



# The prognostic utility of regadenoson SPECT myocardial perfusion imaging in patients with end-stage renal disease: The largest cohort to date

Ahmed A. Kolkailah, MD, MSc,<sup>a</sup> Mina Iskander, MD, MSc,<sup>b</sup> Fady Iskander, MD, MSc,<sup>b</sup> Priya P. Patel, MD,<sup>c</sup> Rozi Khan, MD,<sup>d,e</sup> and Rami Doukky, MD, MSc, FASNC<sup>a,b,c,d</sup>

<sup>a</sup> Department of Medicine, Cook County Health, Chicago, IL

<sup>b</sup> Division of Cardiology, Cook County Health, Chicago, IL

<sup>c</sup> Department of Medicine, Rush University Medical Center, Chicago, IL

<sup>d</sup> Division of Cardiology, Rush University Medical Center, Chicago, IL

<sup>e</sup> Department of Medicine, Medstar Union Memorial Hospital, Baltimore, MD

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**Background.** There are limited data on the prognostic utility of regadenoson SPECT myocardial perfusion imaging (MPI) in patients with end-stage renal disease (ESRD).

**Methods and Results.** In a single-center, retrospective study, we analyzed consecutive ESRD patients who underwent regadenoson SPECT-MPI. The severity of MPI abnormalities and ischemic burden were determined quantitatively. The primary endpoint was major adverse cardiac events (MACE), defined as the composite of cardiac death or myocardial infarction. Among 1,227 subjects (mean age  $54 \pm 13$  years, 47% men), 60 (5%) MACE were observed during a mean follow-up of  $2.5 \pm 1.8$  years. The presence and severity of MPI abnormalities and ischemic burden were associated with a stepwise increase in MACE risk. Abnormal MPI (SSS  $\geq 4$ ) was associated with increased MACE risk, independent and incremental to relevant clinical covariates; adjusted hazard ratio, 1.95; 95% confidence interval, 1.15-3.32;  $\Delta\chi^2 = 5.97$ ;  $P = .013$ . Myocardial ischemia (SDS  $\geq 2$ ) was associated with a trend towards increased MACE risk; adjusted hazard ratio, 1.63; 95% confidence interval, 0.96-2.77;  $\Delta\chi^2 = 3.12$ ;  $P = .072$ .

**Conclusion.** In the largest cohort to date, we demonstrated the incremental prognostic value of abnormal MPI in predicting MACE risk in ESRD patients. Given its size, our study provides improved risk estimates in this population compared to previous reports. (J Nucl Cardiol 2022;29:101–10.)

**Key Words:** Prognosis • myocardial perfusion imaging (MPI) • regadenoson • SPECT • ESRD

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**Author's social text** In the largest cohort to date, #regadenoson #MPI provides independent and incremental #prognostic\_value for predicting #MACE in patients with #ESRD. @RamiDoukky @AKolkailah @CookCtyHealth @RushMedical #CVNuc @JNCjournal @MyASNC.

Reprint requests: Rami Doukky, MD, MSc, FASNC, Division of Cardiology, Cook County Health, 1901 W. Harrison St, Chicago, IL 60612; [rdoukky@cookcountyhhs.org](mailto:rdoukky@cookcountyhhs.org)

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**Abbreviations**

CAD	Coronary artery disease
CD	Cardiac death
CKD	Chronic kidney disease
CR	Coronary revascularization
ESRD	End-stage renal disease
LCR	Late coronary revascularization
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
ROC	Receiver operating characteristic
SDS	Summed difference score
SSS	Summed stress score
TID	Transient ischemic dilation

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**INTRODUCTION**

Myocardial perfusion imaging (MPI) via single photon emission computed tomography (SPECT) is a well-established modality for the diagnosis and risk stratification of patients with suspected or known coronary artery disease (CAD).<sup>1,2</sup> Regadenoson, a selective A<sub>2A</sub> adenosine receptor agonist, has been the most commonly used vasodilator agent for SPECT-MPI in the United States in virtue of its excellent safety and tolerability profile.<sup>3</sup> Renal excretion accounts for 57% of regadenoson systemic elimination, which translates to delayed clearance in patients with impaired renal function.<sup>4,5</sup> Nonetheless, previous studies have demonstrated the safe use of regadenoson in patients with advanced chronic kidney disease (CKD; stages III/IV), who are not yet on dialysis.<sup>6,7</sup> Additionally, small observational studies validated its safety profile in patients with end-stage renal disease (ESRD).<sup>8–10</sup> Despite the high prevalence of CAD in ESRD patients and the importance of ischemic evaluation for cardiac risk stratification in renal transplant candidates,<sup>11–13</sup> there remains a paucity of data on the prognostic value of regadenoson SPECT-MPI in these patients. Hage et al previously concluded that regadenoson SPECT-MPI had excellent prognostic utility in a large retrospective study of all-comers, among whom 362 had ESRD.<sup>14</sup> Subsequently, in a small prospective cohort of non-consecutive 303 ESRD patients enrolled in the ASSUAGE and ASSUAGE-CKD trials, our group demonstrated the prognostic utility of regadenoson SPECT-MPI in this population.<sup>15–17</sup> In this investigation, we sought to assert the prognostic utility of regadenoson SPECT-MPI in a large, consecutive ESRD patient cohort.

