Severe chronic kidney disease as a predictor of benefit from aminophylline administration in patients undergoing regadenoson stress myocardial perfusion imaging: A substudy of the ASSUAGE and ASSUAGE-CKD trials

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Background. **Regadenoson is predominantly renally metabolized. Patients with severe chronic kidney disease (CKD) experience more frequent gastrointestinal adverse effects (AE) from regadenoson. Aminophylline use following regadenoson reduces the incidence of regadenoson-related AE. We investigated whether patients with severe CKD receive incremental benefit from aminophylline administration in reducing regadenoson AE.**

Methods. **We performed post hoc analysis of the pooled database of the ASSUAGE and ASSUAGE-CKD trials. These were randomized placebo-controlled clinical trials which tested the benefit of intravenous aminophylline vs placebo after regadenoson injection in patients undergoing a clinically indicated stress MPI. Patients were categorized into two treatment arms: aminophylline vs placebo; and two groups: Severe CKD (GFR < 30 mL·min^{-1}/1.73 m^2 or dialysis) and Control (GFR ≥ 30 mL·min^{-1}/1.73 m^2). The study endpoints were gastrointestinal AE, non-gastrointestinal AE and composite of any regadenoson AE.**

Result. **The pooled database of the two trials yielded 548 patients, of whom 274 patients received aminophylline and 274 received placebo. Aminophylline was associated with greater absolute risk reduction (ARR) in gastrointestinal AE among patients with severe CKD vs controls (25% vs 4%, $p < .001$). A significant interaction was identified between severe CKD and aminophylline in reducing gastrointestinal AE ($p = .007$), indicating greater reduction in gastrointestinal AE with aminophylline use among patients with severe CKD. Aminophylline use was associated with a trend toward greater ARR in any regadenoson-related AE (32% vs 21%, $p = .08$).**

Conclusion. **Aminophylline is associated with incremental benefit in reducing gastrointestinal AE in patients with severe CKD undergoing regadenoson stress MPI. Potentially, this population could be targeted for prophylactic administration of aminophylline in order to improve their overall experience with the test. (J Nucl Cardiol 2015;22:1008–18.)**

Key Words: ASSUAGE • aminophylline • regadenoson • adverse effects • chronic kidney disease (CKD) • end-stage renal disease (ESRD)

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INTRODUCTION

Regadenoson is a selective A_{2A} adenosine receptor agonist, used as a pharmacologic stress agent for myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT).[1,2] The ADVANCE MPI trials (1 and 2) demonstrated that, as compared to standard adenosine infusion, regadenoson is associated with fewer adverse effects (AE) of flushing, chest pain and dyspnea but more frequent symptoms of headache and abdominal discomfort.[3,4] These trials and others showed that, although well tolerated, nearly three-quarters of the patients reported at least one or more AE with regadenoson.[4,5] However, the ADVANCE MPI trials included a limited number of patients with severe chronic kidney disease (CKD) and excluded those with end-stage kidney disease (ESRD).[3,4] This is important, as one would expect a higher rate of AE among subjects with impaired renal function since 57% of the drug is excreted unchanged in the urine.[6] Despite that, there is a growing body of evidence demonstrating that regadenoson can be safely used in patients with severe CKD, including those with dialysis-dependent ESRD.[7-10] The frequency and severity of regadenoson-related AE can be effectively reduced with intravenous aminophylline administered following regadenoson injection, as it has been demonstrated in the ASSUAGE and the ASSUAGE-CKD trials.[11,12] These were identically designed, randomized, double-blinded, placebo-controlled clinical trials, except that the ASSUAGE trial enrolled all-comers regardless of renal function, whereas the ASSUAGE-CKD trial enrolled only patients with severe CKD (GFR < 30 mL·min^{-1}/1.73 m^2 or ESRD). A subsequent analysis of the pooled data of the placebo arms of the ASSUAGE and ASSAUGE-CKD trials demonstrated that regadenoson was safe and well tolerated in patients with ESRD (dialysis or GFR < 15 mL·min^{-1}/1.73 m^2), but these patients had an excess incidence of diarrhea (29% vs 14%, $P = .009$) and gastrointestinal AE (51% vs 31%, $P = .02$) as compared to patients with GFR > 30 mL·min^{-1}/1.73 m^2.[10] Thus, there is a need to further reduce the rate of regadenoson-induced AE among patients with severe CKD. Given the predominant renal clearance of regadenoson, we hypothesized that aminophylline administration following regadenoson is associated with a greater reduction in the rate of regadenoson-induced AE among patients with severe CKD than those without severe CKD. If confirmed, patients with severe CKD could be selectively targeted to receive intravenous aminophylline to improve their experience with regadenoson stress.

