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ORIGINAL PAPER

Clinical experience with regadenoson SPECT myocardial perfusion imaging: insights into patient characteristics, safety, and impact of results on clinical management

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Abstract
The Henry Ford Hospital (HFH) regadenoson (REG) registry includes patients with a variety of comorbidities allowing for the evaluation of outcomes in a large, unselected population. Using a database of electronic medical records and nuclear cardiology reports, patients aged > 18 years who underwent REG-facilitated single-photon emission computed tomography (SPECT) testing at HFH between January 2009 and August 2012 were identified. The primary objective was to describe the clinical and demographic characteristics of patients who had undergone REG only vs REG WALK (REG + low-level exercise) SPECT. A total of 2104 patients were included in the analysis (mean age 65.3 years; 50% women; 51% African American, 43% Caucasian). For the REG only (n = 1318) and REG WALK (n = 786) cohorts, SPECT was abnormal in 37% of patients (REG only, 39%; REG WALK, 34%; $P < 0.01$). No differences in diagnostic modalities or interventions in 90 days after SPECT were observed. Immediate safety analysis showed no deaths 48 h after REG SPECT testing. Although they guide invasive therapy, abnormal scans do not automatically lead to invasive testing. This demonstrates the focus on initial medical management, which reflects the existing evidence of initial goal-directed medical management of stable coronary disease.

Keywords Regadenoson · Single-photon emission computed tomography · Pharmacological stress agent · Coronary artery disease · Stress testing outcomes

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States (US), and disproportionate rates persist in racial and ethnic minority populations [1]. Single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) with cardiac stress induced by exercise or a pharmacological stress agent (PSA) is an extensively validated method for the diagnosis and prognostic assessment of coronary artery disease (CAD) [2, 3]. Patients able to walk on a treadmill are often referred for exercise SPECT-MPI; however, ambulatory patients unable to achieve at least 85% of the maximum predicted heart rate and five metabolic equivalents with exercise alone are often referred for pharmacologic stress testing combined with low-level exercise [4–6]. Relative to PSA alone, this approach is well tolerated and improves image quality.

Regadenoson (REG) is the most commonly used PSA with SPECT-MPI largely because of its A2a selectivity, ease of preparation, standardized dosing, proven efficacy, and comparability to adenosine myocardial perfusion imaging [7–10]. REG has demonstrated safety and tolerability in both clinical trials and in real-world studies. Indeed, clinical trial results show REG is well tolerated irrespective of age, gender, or presence of comorbidities (eg, diabetes, chronic obstructive pulmonary disease, asthma, chronic kidney disease) [11–16]. In an unpublished, previously conducted, single-center, retrospective analysis of patients undergoing REG SPECT, we compared hemodynamic and stress variables and immediate safety outcomes between REG

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SPECT and REG WALK SPECT (ie, REG combined with low-level exercise). In this study, no major adverse events (AEs) occurring immediately after testing were reported, and aminophylline use was more commonly reported with REG SPECT compared to REG WALK SPECT (11.4% vs 5.6%; $P = 0.001$).

Less is known, however, about the immediate and downstream effects of REG SPECT in real-world practice, including the effects on treatment decisions, and how certain baseline patient clinical and demographic characteristics impact these effects. Although revascularization has shown survival benefits for patients with moderate to severe ischemia per SPECT [17], several studies conducted over the past decade have demonstrated that patients with stable coronary disease can be effectively managed with optimized medical management [18, 19]. Describing the daily clinical use of REG SPECT in a larger unselected patient population with regard to patient characteristics and the downstream effects on patient management (eg, revascularization vs medical management) may provide valuable insight to clinicians considering REG SPECT for their patients. Consequently, the purpose of this study was to gain a better understanding of the immediate and downstream outcomes of REG SPECT stress testing with and without low-level exercise according to baseline patient characteristics among an unselected real-world population of varying ages and races/ethnicities and with various comorbidities and/or receiving concomitant medications.

Materials and methods

Study design

This was a retrospective, secondary analysis of data obtained from the Henry Ford Hospital (HFH) REG SPECT registry, a registry containing patient demographics, characteristics, stress test and SPECT variables, and outcomes obtained from unselected patients who underwent REG SPECT. Patient records, nuclear cardiology reports, and information from electronic medical records were manually extracted to further populate the database for this study, containing deidentified patient-level data on clinical and demographic characteristics and patient outcomes. Per our lab protocol, standardized semiquantitative SPECT perfusion interpretation was used; study results were classified as normal (summed stress score [SSS] = 0), probably normal (SSS 1–3 and summed difference score [SDS] < 2), and abnormal (SSS ≥ 4 and SDS ≥ 2). Furthermore, SSS was categorized as mildly (4–7), moderately (8–12), and severely (≥ 13) abnormal; and SDS as mild (2–4), moderate (5–7), and severe (> 7) ischemia. Abnormal study results also considered were low ejection fraction (< 50%) and ischemic electrocardiographic responses with pharmacologic stress. All program software scoring was reviewed by the SPECT reader and adjusted, as needed. All studies were read by certified nuclear cardiologists or nuclear medicine physicians integrating clinical and SPECT data into a final impression. All semiquantitative scoring by the program was reviewed and adjusted routinely by the readers prior to final reporting.