**METHODS**

In a retrospective cohort study design, we analyzed consecutive ESRD patients who underwent regadenoson SPECT-MPI at Rush University Medical Center (Chicago, IL) in the period from July 1, 2009 to September 11, 2015. We excluded subjects with missing stress MPI data. Only the first regadenoson SPECT-MPI was analyzed in case there was more than one test performed during the study period. The detailed methodology of this cohort derivation was described elsewhere.<sup>18,19</sup>

**Stress MPI Protocol and Analysis**

All regadenoson SPECT-MPIs were performed per the American Society of Nuclear Cardiology guidelines.<sup>20,21</sup> We have previously reported the specifics of stress testing, image acquisition, and processing.<sup>22,23</sup> Standard 1-day rest/regadenoson stress protocol using <sup>99m</sup>Tc-tetrofosmin was done for almost all patients. However, dual-isotope protocol was occasionally used during periods of <sup>99m</sup>Tc shortage and 2-day protocol with <sup>99m</sup>Tc-tetrofosmin in morbidly obese individuals (body mass index  $\geq 40$  kg·m<sup>-2</sup>). Dual-head Siemens Ecam® camera (Siemens; Hoffman Estates, IL) was used to acquire the SPECT-MPI, without attenuation correction. Investigators, blinded to clinical and outcome data, assessed MPI scans quantitatively via Corridor 4DM software package (INVIA-Ann Arbor, MI), on a 17-segment model and the standard 5-point scale (0: normal, 1: mild, 2: moderate, 3: severe, 4: absent radiotracer activity). The total summed scores were used to generate summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS). MPI studies were categorized, based on SSS, as normal (SSS = 0-3), mildly abnormal (SSS = 4-8), moderately abnormal (SSS = 9-13), and severely abnormal (SSS  $\geq 14$ ). Ischemic burden was categorized, based on SDS, into no ischemia (SDS = 0-1), mild ischemia (SDS = 2-4), and moderate to severe ischemia (SDS  $\geq 5$ ).<sup>1</sup> Transient ischemic dilation (TID) was measured by calculating the ratio of stress to rest left ventricular (LV) volumes, derived from the ungated SPECT images. Abnormal TID ratio was considered for values of 1.31 and above.<sup>24,25</sup> We quantitatively measured rest and post-stress LV ejection fraction (LVEF). The LVEF reserve was calculated from subtracting rest LVEF from post-stress LVEF.<sup>26</sup> LV dysfunction was defined as an abnormal LVEF (< 50%).

**Endpoints**

We observed the patients for the following outcomes of interest: death, cardiac death (CD), myocardial infarction (MI), surgical or percutaneous coronary revascularization (CR), and renal transplantation. We defined late CR (LCR) as revascularization taking place over 90 days following the stress MPI, which were deemed as events not directly triggered by the results of MPI.<sup>15</sup> We obtained death events using the social security death index or chart review done by investigators blinded to clinical and imaging data. Detailed chart review (whenever possible) or death certificates were used to

**Table 1.** Baseline clinical and imaging characteristics

Variable	Mean ± SD/ N (%)
N	1,227
Age (years)	54 ± 13
Male	737 (60.1)
Race	
White	257 (20.9)
Black	725 (59.1)
Other	245 (20)
MPI indications	
Renal transplant evaluation	949 (77.3)
Chest pain	130 (10.6)
CAD evaluation	38 (3.1)
Dyspnea	35 (2.9)
Heart failure	18 (1.5)
Abnormal electrocardiogram	15 (1.2)
Pre-operative evaluation (other than transplant)	13 (1.1)
Comorbidities	
Smoking	125 (10.2)
Hypertension	1,142 (93.1)
Diabetes mellitus	345 (28.1)
Dyslipidemia	610 (49.7)
Family history of CAD	298 (24.3)
MI history	161 (13.1)
PCI history	150 (12.2)
CABG history	83 (6.8)
Medications	
Aspirin	537 (43.8)
ACE-I/ARB	501 (40.8)
Lipid lowering agent	542 (44.2)
Imaging characteristics	
LVEF < 50%	221 (18.0)
EDV (mL)	142 ± 62.5
SSS	3.2 ± 6.2
Abnormal MPI (SSS ≥ 4)	321 (26.2)
MPI finding	
Normal (SSS = 0-3)	906 (73.8)
Mildly abnormal (SSS = 4-8)	189 (15.4)
Moderately abnormal (SSS = 9-13)	67 (5.5)
Severely abnormal (SSS ≥ 14)	65 (5.3)
SDS	1.3 ± 3.7
Ischemia (SDS ≥ 2)	299 (24.4)
Myocardial ischemia	
No ischemia (SDS = 0-1)	928 (75.6)
Mild Ischemia (SDS = 2-4)	207 (16.9)