METHODS

We addressed the study question using the pooled database of the ASSUAGE and ASSUAGE-CKD trials.[11,12] Briefly, these were double-blinded, placebo-controlled clinical trials in which patients referred for a clinically-indicated regadenoson-stress MPI were randomized in a 1:1 ratio to receive 75 mg of intravenous aminophylline or a matching placebo administered 90 seconds following the radioisotope injection or approximately 2 minutes following regadenoson (Figure 1).[11,12] These trials were identical in their design, methods, inclusion and exclusion criteria except that the ASSUAGE-CKD trial ($n = 300$) was limited to patients with GFR < 30 mL·min^{-1}/1.73 m^2 (CKD stage 4) or ESRD (CKD stage V), whereas the ASSUAGE trial ($n = 248$) was open for all comers regardless of renal function.[11,12] Patients with ESRD typically presented for testing on non-dialysis days. The GFR was calculated using the Cockcroft-Gault formula.[13] In both trials, two questionnaires inquiring about patients' symptoms and overall stress test experience were conducted by blinded outcome assessors after completion of the stress SPECT acquisition (right before patient dismissal from the nuclear cardiology laboratory) and repeated 24 hours later. The key endpoints assessed in these questionnaires are outlined in Table 1. The primary endpoint of the ASSUAGE trial was the composite of diarrhea or abdominal discomfort; while the primary endpoint of the ASSUAGE-CKD trial was diarrhea. The secondary endpoints for both trials included: any regadenoson AE and test tolerability and acceptability (Table 1). Major exclusion criteria for the trials were: pre-existing headache or gastrointestinal symptoms (nausea, vomiting, abdominal cramps or diarrhea) and any contraindication for aminophylline or regadenoson use. The detailed methodology, inclusion and exclusion criteria, and results of these trials were published elsewhere.[11,12]

Both trials were conducted at Rush University Medical Center (Chicago, IL). The John H. Stroger, Jr. Hospital of Cook County (Chicago, IL) was a participating center in the ASSUAGE-CKD trial. Both trials were approved by the institutional review boards of the participating institutions. All patients signed HIPAA and informed consent forms. The ASSUAGE and ASSUAGE-CKD trials were registered on clincialtrials.org (NCT01250496 and NCT01336140, respectively). An investigational new drug application (IND) for aminophylline was approved by the Food and Drug Administration (IND # 110129).

Patients

All 248 subjects enrolled in the ASSUAGE trial and 300 subjects enrolled in the ASSAUGE-CKD trials (total 548 subjects) were pooled. Patients were categorized into aminophylline or placebo treatment arms based on the randomized assignment of the original trials. Study subjects were further categorized based on CKD status into two groups: (1) *Severe CKD* with GFR < 30 mL·min^{-1}/1.73 m^2 or ESRD; (2) *Control* with GFR ≥ 30 mL·min^{-1}/1.73 m^2.

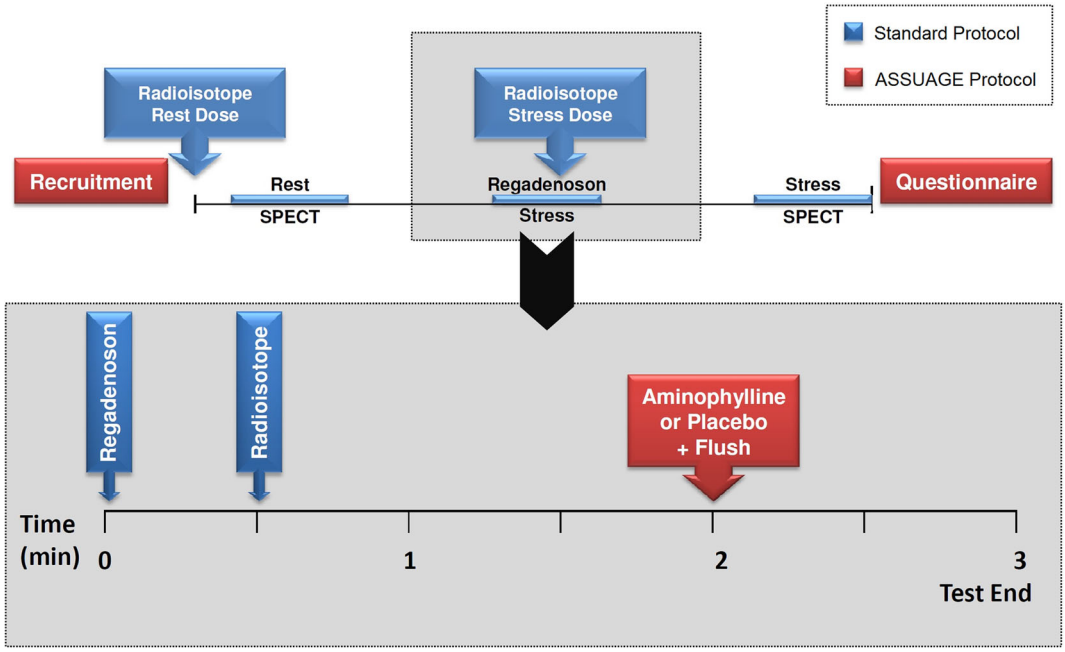

Figure 1. The ASSUAGE protocol reproduced from Doukky et al.,[11] with permission.