The primary objective of this study was to describe the clinical and demographic characteristics of the patient population who have undergone SPECT-MPI using adjunct low-level exercise (REG WALK) or REG alone (REG only) or who have converted from an inadequate exercise test (REG CONVERT). The secondary objectives included (1) assessing healthcare resource utilization and clinical outcomes in the overall population and within racial and ethnic subgroups (African American, Caucasian, Hispanic, and non-Hispanic patients), and (2) to determine patient characteristics associated with downstream outcomes (eg, cardiac and non-cardiac death, myocardial infarction [MI], heart failure) in the overall REG-SPECT population and in specific subgroups (ie, patients with asthma, chronic obstructive pulmonary disease, end-stage renal disease on dialysis, obesity, severe left ventricular dysfunction, left bundle branch block/paced rhythm, history of stroke and seizures) over a 90-day period following SPECT. Exploratory outcomes included describing immediate clinical events and use of aminophylline for AEs in the overall population and within racial and ethnic subgroups (African American, Caucasian, Hispanic, and non-Hispanic patients). Medical management decisions were evaluated as addition of cardiac specific medications in the time period of 90 days post SPECT (antiplatelets, beta blockers, calcium channel blockers, nitrates and statins).

Selection of the study population

Patients aged ≥ 18 years who underwent REG-facilitated SPECT testing at HFH (January 2009–August 2012) were identified. Exclusion criteria were limited to research protocol participation (in HFH research trials of SPECT) and pregnancy. At HFH, trained stress lab nurses or cardiac diagnostic technicians assess all patients regarding their ability to perform adjunctive low-level exercise as part of REG SPECT by asking directed questions regarding ability to perform daily activities. If it is determined that the patient is unable to exercise based on physical limitations or refusal, they are offered REG SPECT alone. Other exclusions for REG WALK included those with left bundle branch blocked or paced rhythm. Those deemed appropriate for REG WALK and able to exercise then perform adjunctive low-level exercise for 1.5 min on Stage 1 of the modified Bruce protocol followed by REG and saline flush with continued exercise for another 2 min (Fig. 1).

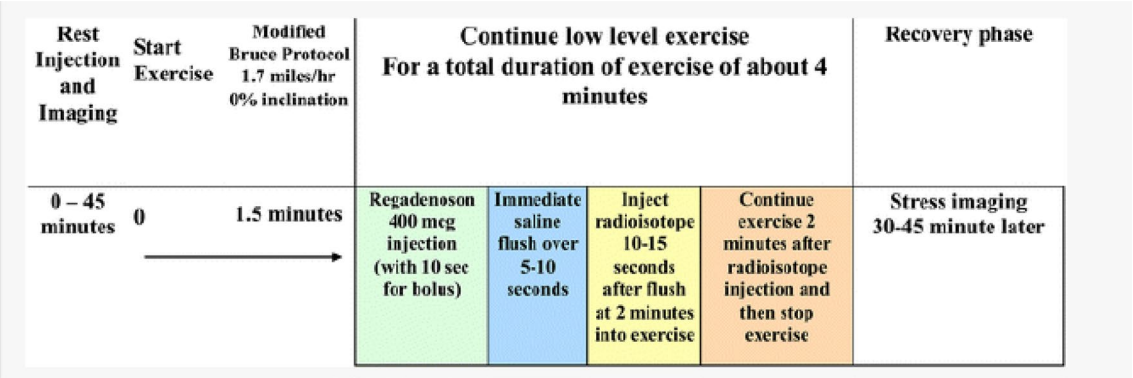

Fig. 1 REG WALK Protocol. *mcg* microgram, *REG* regadenoson

Analysis

A total of 2104 patients undergoing REG-facilitated SPECT in the specified time period were included in this analysis. Categorical variables were compared between groups using chi-square tests, while continuous variables were compared using independent 2-group *t*-tests. In the case of pairwise comparisons, a Benjamini–Hochberg correction was applied, and the adjusted *P*-value was reported. Analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA), with statistical significance set at $P < 0.05$.