**Table 1** continued

Variable	Mean ± SD/ N (%)
Moderate-Severe ischemia (SDS ≥ 5)	92 (7.5)
Rest LVEF (%)	58.8 ± 13.4
Stress LVEF (%)	61.2 ± 13.6
TID	1.0 ± 0.2

SD, standard deviation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; EDV, end-diastolic volume; SSS, summed stress score; SDS, summed difference score; TID, transient ischemic dilation.

determine the cause of death. CD was defined as death due fatal MI, fatal arrhythmias, or heart failure. Non-fatal MI was defined as an elevation in cardiac biomarkers ≥ 3 times above the upper limit of normal and the clinical determination of the managing cardiologist, guided by the global definition of MI. The primary endpoint was major adverse cardiac events (MACE), defined as the composite of CD or MI. The secondary endpoints were (i) composite of Death/MI, (ii) composite of CD/MI/LCR, and (iii) all-cause mortality.

### Statistical Analysis

Continuous data were presented as mean ± standard deviation while categorical data were presented as frequencies and percentages. Kaplan-Meier plots and the log-rank test were used to compare event-free survival. Univariate and multivariate Cox regression models were used to assess the unadjusted and adjusted risk of adverse outcomes, with risk estimates expressed as hazard ratios (HR) and 95% confidence intervals (CI). We adjusted for the following clinically relevant covariates: age, sex, smoking, dyslipidemia, diabetes mellitus, and prior history of CAD. Covariates were limited to 1 degree of freedom for every 10 events. Hypertension was not included in multivariate adjustment since it was prevalent in over 90% of the study cohort. The date of stress MPI was considered time zero in the survival analysis, whereas follow-up time was defined by either a qualifying event, last event-free encounter, or a maximum follow-up duration of 6.5 years, whichever took place first. Since renal transplant is known to improve the outcomes of ESRD patients,<sup>12</sup> we performed additional sensitivity survival analyses in which we terminated the follow-up at the date of transplant and censored all ensuing outcome events. Nested stepwise Cox regression models were used to determine the incremental prognostic value of abnormal MPI, myocardial ischemia, or LV dysfunction, using the absolute increase in global chi-square ( $\chi^2$ ) statistic, calculated by

likelihood ratio test, and the corresponding *P* value. Using the coordinates of the receiver operating characteristic (ROC) curve for TID ratio as a predictor of MACE, we aimed to identify an exploratory threshold that optimizes the discriminatory prognostic capacity of TID for the primary outcome. A two-tailed *P* value of < .05 was the criterion for statistical significance. We used SPSS software package, version 23 (IBM, Inc., Armonk, NY) to perform all statistical analyses.

### RESULTS

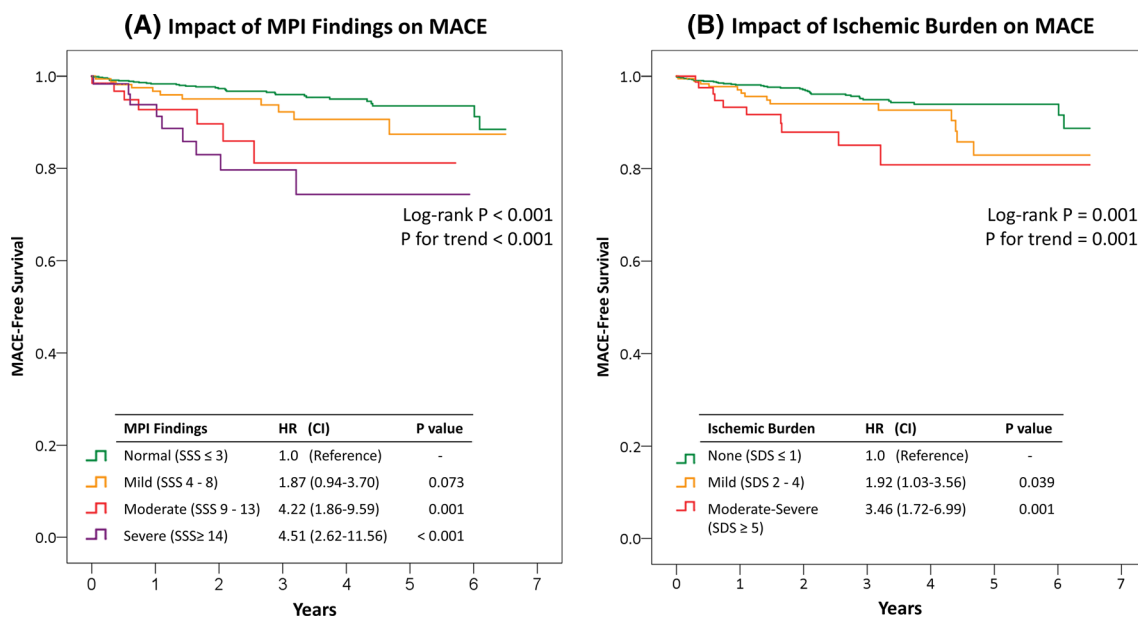
Among 1,250 ESRD patients who underwent regadenoson SPECT-MPI, 23 were excluded due to missing imaging data. Table 1 summarizes the baseline clinical and imaging characteristics of the 1,227 patients included in the final cohort. Briefly, the mean age was  $54 \pm 13$  years and 47% were men. Renal transplant evaluation was the most common indication for MPI (*N* = 949, 77.3%). A total of 321 (26.2%) had an abnormal MPI and 299 (24.4%) had myocardial ischemia. The mean follow-up period for clinical and composite events was  $2.5 \pm 1.8$  years. The duration of follow-up for all-cause mortality (as a single outcome) was slightly longer at  $2.8 \pm 1.8$  years, since a clinical encounter is not needed to determine the last vital status. During follow-up, there were 204 (16.6%) deaths, 27 (2.2%) confirmed CD, 38 (3.1%) MI, 85 (6.9%) CR, and 47 (3.8%) LCR events. Notably, 365 (29.7%) patients underwent renal