Table 1. ASSUAGE abbreviated outcome assessment questionnaire

*A. Since you received the study medication (aminophylline or placebo) up to this moment, did you experience any of the following symptoms?**	
1. Flushing	6. Feeling hot
2. Shortness of breath	8. Dizziness
3. Headache	7. Nausea/vomiting
4. Chest discomfort	9. Abdominal cramps
5. Chest pain—describe†	10. Diarrhea
B. How did you feel overall?	
1. Comfortable	3. Somewhat uncomfortable
2. Somewhat comfortable	4. Uncomfortable
C. Would you take the test again in the future?	
1. Definitely	3. Probably not
2. Probably	4. Absolutely not

* For each symptom listed under question A the answer was "YES" or "NO"; for symptoms answered as "YES", the severity was graded as mild, moderate or severe
†Chest pain was coded as angina if it was described as "retrosternal heaviness or pressure"

Endpoints

We evaluated the impact of aminophylline use (vs placebo) on the incidence of AE prior to patients' dismissal from the laboratory, within two hours of regadenoson stress test (survey #1). The study endpoints include: (1) gastrointestinal AE (composite of nausea, vomiting, abdominal cramps, or diarrhea); (2) non-gastrointestinal AE (composite of flushing, shortness of breath, headache, chest discomfort, chest pain, feeling hot, dizziness); (3) composite of any regadenoson AE (Table 1). To determine the baseline risk of regadenoson-related AE, we analyzed the rates of the study endpoints in patients with severe CKD and controls who received placebo (regadenoson followed by placebo), assuming this as an equivalent to a standard regadenoson stress test.

Study Aims and Statistical Analysis

We sought to evaluate whether aminophylline use had a differential effect in reducing regadenoson-related AE based on severe CKD status, such that patients with severe CKD experience greater reduction in AE. The reduction in AE with

aminophylline was compared between Severe CKD and Control groups in absolute and relative terms.

(1) *The absolute risk reduction (ARR)* in the rate of AE with aminophylline use was compared in patients with severe CKD to controls. We tested for statistical significance of the difference in ARR between patients with severe CKD and controls by calculating the z-ratios and corresponding *P* values.
(2) *The relative reduction* in the rate of AE with aminophylline vs placebo was expressed in odds ratios with 95% confidence intervals. Using binary logistic regression models, we tested for interactions between treatment arm (aminophylline vs placebo) and Severe CKD group (Severe CKD vs control) as a determinant of the study endpoints. In each of these models, the treatment arm, severe CKD status, and the interaction term (treatment arm * severe CKD status) were independent variables, while the study endpoint was the dependent outcome variable. The *P* value of the interaction term was used to determine the presence of a significant interaction.

The chi-square test was used to compare dichotomous variables which were expressed as a number (percentage). The Fisher's exact test was used for dichotomous comparisons when the number of events was less than 5. The Student's *t* test was used to compare continuous variables which were expressed as mean ± standard deviation. Analysis of covariance (ANCOVA) was performed to demonstrate whether severe CKD status or the study arm (aminophylline vs placebo) was predictive of perfusion abnormality burden, as assessed by quantitatively measured summed difference score (SDS) and summed stress score (SSS) on a 17-segment model. P value $< .05$ was considered statistically significant.

RESULTS

Patients

The study population was derived from the pooled database of the ASSUAGE (n = 248) and ASSUAGE-CKD (n = 300) trials, yielding 548 subjects who were randomized in their respective trial into two treatment arms: *Aminophylline* ($n = 274$) and *Placebo* ($n = 274$).[11,12] Based on severe CKD status, we defined two study groups: a *Severe CKD group* (GFR < 30 mL·min^{-1}/1.73 m^2 or ESRD) of 357 (65.1%) subjects (182, aminophylline; 175, placebo) and a *Control group* (GFR ≥ 30 mL·min^{-1}/1.73 m^2) of 191 (34.9%) subjects (92, aminophylline; 99, placebo), as illustrated in Figure 2. As shown in Table 2, the baseline characteristics of the study subjects, including CKD stage, were well matched between the two treatment arms, as the patients were randomized in their respective trials. Table 3 compares the baseline characteristics of the Severe CKD and Control groups. Notably, subjects with severe CKD were younger and mostly men, had a lower body mass index, and were dominated by ethnic minorities. Furthermore, severe CKD patients had a higher prevalence of hypertension and diabetes mellitus and a lower prevalence of coronary artery disease.

Baseline Incidence of Adverse Effects

To determine the baseline risk of AE in patients with severe CKD and controls undergoing standard regadenoson stress study, we analyzed the rates of the study endpoints within the placebo arm (regadenoson + placebo), assuming this to be equivalent to a standard regadenoson stress test. As depicted in Figure 3, there was no statistically significant difference in the rate of regadenoson-related AE between patients with severe CKD and controls, except that patients with severe CKD trended toward having higher rate of gastrointestinal AE but lower rate of non-gastrointestinal AE. Table 4 reports the rates of AEs for Severe CKD and Control groups in the placebo arm and compares them to the aminophylline arm.

Response to Aminophylline: Severe CKD vs Control

Absolute risk reduction of adverse effects. As illustrated in Figure 4, a reduction in the rate of regadenoson-related AE was observed with aminophylline use (vs placebo) in Severe CKD and Control groups. As compared to controls, subjects with severe CKD received significantly greater ARR in gastrointestinal AEs and trended toward having greater reduction in the incidence of any AEs, whereas the difference in the ARR in non-gastrointestinal AE was not statistically significant.

Relative reduction in the likelihood of adverse effects. As illustrated in Figure 5, a significantly lower likelihood of gastrointestinal, non-gastrointestinal, and any regadenoson-related AE was observed with aminophylline use in the Severe CKD group, as the odds-ratios for all endpoints were <1.0 and none of the confidence intervals crossed the line of identity. This was also true for the Control group for non-gastrointestinal and any regadenoson related AE. Notably, the likelihood of gastrointestinal AE was not significantly lower with aminophylline use in the Control group, as the confidence interval crossed the line of identity. Nonetheless, there was a consistent trend toward benefit from aminophylline administration for all study endpoints (all odds-ratios <1.0).