Results

Patient characteristics

A total of 2126 patients met the eligibility criteria. For the analyses, 22 patients (1%) undergoing REG CONVERT were excluded, owing to the low patient numbers, and are not discussed further herein. Patient characteristics at the time of index SPECT testing and proportion of patients with a normal, mildly abnormal, and moderate to severe SSS and normal, mildly abnormal, moderately abnormal, and severely abnormal SDS are summarized in Table 1. The primary indications of SPECT included evaluating patients presenting with chest pain or equivalent symptoms for CAD, screening for preoperative evaluations, screening for CAD in high-risk asymptomatic patients, and screening for other miscellaneous causes. Overall, for the 2104 patients included in the analysis, mean age was 65.3 years, with women and African Americans comprising 50% and 51% of the sample, respectively (43% were Caucasian). Significant differences between the REG only (n = 1318) and REG WALK (n = 786) cohorts with respect to age, sex, ethnic group, and points of origin, but not race, were observed. The REG only cohort had a significantly higher rate of diabetes and most other cardiopulmonary comorbidities, and the majority of all patients (60–67%) were receiving at least 3 of the most commonly used cardiac medications, namely aspirin, statins, or beta blockers. Comorbidities according to race are summarized in Table 2. For the REG only (n = 1318) and REG WALK (n = 786) cohorts, SPECT was abnormal in 37% of patients (REG only, 39%; REG WALK, 34%; $P < 0.01$). The overall burden of severe ischemia (defined as SDS > 7) was low, at 4.8% in the entire study population. Eighty-seven percent of the entire study group had no to mild ischemia (SDS 0–4), with only 19% of patients having clinically significant ischemia (SDS ≥ 2; n = 394).

Safety

Overall, 43% of patients undergoing REG SPECT had arrhythmias, with similar rates occurring in the REG only and REG WALK cohorts (45.1% [595/1318] and 40.6% [319/786] respectively; $P = 0.123$). Premature atrial contraction/atrial premature beats were reported in 8% of patients overall and 9% and 6% of patients undergoing REG only and REG WALK, respectively; premature ventricular contraction was reported in 25% of patients overall and 26% and 24% of patients after REG only and REG WALK, respectively. No significant bradyarrhythmias, tachyarrhythmias, atrial flutter, atrial fibrillation, or ventricular tachycardia requiring immediate intervention were documented.

The need for aminophylline and other immediate clinical events is summarized in Fig. 2. The significantly higher rates of aminophylline use and flushing in the REG only cohort could be secondary to lack of supplemental exercise, which is known to minimize side effects, and higher comorbidity rates relative to the REG WALK cohort. The use of adjunctive low-level exercise was associated with a lower incidence of flushing (Fig. 2). Immediate safety analysis showed no deaths within 48 h for both REG only and REG WALK SPECT.

Table 1 Patient demographics and clinical characteristics at index SPECT test and reported SPECT results categorized by SSS and SDS

Baseline characteristics, n (%)		All patients (n = 2104)	REG only (n = 1318)	REG WALK (n = 786)	*P*-value (REG only vs REG WALK)
Age, mean ± standard deviation		65.3 ± 12.5	67.7 ± 12.3	61.2 ± 11.9	< 0.001
Male		1055 (50%)	591 (45%)	464 (59%)	< 0.001
Female		1049 (50%)	727 (55%)	322 (41%)	< 0.001
Caucasian		846 (43%)	532 (43%)	314 (43%)	0.989
African American		988 (51%)	618 (50%)	370 (51%)	0.989
Other		121 (6%)	76 (6%)	45 (6%)	0.989
Hispanic/Latino		53 (3%)	24 (2%)	29 (4%)	< 0.001
Not Hispanic/Latino		1711 (92%)	1051 (92%)	660 (93%)	< 0.001
Other		89 (5%)	70 (6%)	19 (3%)	< 0.001
Point of service		1 (0%)	0 (0%)	1 (0%)	0.195
PPO		33 (2%)	16 (1%)	17 (2%)	0.090
HMO		77 (4%)	42 (3%)	35 (4%)	0.135
Commercial		282 (13%)	163 (12%)	119 (15%)	0.071
Medicare/Medicaid		1150 (55%)	821 (62%)	329 (42%)	< 0.001
Unknown/missing		616 (29%)	314 (24%)	302 (38%)	< 0.001
Outpatient		1440 (68%)	821 (62%)	619 (79%)	< 0.001
Inpatient		663 (32%)	497 (38%)	166 (21%)	< 0.001
Diabetes		918 (44%)	604 (46%)	314 (40%)	0.009
Chronic obstructive pulmonary disease		225 (11%)	185 (14%)	40 (5%)	< 0.001
Asthma		273 (13%)	182 (14%)	91 (12%)	0.144
Cerebrovascular accident		264 (13%)	201 (15%)	63 (8%)	< 0.001
Smoking		1118 (54%)	716 (55%)	402 (52%)	0.117
Hypercholesterolemia		1497 (71%)	946 (72%)	551 (70%)	0.412
Coronary artery disease		728 (35%)	494 (37%)	234 (30%)	< 0.001
Hypertension		1848 (88%)	1186 (90%)	662 (84%)	< 0.001
Myocardial infarction		569 (27%)	379 (29%)	190 (24%)	0.020
Ejection fraction < 50%		180 (20%)	134 (22%)	46 (15%)	0.009
Seizure		38 (2%)	25 (2%)	13 (2%)	0.682
End-stage renal disease		113 (11%)	55 (9%)	58 (14%)	0.020
Medications (yes)					
Antihypertensive		–	907 (69%)	502 (64%)	0.017
Antiplatelet		–	191 (15%)	90 (11%)	0.047
Aspirin		–	844 (64%)	472 (60%)	0.068
Beta blocker		–	861 (65%)	527 (67%)	0.433
Calcium channel blocker		–	428 (32%)	262 (33%)	0.655
Glucose lowering		–	511 (39%)	263 (33%)	0.014
Nitrate		–	312 (24%)	153 (20%)	0.026
Statin		–	875 (66%)	497 (63%)	0.139
Summed stress scores					
Normal (0–3)	–	1521 (75.6%)	–	–	
Mildly abnormal (4–7)	–	210 (10.4%)	–	–	
Moderate-severe (8–13)	–	282 (14.0)	–	–	
Missing	–	91	–	–	
Summed difference score					
Normal (< 2)	–	1624 (80.5%)	–	–	
Mildly abnormal (2–4)	–	196 (9.7%)	–	–	
Moderately abnormal (5–7)	–	102 (5.1%)	–	–	
Severely abnormal (> 7)	–	96 (4.8%)	–	–	
Missing	–	86	–	–	