transplant during follow-up, at a mean of  $2.4 \pm 1.9$  years after MPI.

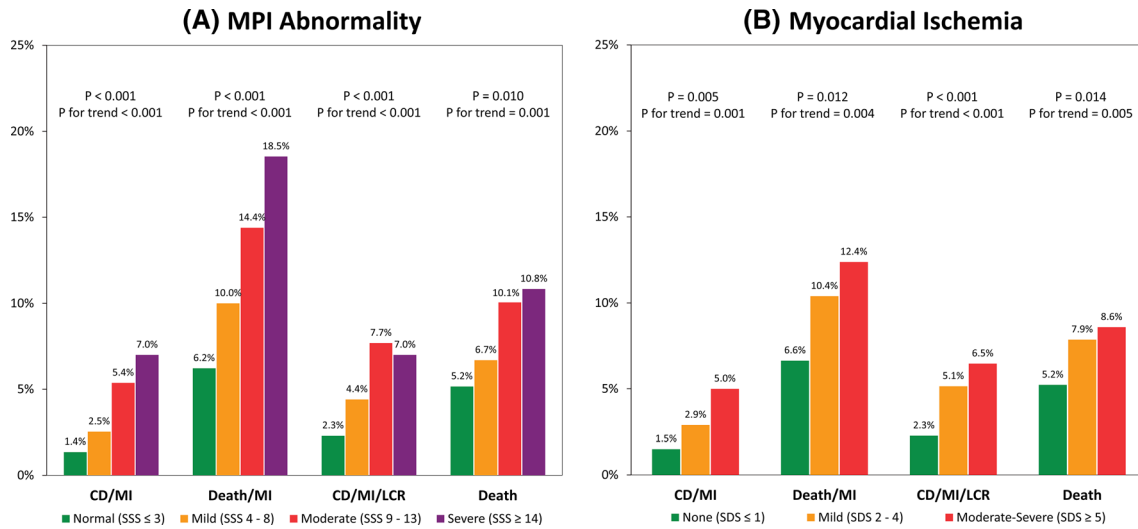
### Primary Endpoint

During the follow-up period, 60 (5%) MACE were observed. SSS, as a continuous variable, was independently predictive of MACE after adjusting for clinical covariates (age, sex, smoking, dyslipidemia, diabetes mellitus, prior history of CAD); adjusted HR, 1.03 per 1 SSS point increment; CI, 1.01-1.06; *P* = .013. The frequency of MACE rate was more than double in patients with an abnormal MPI (SSS  $\geq 4$ ) compared to patients with a normal MPI (8.4% vs 3.6%, *P* = .001). The presence and severity of MPI abnormalities and ischemic burden were associated with a stepwise increase in MACE (Figure 1A). Abnormal MPI was associated with an increased MACE risk, independent of clinical covariates; adjusted HR, 1.95; CI, 1.15-3.32; *P* = .013 (Figure 1A). Annualized MACE rate among patients with normal MPI was 1.4% and there was a stepwise increase in MACE rates with increasing severity of MPI abnormalities (Figure 2A). MPI findings provided further incremental prognostic value for predicting MACE beyond clinical covariates alone ( $\Delta\chi^2 = 5.97$ , *P* = .015), as shown in Figure 3.