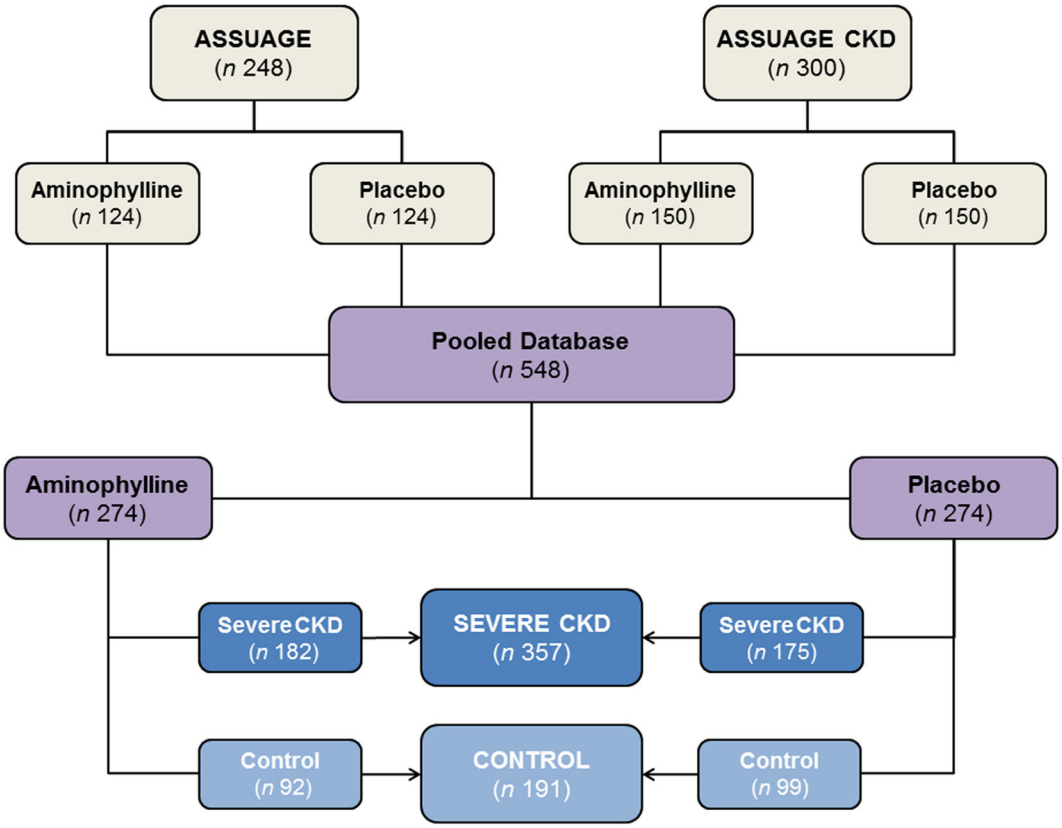

Figure 2. Diagram: derivation of study population. Severe CKD: subjects with glomerular filtration rate <30 mL·min^{-1}/1.73 m^2 or dialysis. Control: subjects with glomerular filtration rate ≥30 mL·min^{-1}/1.73 m^2.

Binary logistic regression analysis identified an interaction between the treatment arm (aminophylline vs placebo) and the study group (Severe CKD vs Control) as a determinant of any gastrointestinal AEs [Interaction odds-ratio = .32 (95% confidence interval .14-.73), interaction P value = .007]. In other words, patients with severe CKD received greater benefit with aminophylline use in reducing gastrointestinal adverse effects than patients without Severe CKD. To ensure that the identified interaction between severe CKD and aminophylline use is not biased by differences in the baseline characteristics (Table 3), we adjusted the described interaction model for covariates of age, gender, body mass index, ethnicity (African American or Hispanic vs other), hypertension, diabetes mellitus, and known CAD. Despite this adjustment, the interaction term (treatment arm * severe CKD) remained significant (adjusted interaction P value = .004). There was no interaction between the treatment arm and study group as determinant of any other study endpoints (interaction P values > .05). This indicates that aminophylline reduces the likelihood of non-gastrointestinal and any regadenoson-related AE to the same extent among patients with and without severe CKD.

Incidence of Serious Adverse Effects

There were no events of death, myocardial infarction, cardiac arrest, bronchospasm, or seizures regardless of severe CKD status or treatment arm. Patients with severe CKD had higher prevalence of first degree atrioventricular block at baseline as compared to the controls (9.5% vs 3.1% respectively, P = .25). However, as illustrated in Table 5, stress-induced first degree and second degree—type I atrioventricular block events were rare and not significantly different on the basis of treatment arm or severe CKD status. There were no cases of type II second degree or third degree atrioventricular block irrespective of treatment arm or severe CKD status. There were no documented ventricular tachyarrhythmias. Subjects with severe CKD had a higher incidence of premature ventricular contractions as compared to controls; however this was not affected by aminophylline use (Table 5). Other arrhythmic

Table 2. Baseline characteristics of patients in the ASSUAGE and ASSUAGE CKD trials