HMO health maintenance organization, *PPS* preferred provider organization, *REG* regadenoson, *SDS* summed difference score, *SPECT* single-photon emission computed tomography, *SSS* summed stress score

Downstream effects

A significantly higher rate of medical management change was noted with REG only vs REG WALK ($P < 0.001$), but no differences in cardiac catheterizations or interventions in the 90 days after SPECT were observed between the REG only and REG WALK groups (Fig. 3, Fig. 2).

When stratified by SSS (0–3, 4–7, 8–13), we observed progressively higher rates of catheterization with worsening summed scores in both REG only and REG WALK groups ($P < 0.001$ between all stratums of SSS in both groups; Fig. 4A).

Also, with increasing ischemia burden (SDS ≥ 2), there were progressive increases in catheterization and percutaneous coronary intervention (PCI) rates in all patients ($P \leq 0.001$ for pairwise comparisons; Table 3) as well as in the REG only and REG WALK groups ($P < 0.001$ for all groups; Fig. 4B and C).

With regard to medical management decisions, REG SPECT significantly affected downstream management with worsening SSS and SDS. As shown in Fig. 5, there were progressive increases in medical management changes as the severity of abnormal scans increased in both the REG and REG WALK groups.

Table 2 Comorbidities stratified by race

Variable		Caucasians (n = 854)	African Americans (n = 997)	*P*-value
Comorbidities	Diabetes	347 (41%)	454 (46%)	0.032
	Chronic obstructive pulmonary disease	111 (13%)	99 (10%)	0.039
	Asthma	102 (12%)	145 (15%)	0.099
	Cerebrovascular accident	85 (10%)	156 (16%)	< 0.001
	Smoking	432 (51%)	573 (58%)	0.003
	Hypercholesterolemia	627 (73%)	676 (68%)	0.008
	Coronary artery disease	328 (38%)	302 (30%)	< 0.001
	Hypertension	713 (83%)	914 (92%)	< 0.001
	Myocardial infarction	226 (27%)	277 (28%)	0.519
	Ejection fraction < 50%	70 (18%)	86 (21%)	0.328
	Seizure	11 (1%)	24 (2%)	0.080
	End-stage renal disease	25 (5%)	72 (16%)	< 0.001

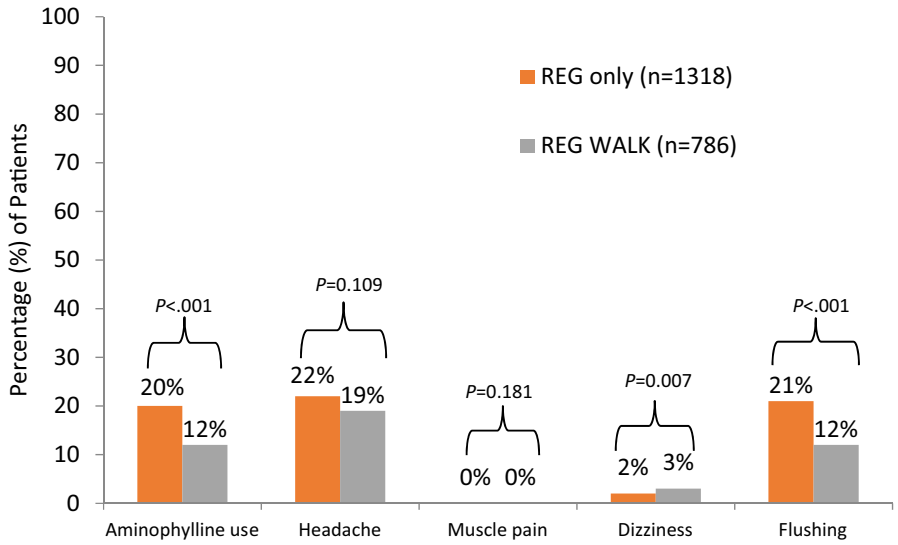

Fig. 2 Immediate clinical events. *REG* regadenoson

Discussion

The HFH REG registry is a large database containing data from an unselected real-world population who underwent REG SPECT. Our sample of > 2000 patients represent a broad, diverse, and unselected population that serves to both characterize the various combinations of demographic and clinical factors in patients undergoing REG SPECT and enable the evaluation of post-test experience and outcomes in a wide variety of patient subpopulations. Women, African Americans, and patients with a wide range of comorbidities were represented.