MACE rate was almost double in patients with myocardial ischemia (SDS  $\geq 2$ ) compared to those



**Figure 1.** Impact of MPI findings on MACE-free survival. Kaplan-Meier survival plots. *MPI*, SPECT myocardial perfusion imaging; *MACE*, major adverse cardiac events (cardiac death or myocardial infarction); *SSS*, summed stress score; *SDS*, summed difference score; *HR*, hazard ratio; *CI*, 95% confidence interval.

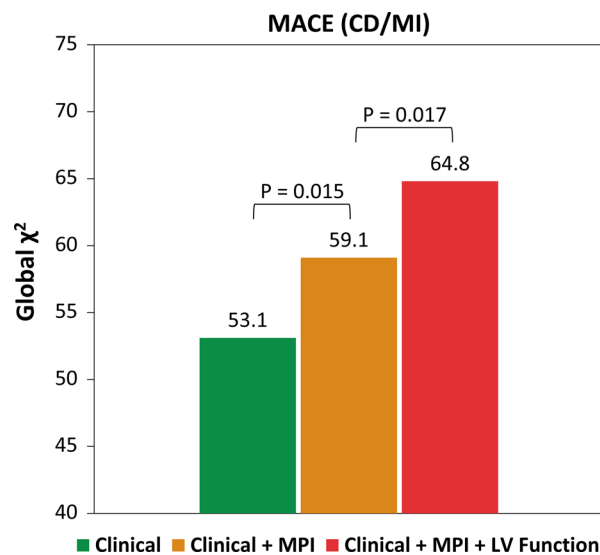


**Figure 2.** Annualized event rates of primary and secondary outcomes. *MPI*, SPECT myocardial perfusion imaging; *CD*, cardiac death; *MI*, myocardial infarction; *CR*, coronary revascularization; *LCR*, late coronary revascularization; *SSS*, summed stress score; *SDS*, summed difference score.

without myocardial ischemia (8.0% vs 3.9%,  $P = .004$ ). As a continuous variable, unadjusted *SDS* was significantly associated with *MACE*; HR, 1.05 per 1-point increment; CI, 1.01-1.09;  $P = .026$ , but statistical significance was lost after adjusting for clinical covariates; HR, 1.03; CI, 0.98-1.09;  $P = .243$ . As a dichotomous variable, and after adjusting for clinical covariates, myocardial ischemia was associated with a trend towards an increase in *MACE* risk; adjusted HR, 1.63; CI, 0.96-2.77;  $P = .072$ . The presence and severity of myocardial ischemia were associated with a stepwise increase in *MACE* (Figure 1B) which translated to a stepwise increase in annualized *MACE* rates with increasing ischemic burden (Figure 2B). Myocardial ischemia provided a borderline incremental prediction of *MACE* risk to clinical covariates alone ( $\Delta\chi^2 = 3.12$ ,  $P = .077$ ).

In sensitivity survival analyses, in which we censored follow-up at the time of renal transplantation (if occurred during the study period), abnormal *MPI* was significantly associated with an increased *MACE* risk, after adjusting for clinical covariates (Supplemental Table 1). On the other hand, myocardial ischemia was associated with a trend towards an increase in *MACE* risk, after adjusting for clinical covariates (Supplemental Table 2).

In ROC analysis, *TID* provided a modest discriminatory capacity for predicting *MACE* (area under the curve, 0.62; CI, 0.54-0.69;  $P = .002$ ). *TID*, as a continuous variable, was associated with an increased *MACE* risk, after adjusting for clinical covariates (adjusted HR, 1.18; CI, 1.07-1.30;  $P = .001$ ). A



**Figure 3.** Incremental prognostic value of regadenoson SPECT-MPI. Bar chart depicts global chi-square statistics derived from 3-step nested Cox proportional hazards models. *MACE*, major adverse cardiac events; *CD*, cardiac death; *MI*, myocardial infarction; *MPI*, SPECT myocardial perfusion imaging. Clinical variables include age, sex, diabetes mellitus, dyslipidemia, active smoking, and known coronary artery disease status. *MPI* is defined as normal vs. abnormal (summed stress score  $\geq 4$  vs  $\leq 3$ ). *LV Function* is defined as normal vs. abnormal (left ventricular ejection fraction  $\geq 50\%$  vs  $< 50\%$ ).

previously published *TID* threshold of  $\geq 1.31$ ,<sup>24</sup> provided a prognostic sensitivity and specificity for *MACE* of 8% and 96%, respectively. However, a dichotomous

TID of  $\geq 1.31$  was not associated with a statistically significant increase in MACE risk, after adjusting for clinical covariates (adjusted HR; 1.91, CI, 0.76-4.81;  $P = .170$ ). On further exploratory analyses of the TID/MACE ROC curve coordinates, we iteratively identified a TID ratio of  $\geq 1.15$  as a threshold that can provide an improved prognostic discriminatory capacity, with a sensitivity and specificity for MACE of 28% and 84%, respectively. TID ratio of  $\geq 1.15$  was associated with a significant increase in MACE risk, after adjusting for clinical covariates (adjusted HR, 1.82; CI, 1.03-3.22;  $P = .041$ ).