	Combined trials (n = 548)	Aminophylline (n = 274)	Placebo (n = 274)	*p* value
Age (years), mean ± SD	58.3 ± 13.5	57.8 ± 13.5	58.9 ± 13.6	.37*
Female, n (%)	218 (39.8)	110 (40.1)	108 (39.4)	.93†
Ethnicity, n (%)				.32†
African American	282 (51.5)	139 (50.7)	143 (52.2)	
Caucasian	114 (20.8)	51 (18.6)	63 (23.0)	
Hispanic	130 (23.7)	72 (26.3)	58 (21.2)	
Other	22 (4.0)	12 (4.4)	10 (3.7)	
GFR ($mL \cdot min^{-1}/1.73\ m^2$), mean ±SD	53.9 ± 36.4	50.4 ± 34.8	57.5 ± 37.7	.11*
CKD Stage, n (%)				0.93†
Stage I/II (GFR $\geq$ 60)	136 (24.8)	66 (24.1)	70 (25.5)	
Stage III (GFR 30 $\geq$ 60)	55 (10.0)	26 (9.5)	29 (10.6)	
Stage IV (GFR 15 $\geq$ 30)	58 (10.6)	30 (10.9)	28 (10.2)	
Stage V (GFR < 15) or ESRD	299 (54.6)	152 (55.5)	147 (53.6)	
Dialysis	289 (52.7)	145 (52.9)	144 (52.6)	0.93†
Hypertension, n (%)	505 (92.2)	253 (92.3)	252 (92.0)	1.00†
Diabetes mellitus, n (%)	271 (49.5)	127 (46.4)	144 (52.6)	.17†
Coronary artery disease, n (%)	171 (31.2)	78 (28.5)	93 (33.9)	.20†
Heart failure, n (%)	94 (17.2)	43 (15.7)	51 (18.6)	.43†
Ejection fraction, mean ± SD	62.3 ± 13.7	63.3 ± 13.4	61.4 ± 14.1	.11*
BMI ($Kg \cdot m^{-2}$), mean ± SD	30.4 ± 7.2	30.1 ± 6.9	30.6 ± 7.6	.36*

SD, standard deviation; *GFR*, glomerular filtration rate in $mL \cdot min^{-1}/1.73\ m^2$ (Cockcroft-Gault formula); *BMI*, body mass index
*2-tailed Student's *t* tailed test; † 2-tailed chi-square (χ^2) test

Table 3. Comparison of baseline characteristics between severe CKD and control groups

	Severe CKD (n = 354)	Control (n = 194)	*P* value
Age, (years), mean ± SD	55.3 ± 13.0	64.1 ± 12.5	<.001*
Female, n (%)	128 (35.9)	90 (47.1)	.01†
Ethnicity, n (%)			<.001†
African American	194 (54.3)	88 (46.1)	
Caucasian	51 (14.3)	63 (33)	
Hispanic	100 (28)	30 (15.7)	
Other	10 (5.3)	12 (3.4)	
Hypertension, n (%)	339 (95)	166 (86.9)	.001†
Diabetes mellitus, n (%)	199 (55.7)	72 (37.7)	<.001†
Coronary artery disease, n (%)	89 (24.9)	82 (42.9)	<.001†
Heart failure, n (%)	63 (17.6)	31 (16.2)	.72†
Ejection fraction, mean ± SD	62.2 ± 13.1	62.6 ± 14.8	.77*
BMI ($Kg \cdot m^{-2}$), mean ± SD	29.6 ± 6.9	31.7 ± 7.7	.002*

SD, standard deviation; *BMI*, body mass index
*2-tailed student's *t* tailed test; † 2-tailed chi-square (χ^2)

events, such as atrial fibrillation, supraventricular tachycardia, and premature atrial contractions were rare and not significantly different between the study groups. In the aminophylline arm, open label aminophylline was rarely used in severe CKD subjects (1.6%) and none was used in the Control group. Expectedly, the use of open label aminophylline was more common in the placebo arm for both groups (Table 5).