Overall, the important conclusions from our study were that (1) use of REG SPECT in a diverse population with multiple comorbidities is safe, with no serious immediate AEs and excellent survival; (2) the majority of the study population had minimal side effects, with REG WALK patients experiencing fewer side effects and less frequent use of aminophylline, supporting the addition of low-level adjunctive exercise when feasible; (3) REG SPECT results and the severity of abnormal scans and extent of ischemia appear to influence downstream decision making, including referral to catheterization and revascularization and medical management changes, although many patients with abnormal scans appear to also be managed medically.

Based on conclusions from post-hoc clinical trial analyses, it was anticipated that during real-world use, REG SPECT would be safely used regardless of patient age, gender, comorbidity, or concomitant medications. Using data from over 2000 participants in 2 randomized phase 3 clinical trials (ADVANCE MPI 1 and 2), REG was found to be safe and effective irrespective of patient age, gender, BMI, and the presence of comorbid diabetes, with improved tolerability over adenosine in all subgroups [20]. Clinical trials evaluating REG specifically in patients with comorbid asthma, chronic obstructive pulmonary disease, or chronic kidney disease collectively support its safety with no negative impact on pulmonary function [13, 14, 16, 21]. Other retrospective findings support safety and tolerability in the setting of pulmonary hypertension and cardiac transplantation [22, 23]. Limited real-world data are available on the impact of some characteristics, including sex, race, and ethnicity, on the outcomes of patients undergoing REG SPECT. One study sought to assess the impact of race and ethnicity on the efficacy and safety of REG using clinical trial data but was limited by the small sample sizes of several subgroups, including African Americans [12]. Regarding our study sample, half of the patients were female, and half were African Americans, thus providing a large subset to glean information from with regard to REG SPECT use in these patient subsets. Regarding the impact of race, we found that while baseline characteristics comorbidities were higher in African Americans vs Caucasians, abnormal SPECT findings were lower. While cardiac catheterization rates were similar between races, PCI rates were lower and medical management changes were higher in African Americans (Table 4).

Overall, the types and incidences of immediate clinical events and AEs were consistent with those expected based on randomized clinical trial experiences. The most common AEs reported here were headache and flushing, at 21% and 17%, respectively; corresponding incidences for REG in the combined analysis of the ADVANCE MPI 1 and 2 trials

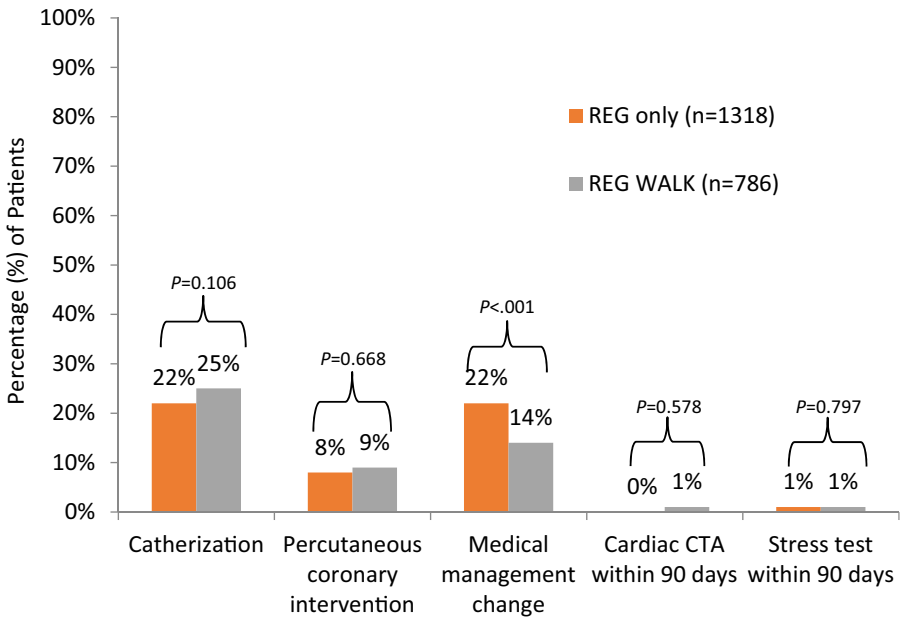

Fig. 3 Downstream effects (within 90 days of SPECT). *CTA* computed tomography angiogram, *REG* regadenoson

