5 are defined in 15 ml/min/1.73 m^2 eGFR decrements yet these stages do not define equivalent risk bands. Similarly, as previously mentioned, KDIGO defines a decline in eGFR of >5 ml/min/1.73 m^2 per year as "rapid progression" of CKD without reference to an individual's eGFR. Weighting by population distribution risk is a standard and accepted means of calculating mean population risk.[38] As with all such metrics, the application of these results to patient care requires that physicians make decisions that take into account the greater clinical context, such as clinical events and individual patient differences. It is also likely that the eGFR trajectory prior to 1 year post-transplant may influence an individual

patient's long-term risk. A data source with eGFR measurements at more frequent intervals than those in OPTN would be useful to explore this issue. Future studies would further be enhanced by the collection of relevant longitudinal data, such as intercurrent events and therapeutic interventions, with the potential to improve prediction as well as clinical application. Intercurrent events, such as BK or CM viral infections, likely affect renal function at 12 months; availability of administrative claims data would help clearly estimate the impact of such intercurrent events. An additional limitation is that the analyses of published epidemiologic study data and the OPTN database may be subject to residual confounding of observational data and the effects cannot be interpreted as causal. Confirmation of the relationships by the prospective clinical trials provides some reassurance on this front.

In conclusion, the data presented support the proposition that a 5 ml/min/1.73 m^2 difference in 12-month eGFR in patients who have undergone renal transplantation represents a MCMD in the setting of renal transplantation clinical trials.

CONFLICT OF INTEREST

Sumit Mohan, Jesse Schold, and Matthew Weir have received research funding and/or consultancy fees unrelated to this study from Angion Biomedica. Tracy Mayne was an employee of Angion Biomedica at the time of this study. Robert Nordyke is an employee of Angion Biomedica and owns stock/stock options.

AUTHOR CONTRIBUTIONS

All authors were involved in aspects of study design. Tracy Mayne, Robert Nordyke, Sumit Mohan, and Jesse Schold were involved in data analysis. Tracy Mayne and Robert Nordyke were involved in initial medical writing. All authors were involved in data review and interpretation, manuscript review and editing, and approval of the final manuscript.

DISCLAIMER

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from OPTN. Restrictions apply to the availability of these data, which were used under a Data Use Agreement for this study. Data requests may be made at https://optn.transplant.hrsa.gov/data/request-data/.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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