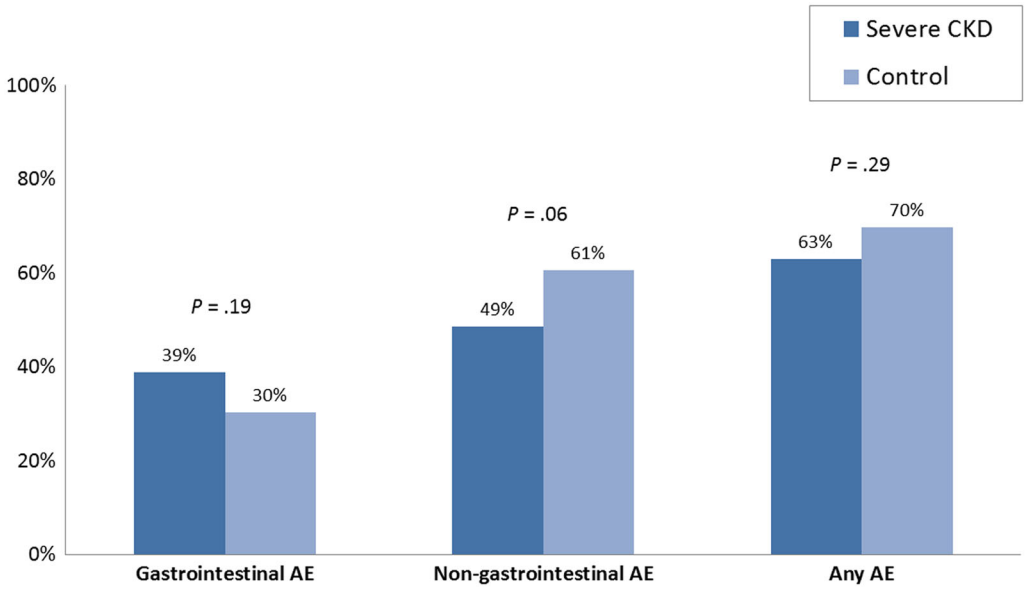

Figure 3. Incidence of adverse effects in the placebo arm of the ASSUAGE trials in severe CKD and control groups. Severe CKD: glomerular filtration rate <30 mL·min^{-1}/1.73 m^2 or dialysis; Control: glomerular filtration rate ≥30 mL·min^{-1}/1.73 m^2; AE: adverse effects; Gastrointestinal AE: composite of diarrhea, abdominal cramps, nausea and vomiting; Non-gastrointestinal AE: composite of flushing, shortness of breath, headache, chest discomfort, chest pain, feeling hot or dizziness. *P* values derived from the chi-square test.

Impact on Perfusion Imaging

The mean SDS, as a measure of stress-induced ischemic burden, was similar in the aminophylline and placebo arms (1.4 ± 2.7 vs 1.6 ± 3.1, $P = .34$). Similarly, the mean SSS was not significantly different between the study arms ($P = .10$). Analysis of covariance (ANCOVA) demonstrated that neither severe CKD status nor the study arm was predictive of SDS or SSS ($P = .46$ and .29, respectively), after adjusting for premorbid CAD, which was the sole predictor of higher SDS and SSS ($P = .005$, ≤.001, respectively).

DISCUSSION

In this post hoc analysis of the pooled database of the ASSUAGE and ASSUAGE-CKD trials, we observed similar incidences of AE between Severe CKD and Control groups, with a trend toward higher baseline incidence in gastrointestinal AE and lower baseline incidence of non-gastrointestinal AE in patients with severe CKD as compared to controls. Furthermore, we demonstrated that intravenous aminophylline use following regadenoson has an incremental benefit in reducing regadenoson-related gastrointestinal AE among patients with severe CKD as compared to those without severe CKD. This conclusion was illustrated in a greater reduction in the absolute risk and relative risk (odds-ratio) of gastrointestinal AE in patients with severe CKD as compared to controls without severe CKD. Furthermore, there was a trend toward a greater reduction in the absolute rates of any regadenoson-related AE in patients with severe CKD as compared to controls (Figure 4).

It has been well established that severe CKD is associated with a higher burden of ischemic heart disease as compared to the general population.[14] Thus, CKD patients are frequently referred for pharmacologic stress MPI.[14,15] To date, regadenoson is not FDA approved in patients with ESRD, but it has been used off-label in some nuclear cardiology laboratories. A retrospective and a prospective study have demonstrated that it is safe to use regadenoson in patients with ESRD[9,10] but with a greater frequency of gastrointestinal AE.[10] Although regadenoson is a selective A_{2A} adenosine receptor agonist with predominant vasodilatory effect in the coronary circulation, it has been shown in animal models that it also causes dose dependent mesenteric vasodilation similar to that induced by adenosine.[1] Since the half-life of regadenoson is significantly longer than adenosine, prolonged regadenoson-induced mesenteric vasodilation seems to lead to more frequent gastrointestinal AE. The frequency and severity of gastrointestinal AE seems to be further enhanced by prolonged regadenoson half-life in subjects with severe

Table 4. Adverse effects according to CKD stage and study arm

	Gastrointestinal AE			Non-gastrointestinal AE			Any AE		
	AMP	PL	*P* value*	AMP	PL	*P* value*	AMP	PL	*P* value*
Control (n = 191), fraction (%)	24/92 (26)	30/99 (30)	.53	40/92 (44)	60/99 (61)	.02	45/92 (49)	69/99 (70)	.005
GFR ≥ 60	18/66 (27)	24/70 (34)	.46	29/66 (44)	44/70 (63)	.04	32/66 (49)	51/70 (73)	.003
GFR 30 ≥ 60	6/26 (23)	6/29 (23)	1.00	11/26 (42)	16/29 (55)	.42	13/26 (50)	18/29 (62)	.27
Severe CKD (n = 357), fraction (%)	26/182 (14)	68/175 (39)	<.001	45/182 (25)	85/175 (49)	<.001	57/182 (31)	110/175 (63)	<.001
GFR 15 ≥ 30	4/30 (13)	9/28 (32)	.12	5/30 (17)	12/28 (43)	.04	8/30 (27)	15/28 (54)	.03
GFR < 15 or dialysis	22/152 (15)	59/147 (40)	<.001	40/152 (26)	73/147 (50)	<.001	49/152 (32)	95/147 (65)	<.001

Gastrointestinal AE, composite of diarrhea, abdominal cramps, nausea, and vomiting; *Non-gastrointestinal AE*, composite of flushing, shortness of breath, headache, chest discomfort or pain, feeling hot, dizziness. *AE*, adverse effect; *AMP*, aminophylline; *PL*, Placebo; *GFR*, glomerular filtration rate in mL·min^{-1}/1.73 m^2
*Two-tailed chi-square test or Fisher's exact test if number of events is <5