LVEF, as a continuous variable, was associated with MACE risk after adjusting for clinical covariates; adjusted HR, 1.25 per 10-point decrement in LVEF; CI, 1.03-1.49;  $P = .022$ . Similarly, LV dysfunction (LVEF < 50%), was associated with an increased MACE risk after adjusting for clinical covariates; adjusted HR, 2.43; CI, 1.40-4.23;  $P = .002$ . LV function (normal vs abnormal) provided incremental prognostic value to clinical covariates and abnormal MPI, as shown in Figure 3.

## Secondary Endpoints

During the study follow-up period, there were 229 (18.7%) composite Death/MI and 93 (7.6%) composite CD/MI/LCR events. The frequencies of composite Death/MI, composite CD/MI/LCR, and all-cause mortality were higher in patients with an abnormal MPI (SSS  $\geq 4$ ) compared to patients with normal MPI (25.9% vs 16.1%, 11.8% vs 6.1%, 21.8% vs 14.8%, all  $P < .01$ ). After adjusting for clinical covariates, abnormal MPI (SSS  $\geq 4$ ) was independently associated with an increased risk of composite Death/MI (adjusted HR, 1.73; CI, 1.31-2.29;  $P < .001$ ), composite CD/MI/LCR (adjusted HR, 1.56; CI, 1.02-2.40;  $P = .040$ ), and all-cause mortality (adjusted HR, 1.43; CI, 1.06-1.93;  $P = .021$ ). Among patients with normal MPI, annualized events rates were as follows: composite Death/MI 6.2%, composite CD/MI/LCR 2.3%, and all-cause mortality 5.2%. There was a stepwise increase in the rates of the secondary endpoints with increasing MPI abnormality (Figure 2A).

The frequencies of composite Death/MI, composite CD/MI/LCR, and all-cause mortality were higher in patients with myocardial ischemia (SDS  $\geq 2$ ) compared to patients without myocardial ischemia (24.4% vs 16.8%, 12.7% vs 5.9%, 22.1% vs 14.9%; all  $P < .05$ ). After adjusting for clinical covariates, myocardial ischemia (SDS  $\geq 2$ ) was associated with an increased risk of the composite Death/MI (adjusted HR, 1.41; CI, 1.06-1.87;  $P = .019$ ), the composite CD/MI/LCR (adjusted HR, 1.64; CI, 1.07-2.50;  $P = .022$ ), and all-cause mortality (adjusted HR, 1.43; CI, 1.06-1.94;  $P = .019$ ).

Increasing severity of myocardial ischemia was associated with a stepwise increase in annualized event rates of all secondary outcomes (Figure 2B).

In sensitivity survival analyses, in which we censored follow-up at the time of renal transplantation (if occurred during the study period), abnormal MPI and myocardial ischemia were associated with significant increases in the risk of Death/MI and CD/MI/LCR, after adjusting for clinical covariates. On the other hand, abnormal MPI and myocardial ischemia were associated with a trend towards an increased risk of all-cause mortality (Supplemental Tables 1 and 2).

After adjusting for clinical covariates, TID, as a continuous variable, was associated with an increased risk of the composite Death/MI (adjusted HR, 1.13 per 0.1-point increment; CI, 1.07-1.19;  $P < .001$ ), the composite CD/MI/LCR (adjusted HR, 1.10 per 0.1-point increment; CI, 1.01-1.20;  $P = .023$ ), and all-cause mortality (adjusted HR, 1.14 per 0.1-point increment; CI, 1.07-1.21;  $P < .001$ ). When abnormal TID was assessed as a dichotomous variable (ratio  $\geq 1.31$ ), and after adjusting for clinical covariates, it was only associated with a borderline significant increase in the composite Death/MI (adjusted HR, 1.68; CI, 1.00-2.79;  $P = .048$ ), but it was not associated with a significant increase in the risk of the composite CD/MI/LCR (adjusted HR, 1.23; CI, 0.53-2.83;  $P = .630$ ) or all-cause mortality (adjusted HR, 1.60; CI, 0.93-2.77;  $P = .091$ ).