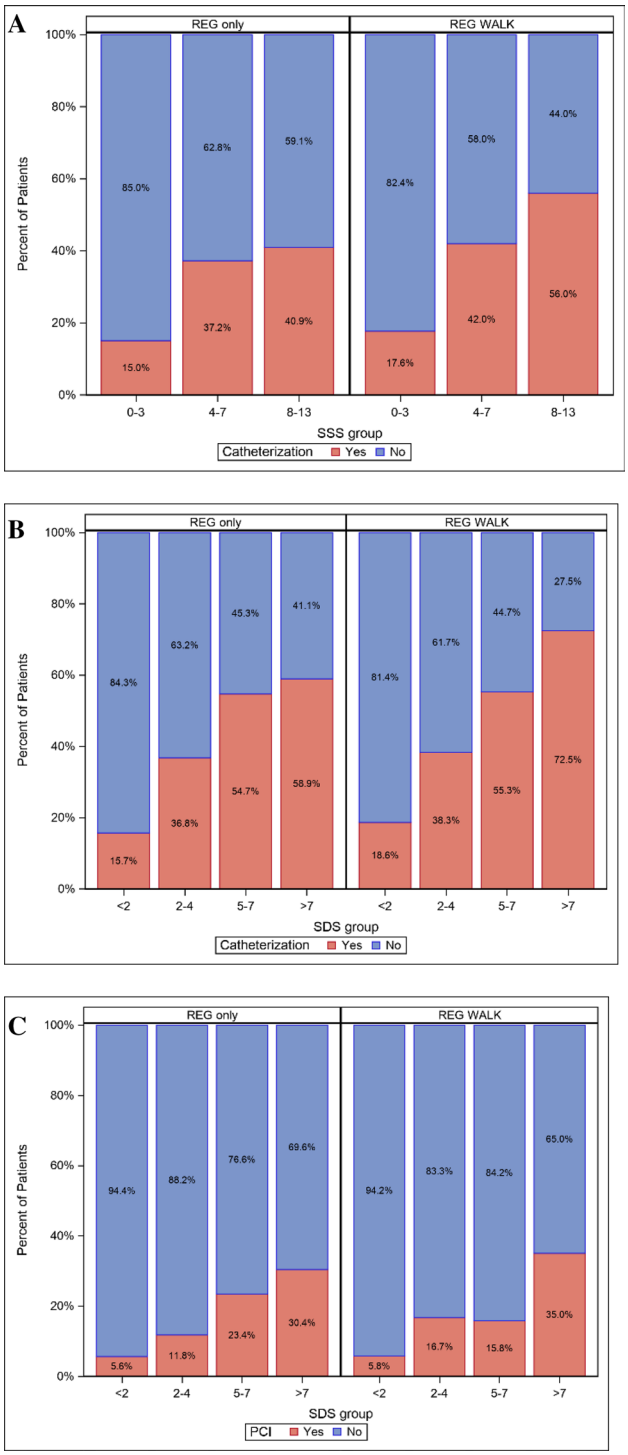

Fig. 4 Catheterization rates (within 90 days of SPECT) based on summed stress score (SSS; **A**) and summed difference score (SDS; **B**) and percutaneous coronary intervention rates (within 90 days of SPECT) based on SDS (**C**) in the REG and REG WALK groups. *PCI* percutaneous coronary intervention, *REG* regadenoson, *SDS* summed difference score, *SSS* summed stress score

were 26% and 22%, respectively [20]. Randomized trials with strict criteria for aminophylline use show lower rates of use [24]. The use of aminophylline was substantially higher in our registry, reflecting real-world differences. Many reasons may account for this finding. The data presented here were from the early years of REG use and hence our clinical team were more cautious and used aminophylline readily. With continued experience with REG, we have noticed a steady decline in aminophylline use, particularly over the subsequent years (2014–2017), to about 7% (unpublished data).

The results of this study also indicate that decisions on use of REG only or REG WALK are driven primarily by patient comorbidities and baseline characteristics, apart from patient limitations and preferences. Compared with the REG WALK cohort, the REG only cohort was older and was composed of a lower proportion of men and higher proportions of Medicare/Medicaid recipients and patients initiating care in an inpatient setting; additionally, those selected for REG only had higher comorbidity rates (Table 1). This reflects the known association of higher PSA use in this group who are unable or unwilling to perform even low-level exercise. Additionally, we found that increasing volume of abnormal scans resulted in progressively higher rates of catheterization and PCI; however, not all patients with abnormal scans underwent invasive workup. This may reflect increasing physician comfort level with initial medical management, which is the current trend for management of stable coronary disease. Since the publication of the COURAGE trial in 2007, there has been an increased focus on optimal medical therapy and an improved comfort level of physicians to use medical treatment as first-line therapy in stable CAD, reserving invasive procedures for those with abnormal tests and symptoms despite pharmacologic treatment [18, 25].