CKD.[6] The manifestation of gastrointestinal AEs, particularly diarrhea, is delayed due to lag-time in bowel transit; thus it is frequently overlooked.[6-9] In another substudy of the ASSUAGE trials, we reported that ESRD subjects had a higher incidence of diarrhea and gastrointestinal AE from regadenoson in the ensuing 24 hours as compared to subjects with GFR ≥ 30 mL·min^{-1}/1.73 m^2 (*P* values = .009 and .02, respectively).[10] In the present analysis, shorter follow up (in laboratory vs 24 hours) and the inclusion of subjects with GFR 15-30 mL·min^{-1}/1.73 m^2 may have minimized the incidence of gastrointestinal AE in the severe CKD cohort. It is reasonable to believe that the mild residual renal function in this subset of subjects was enough to prevent them from developing higher rates of gastrointestinal and non-gastrointestinal AE,[7] as illustrated in Table 4. Nonetheless, in this study we demonstrated that aminophylline administration following regadenoson differentially reduces gastrointestinal AE in patients with severe CKD, including those with ESRD. The use of aminophylline in subjects with severe CKD appears to be safe as there were no serious AE.[16] Additionally, the use of aminophylline does not appear to affect the sensitivity of the stress MPI based on SDS and SSS analysis regardless of severe CKD status.

As expected, the baseline characteristics of the Severe CKD group were distinctly different from controls, as patients with severe CKD were younger and had lower prevalence of CAD. This is likely related to the fact that most patients with severe CKD who participated in the ASSUAGE trials were referred for stress testing as part of kidney transplant evaluation,[11,12] hence they represent a ''healthier'' subset of patients with advanced CKD.[14,15] On the other hand, subjects in the Control group underwent stress testing more frequently for evaluation of suspected or established coronary artery disease.[11,12] The disparity in racial distribution between patients with severe CKD and controls reflects the disproportionate impact of CKD on Hispanics and African Americans.[17] We confirmed that the deferential benefit of aminophylline in patients with severe CKD is independent of patients' baseline characteristics by demonstrating a significant interaction between severe CKD group and treatment arm even after adjusting for significant covariates.

Based on the findings of the present study, the routine use of aminophylline according to the ASSUAGE protocol seems justifiable in order to reduce gastrointestinal AE in patients with Severe CKD. Aminophylline dose of 75 mg intravenously appears to be appropriate for prophylaxis against regadenoson related AE regardless of the level of renal dysfunction but its effect is more profound in patients with severe

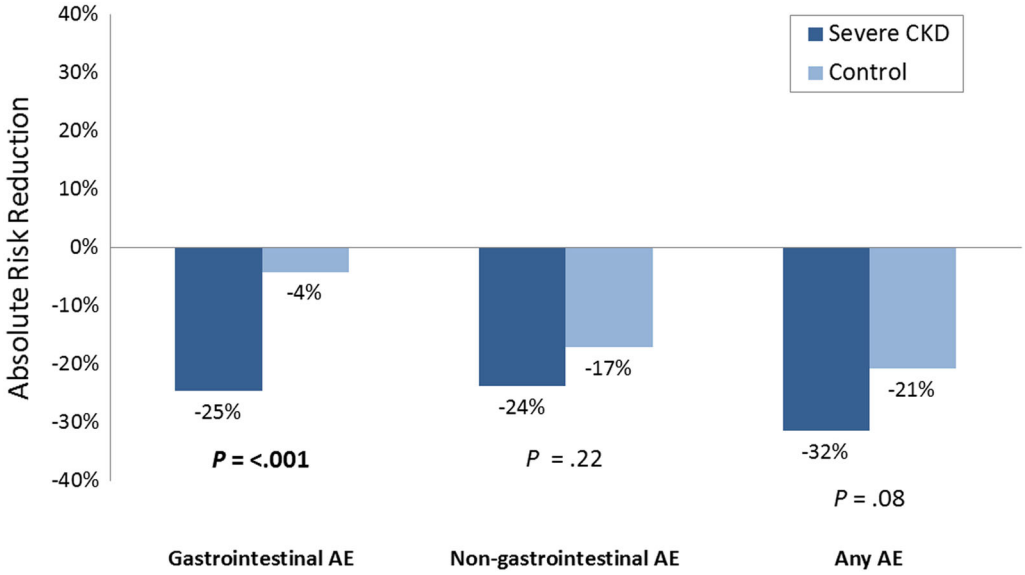

Figure 4. Absolute risk reduction in adverse effects with aminophylline use according to CKD status. Severe CKD: glomerular filtration rate <30 mL·min^{-1}/1.73 m^2 or dialysis; Control: glomerular filtration rate ≥30 mL·min^{-1}/1.73 m^2; AE: adverse effects. *P* values derived from the 2-tailed *z*-ratio significance level for the difference between two proportions.