## DISCUSSION

To our knowledge, this is the largest study to date to report on the prognostic utility of SPECT-MPI in patients with ESRD. The study confirmed that the presence and severity of perfusion abnormalities with regadenoson SPECT-MPI were associated with an independent and incremental prognostic value for MACE of CD or MI, the composite endpoints of Death/MI and CD/MI/LCR, as well as all-cause mortality. The prognostic utility of regadenoson SPECT-MPI was generally consistent when we censored the survival analyses at renal transplantation. Notably, the annualized MACE rate of 1.4% for patients with normal regadenoson SPECT-MPI in the present cohort may have been underestimated on account of the retrospective nature of our study, yet is significantly lower than previously reported in ESRD patients (4.9%).<sup>15</sup> However, the annualized composite of Death/MI among patients with normal MPI was 6.2% which is in line with historic data. Nonetheless, the observed annualized MACE rate is expectedly higher than that reported among all-comers with normal vasodilator SPECT-MPI (1.1%)<sup>27</sup> or, more specifically, those with regadenoson SPECT-MPI (0.9-1.1%).<sup>14,25,28</sup> Moreover, we affirmed

that the presence and severity of regadenoson-induced myocardial ischemia with SPECT-MPI were associated with a stepwise increase in adverse cardiac events and all-cause mortality. Lastly, we demonstrated the independent association of LV dysfunction with MACE, highlighting its incremental prognostic value above and beyond clinical and imaging covariates.<sup>25</sup>

Although our study asserts the significant prognostic value of regadenoson SPECT-MPI in ESRD patients, it is important to note the modest effect sizes of abnormal MPI and myocardial ischemia in this cohort (i.e., HRs < 2), compared to historical data in all-comers. By the same token, the incremental prognostic value of MPI abnormalities, beyond clinical covariates, is rather minimal. It is plausible that outcomes of these patients are more strongly influenced by their ESRD/hemodialysis status and associated comorbidities than by perfusion abnormalities. This elevated baseline risk may result in minimizing the contribution of perfusion imaging in determining the overall prognosis of these patients.<sup>11–13</sup> The prognostic impact of baseline renal function is supported by the earlier findings of Hakeem et al<sup>29</sup> who demonstrated that, in patients undergoing stress MPI (32% exercise and 68% adenosine), both MPI results as well as CKD are independent and incremental predictors of cardiac death and all-cause mortality.

Our main findings are concordant with other reports in the literature. For instance, Hage et al<sup>14</sup> previously reported excellent prognostic implications of regadenoson SPECT-MPI in a large retrospective study of 1,400 patients of all-comers, albeit only 362 of whom had ESRD. In their analysis, ESRD was found to be an independent predictor of CD. However, the authors did not specifically study the prognostic value of regadenoson MPI in ESRD.<sup>15</sup> Bhatti et al have shown an independent prognostic value for SPECT-MPI across various degrees of renal dysfunction, predominantly CKD not yet in ESRD status.<sup>30</sup> Our study population was an all-ESRD cohort, many of whom were undergoing routine ischemic evaluation as part of the renal transplantation work-up while on the transplant waiting list. In previously published data from representative overlapping cohorts from our center, we reported that the mean duration of dialysis in our ESRD population was  $3.6 \pm 3.5$  years, with 92% on hemodialysis and 8% on peritoneal dialysis.<sup>15</sup> We also previously reported that 43% of ESRD patients undergoing renal transplant evaluation have unconfirmed etiology of ESRD, while 38% of patients were presumed to have hypertension, diabetes mellitus, or combined hypertension and diabetes as their etiology of ESRD. Glomerular disease and polycystic kidney disease, each comprised 5% of the ESRD population.<sup>13</sup>

It is well established that renal transplant has a favorable impact on the outcome of patients with

ESRD.<sup>12</sup> In the present report, we did not evaluate the impact of MPI findings on post-transplant outcomes. However, our group has previously reported on the impact of pre-transplant MPI, with various stress modalities, on post-transplant outcomes in a cohort of renal transplant recipients. The study demonstrated that the diagnostic and the prognostic utility of stress MPI is dependent on the pre-transplant clinical risk. In fact, the predictive value of MPI followed the Bayes' Theorem, such that patients with an intermediate pre-transplant risk (3–4 transplant risk factors) derived the most value from pre-transplant MPI in prognosticating long-term, post-transplant MACE risk. Pre-transplant MPI findings did not provide a significant prognostic value in patients with lower and higher clinical risk, as their outcomes were primarily commensurate to their baseline clinical risk regardless of MPI findings.<sup>3,11,13</sup>