Typically, the decision to proceed with invasive workup depends on various factors, such as patient risk, presence or absence of symptoms, and preferences of the patient and/or referring physician. The relatively low frequency of referral of patients with abnormal SPECT to cardiac catheterization has been previously reported in the SPARC multicenter registry study evaluating multiple noninvasive diagnostic modalities, including SPECT positron emission tomography and computed tomography angiogram [26–31]. Even in patients with moderate to severe SPECT abnormalities, < 50% of patients in the SPARC registry were referred to cardiac catheterization. Additionally, use of medications following an abnormal scan even in these high-risk groups in SPARC were suboptimal, with 20% to 25% of patients not taking aspirin and statins and > 40% of patients not taking a beta blocker. Similar results were observed in our study, with < 50% of patients receiving a change in medication after abnormal SPECT (Table 4). Furthermore, our study showed that although medication changes occurred more

Table 3 Cardiac catheterization and percutaneous coronary interventions stratified by SPECT results

SDS	Catheterization (N = 464)	Percutaneous coronary intervention (N = 170)
Normal[a]	273 (16.8%)	92 (5.7%)
Mildly abnormal[b]	73 (37.2%)	26 (13.3%)
Moderately abnormal[c]	56 (54.9%)	21 (20.6%)
Severely abnormal[d]	62 (64.6%)	31 (32.3%)
Pairwise comparison	Adjusted *P*-value	Adjusted *P*-value
Normal vs mildly abnormal	< 0.001	< 0.001
Normal vs moderately abnormal	< 0.001	< 0.001
Normal vs severely abnormal	< 0.001	< 0.001
Mildly abnormal vs moderately abnormal	0.007	0.100
Mildly abnormal vs severely abnormal	< 0.001	< 0.001
Moderately abnormal vs severely abnormal	0.165	0.100

SDS summed difference score, *SPECT* single-photon emission computed tomography

[a]Score: 0–3

[b]Score: 4–7

[c]Score: 5–7

[d]Score: > 7

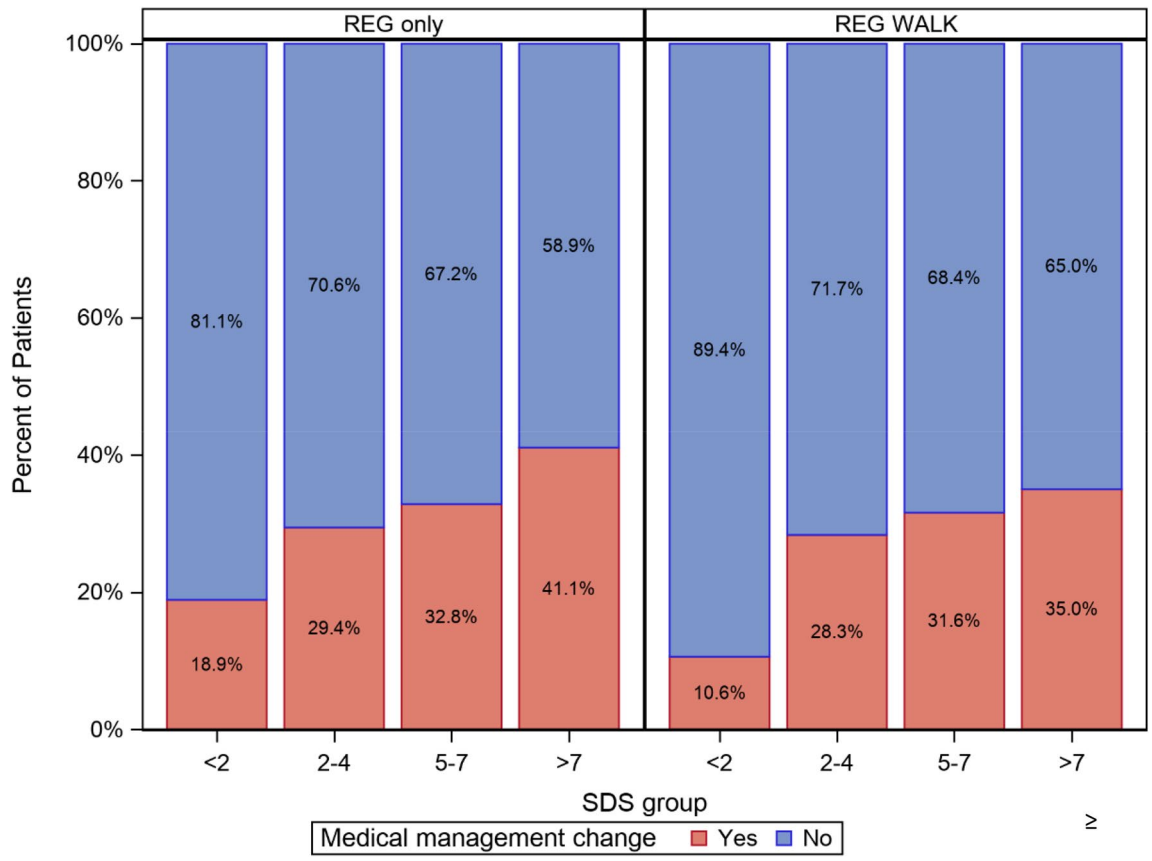

Fig. 5 Medical management changes (within 90 days of SPECT) by burden of ischemia in the REG and REG WALK groups. *REG* regadenoson, *SDS* summed difference score