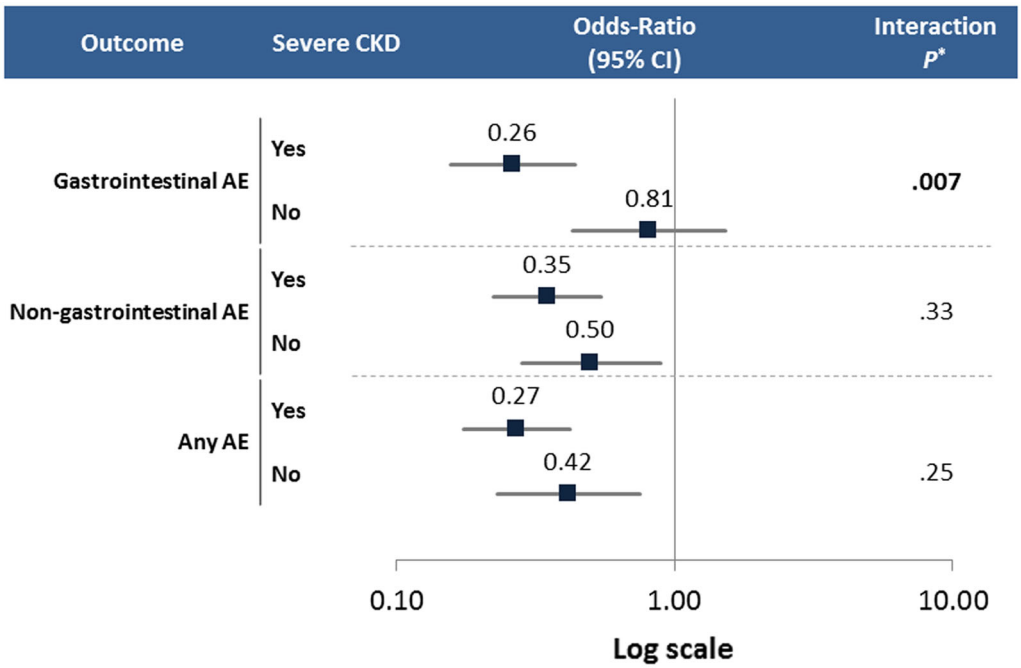

Figure 5. Odds ratio for adverse effects (Aminophylline: Placebo) according to Severe CKD status. *Severe CKD*, glomerular filtration rate <30 mL·min^{-1}/1.73 m^2 or dialysis; *CI*, confidence interval; *AE*, adverse effects. **P* value for the interaction term between severe CKD status and study arm (aminophylline vs placebo) in binary logistic regression analysis.

CKD; thus, this could be a safe and inexpensive approach to improve the experience of patients with severe CKD undergoing regadenoson stress MPI.

LIMITATIONS

Since the original trials were not sufficiently powered for subgroup analysis, minor differences between

Table 5. Serious adverse events according severe CKD status and study arm

	Severe CKD (*n* = 357)				Control (*n* = 191)				
	Total	AMP	PL	*P* value*	Total	AMP	PL	*P* value*	*P* value†
Arrhythmias, n (%)									
Supraventricular tachycardia	1 (0.3)	0	1 (0.6)	.49	0	0	0	NA	1.0
Atrial fibrillation	1 (0.3)	1 (0.5)	0	1.0	2 (1.0)	1 (1.1)	1 (1.0)	1.0	.28
Premature ventricular contractions	26 (7.3)	11 (6.0)	15 (8.6)	.42	2 (1.0)	1 (1.1)	1 (1.0)	1.0	.001
Premature atrial contractions	3 (0.8)	0	3 (1.7)	.12	2 (1.0)	1 (1.1)	1 (1.0)	1.0	1.0
Atrioventricular block, n (%)									
1st degree	1 (0.3)	0	1 (0.6)	.49	2 (1.0)	1 (1.1)	1 (1.0)	1.0	.28
2nd degree type I	2 (0.6)	0	2 (1.1)	.24	0	0	0	NA	.42
2nd degree type II/3rd degree	0	0	0	NA	0	0	0	NA	NA
Open label aminophylline use, n (%)	27 (7.6)	3 (1.6)	24 (13.7)	<.001	7 (3.7)	0	7 (7.1)	.01	.09

There were no events of death, myocardial infarction, ventricular tachyarrhythmia, symptomatic hypotension, seizure, or bronchospasm
AMP, Aminophylline; *PL*, placebo; *NA*, non-applicable
All *P* values were derived from the Chi-square test or Fisher's exact test if event count <5
**P* value for comparison between Aminophylline vs Placebo arms within Severe CKD and Control groups
†*P* value for comparisons between total events in the Severe CKD and Control groups

patients with and without severe CKD in terms of their response to aminophylline could have been missed (type II error); however, such undetected differences are probably too small to be of clinical significance.

NEW KNOWLEDGE GAINED

Aminophylline administration following regadenoson provides consistent reduction in regadenoson AE irrespective of renal function. Nonetheless, aminophylline administration has a differential effect in subjects with severe CKD, as it provides greater absolute and relative reduction in the rate of regadenoson-related gastrointestinal AE.

CONCLUSION

Patients with severe CKD, defined as GFR < 30 mL·min^{-1}/1.73 m^2 or dialysis therapy, enjoy an incremental benefit from aminophylline administration in reducing regadenoson-induced gastrointestinal AE. It seems reasonable to target patients with severe CKD with prophylactic administration of aminophylline following regadenoson stress, in an effort to improve patients' experience.

Conflict of interest

Rami Doukky received research support from Astellas Pharma US (none of which was used to fund this investigation) and serves on the Advisory Board of Astellas Pharma US. No conflict of interests to be reported by other authors.

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