We have previously conducted the first prospective evaluation of the prognostic utility of regadenoson SPECT-MPI in patients with ESRD.<sup>15</sup> This was done on 303 non-consecutive ESRD patient cohort enrolled in the ASSUAGE and ASSUAGE-CKD trials.<sup>16,17</sup> The results were notable for a preserved prognostic utility in this patient population, which is in keeping with our findings herein. Interestingly, in our previous report,<sup>15</sup> the annualized MACE rate in subjects with normal MPI was considerably higher than this cohort (4.9% vs 1.4%). This may be explained by the older age (mean age 62 vs 54 years), more comorbidities (e.g., DM 43% vs 28%), and known symptomatic CAD (e.g., chest pain or dyspnea accounted for ~ 68% of indications for stress MPI) in the prior study's cohort. Furthermore, owing to the retrospective nature of the current study, we speculate that MACE may have been underestimated due to less ascertainment of CD as cause of mortality and possible missed MI events. However, all other outcomes seemed consistent between our previous prospective evaluation<sup>15</sup> and the current report. We have previously reported on the robust prognostic value of blunted heart rate response in ESRD patients and in renal transplant recipients. In fact, heart rate response can refine risk prediction in ESRD patients, particularly among those with normal MPI.<sup>31–33</sup>

TID, as a continuous variable, was associated with an increased risk of adverse cardiac events and all-cause mortality in our current cohort. However, when assessed as a dichotomous variable (ratio  $\geq 1.31$ ), this association was not statistically significant or with a marginal trend towards statistical significance. This may be related to the limited number of events, resulting in "type II error." Golzar et al previously demonstrated that TID does not add useful diagnostic information for severe and extensive CAD.<sup>24</sup> Conversely, Lester et al,<sup>34</sup> who defined abnormal TID as

ratio  $\geq 1.33$ , concluded that it adds important prognostic information in patients with an abnormal MPI. In their analysis of 887 patients,<sup>34</sup> they found a significant association between TID and the composite CD/MI/LCR, which was mostly driven by the LCR events. It is worth noting that the selection of subjects with normal MPI in the aforementioned cohort may have accentuated the predictive value of TID. This contrasts with our non-selected, consecutive patient cohort which may have included borderline or technically inferior studies, translating into “data noise,” which may have curtailed the predictive capacity of TID. Nevertheless, our unselected patient cohort more likely mimics the real-world scenarios. The diagnostic and prognostic value of TID has been somewhat conflicting in recent literature,<sup>24,35</sup> perhaps due to decreasing prevalence of severe and extensive CAD in contemporary cohorts compared to historical data.<sup>36,37</sup> Traditionally, abnormal TID threshold is determined in a population with low likelihood of CAD as a value greater than 2 standard deviations above the mean. Such methodology yields a threshold with low sensitivity, but high specificity, for severe CAD. However, with low prevalence of severe CAD in contemporary cohorts, it is likely that the low sensitivity renders such a threshold ineffective in identifying patients at risk. Therefore, redefining the TID threshold to optimize its diagnostic and prognostic performance may be necessary. In this report, we explored deriving an optimal TID threshold from an iterative examination of the coordinates of the TID/MACE ROC curve. Indeed, we identified the TID ratio of  $\geq 1.15$  as a threshold that can provide an improved prognostic discriminatory capacity. We caution, however, that this threshold was iteratively derived to optimize the prognostic discriminatory capacity in this particular cohort. Thus, external validation of this methodology and threshold is prudent.

Previous studies have reported on the prognostic value of pharmacologic stress MPI in the setting of renal dysfunction. A report from Australia demonstrated the utility of different stress MPI modalities (exercise, dobutamine, right atrial pacing, and dipyridamole) in 387 patients being evaluated for renal transplant.<sup>38</sup> Al-Mallah et al<sup>39</sup> studied a large consecutive patient cohort of 7,348 all-comers undergoing SPECT-MPI (exercise, adenosine, and dobutamine) and demonstrated the modest value it adds in predicting death across various degrees of renal dysfunction, although predominantly not declared ESRD. Our findings in this large, consecutive ESRD patient cohort are a continuum to these reports, specifically in terms of the modest incremental prognostic value that MPI findings provide in this patient population.

## Limitations

Our findings are subject to all limitations inherent to a single-center, retrospective study design. MACE may have been underestimated since the ascertainment of cardiac death was only inclusive of confirmed cardiac death cases. It is also plausible that some MI events may have not been captured. Additionally, owing to its observational nature, the long-term outcomes in our study may have been influenced by MPI-guided CR and medical therapy. We attempted to mitigate this limitation by focusing on LCR rather than CR events. Lastly, the cause of death was occasionally determined via death certificates review, which may have been inaccurate.

## NEW KNOWLEDGE GAINED

Our report is the largest to date to assert the prognostic utility of regadenoson SPECT-MPI, as an independent and incremental predictor of cardiac-specific outcomes as well as all-cause mortality in ESRD patients. Given its size, our study provides improved risk estimates compared to previous reports. The prognostic utility of TID is inconsistent. Further examination of an optimal TID threshold remains warranted.

## CONCLUSIONS

In the largest cohort to date, stress MPI provides independent and incremental prognostic value in predicting adverse cardiac events and all-cause mortality in patients with ESRD.

## Disclosure

*None.*

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