Table 4 Downstream effects stratified by race

Variable		Caucasians (n = 854)	African Americans (n = 997)	*P*-value
Downstream effects	Catheterization	203 (24%)	215 (22%)	0.258
	Percutaneous coronary intervention	87 (10%)	62 (6%)	0.002
	Medical management change	134 (16%)	222 (22%)	< .001
	Cardiac CTA within 90 days	2 (0%)	7 (1%)	0.149
	Stress test within 90 days	9 (1%)	12 (1%)	0.762

CTA computed tomography angiogram

frequently as the burden of ischemia increased, this practice was not consistently observed in all patients with ischemia.

Another notable finding in our registry is the large number of patients with normal or near-normal SPECT scans. As has been shown in recent studies, the declining burden of SPECT-detected ischemia is a national trend [25, 32]. There are several potential reasons for this finding, including the testing of lower-risk populations or declining ischemia detection due to aggressive use of primary and secondary prevention strategies for reducing cardiovascular risk, as shown by high baseline use of cardioprotective medications in our registry [26]. Likewise, there was a progressive increase in catheterization referrals and revascularization with worsening SSS or SDS, yet not all patients with moderate to severe ischemia were referred for catheterization (24% in REG and 25% in REG WALK), similar to prior studies [25–27]. However, a combined 54% of patients with normal and mildly abnormal scans underwent invasive workup, with 19% of this combined group undergoing PCI (Table 3). Although this represents a substantial number of catheterization procedures in low risk SPECT, these data represent real world practice predating contemporary studies such as ISCHEMIA [33] which showed that initial medical management in stable CAD works as well as invasive workup. Currently, with the advances in cardiac CT and its diagnostic accuracy, many such low risk scans get clarified with CTA rather than catheterization and may not require further diagnostic workup. Thus, our data represent a timeline where catheterization was primarily used rather than CT accounting for this observation.

Although our study was not designed to identify the exact reasons for referral and non-referral for invasive testing, based on findings in the COURAGE trial, the growing confidence in medical management of these patients, as previously discussed, may be a generalizable finding. These findings have recently been reinforced by the outcomes of the ISCHEMIA trial. The ISCHEMIA study demonstrated that initial medical therapy was equivalent to invasive and interventional evaluation in patients without significant left main disease and moderate to severe ischemia [33].

Our retrospective registry has several limitations. These include those inherent to non-interventional studies using only secondary data collection conducted outside of a prospective clinical trial, for which variability in the quality of the clinical assessments and event reporting is expected. Furthermore, management decisions (medical and invasive referrals) cannot be accounted for, and missing or inaccurate data are inherent to any retrospective database. At the same time, however, we believe that providing a real-world unselected population undergoing pharmacologic SPECT and its influence on management helps to reflect how clinicians are utilizing available evidence in clinical practice. We acknowledge that the timeline of our study predates contemporary data from studies like ISCHEMIA, but it is important to note that the ISHCHEMIA trial was started many years ago (2012) and took over 8 years to complete, reflecting practice evolution over many years in a rigorous randomized approach, which may not always reflect real life practice.

REG SPECT is overall well tolerated and shows excellent short-term safety in real-world patient populations, regardless of gender, in patients with numerous comorbidities (including those with respiratory diseases), with no immediate safety concerns or major arrhythmic side effects. Routine use of low-level exercise along with REG SPECT allows for reductions in side effects and in the need for aminophylline. The incidence of ischemia detection in patients tested for suspected CAD is declining in the current era of aggressive medical management. However, REG SPECT guides downstream decision making with respect to catheterization and PCI as well as medical management changes based on test abnormality, suggesting that SPECT still serves as an effective gatekeeper in patient care. Higher use of cardiac medications with continued medical management and referral for invasive workup only for patients with very abnormal SPECT results reflects the current real-world practice management trends for stable CAD.

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Declarations

Conflict of interest Rita M. Kristy and James R. Spalding are employees of Astellas Pharma Global Development Inc. (Northbrook, IL). Therese M. Kitt and Yanqing Xu were employees of Astellas Pharma Global Development Inc. at the time the study was conducted; both remained involved in the development of this manuscript after departing. Meredith Van Harn is an employee of Henry Ford Hospital within the Department of Public Health (Detroit, MI). Karthikeyan Ananthasubramaniam and Matthew Saval are employees of Henry Ford Hospital (Detroit, MI). Karthikeyan Ananthasubramaniam received research grants from Astellas Pharma and is on the advisory panel of Astellas Pharma. Pertaining to this study, this was an investigator-initiated, industry-supported registry, and K. Ananthasubramaniam assumes full responsibility and oversight of study results and manuscript content.

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