The International Journal of Cardiovascular Imaging (2022) 38:195–209
https://doi.org/10.1007/s10554-021-02363-4

ORIGINAL PAPER

Safety and tolerability of regadenoson in comparison with adenosine stress cardiovascular magnetic resonance: Data from a multicentre prospective registry

Jose V. Monmeneu Menadas[1] · Maria P. García Gonzalez[1] · Maria P. Lopez-Lereu[1] · Laura Higueras Ortega[1] · Alicia M. Maceira Gonzalez[1]

Received: 3 March 2021 / Accepted: 20 July 2021 / Published online: 31 July 2021

Abstract

To assess the feasibility and incidence of immediate complications of stress cardiovascular magnetic resonance (CMR) with regadenoson in comparison with adenosine in a large referral population. This is a large, multicenter, prospective registry of vasodilator stress-CMR in a referral population. We recorded the clinical and demographic data, quality of test, CMR findings, hemodynamic data, and complications. Between January 2016 and July 2019, 2908 patients underwent stress-CMR, 2253 with regadenoson and 655 with adenosine. 25.1% of patients had previously known coronary artery disease (CAD). In 305 patients regadenoson was used due to presence of chronic obstructive pulmonary disease (COPD) or asthma, while in 1948 subjects regadenoson was used as first-line vasodilator. Quality was optimal in 90.0%, suboptimal in 9.5%, and poor in 0.5%. Images were diagnostic in 98.9%. After stress with regadenoson, aminophylline 200 mg was administered intravenously in all patients. No patient died or had severe immediate complications with regadenoson as opposed to 2 severe bronchospasm with adenosine ($p = 0.05$). 11 patients (0.5%) had non-severe complications with regadenoson and five patients (0.8%) with adenosine (p = n.s.). Only two patients (0.088%) had non-severe bronchospasm after regadenoson administration. All complications were solved in the CMR unit, with no need for further specific care. Factors significantly associated with presence of complications were history of COPD or asthma and detection of inducible ischaemia. Patients had significantly more minor symptoms when adenosine was used (66.0% vs. 18.4%, $p < 0.0001$). Stress-CMR with regadenoson is feasible, providing diagnostic information in a referral population. Regadenoson had an excellent safety profile and better tolerability than adenosine, with no serious immediate complications and low incidence of non-severe complications. Only inducible ischaemia and previous history of COPD or asthma were associated with complications after regadenoson-CMR. The incidence of minor symptoms was low.

Keywords Cardiovascular magnetic resonance · Regadenoson · Feasibility · Registry · Safety

Background

Currently, non-invasive cardiac imaging tests are first-line diagnostic tools in symptomatic patients with known or suspected ischaemic heart disease [1]. Vasodilator stress cardiovascular magnetic resonance (CMR) has shown high diagnostic accuracy for detection of myocardial ischaemia and in the prognostic evaluation of these patients [2–6]. Vasodilators such as adenosine, which has a direct action on adenosine receptors, and dipyridamole, an inhibitor of the cellular reuptake of adenosine, have been used. More recently, regadenoson has been approved for this purpose [7]. Regadenoson has several advantages over other vasodilators, it is administered intravenously as a single dose, with no need for dose adjustment with respect to weight, administration is done in 10 s, thus saving time compared to other stressors, and it is a selective agonist of A_{2A} receptors. This is particularly important in patients with asthma or chronic obstructive pulmonary disease (COPD), in which adenosine and dipyridamole are contraindicated or must be used with caution [8, 9].

✉ Jose V. Monmeneu Menadas
jmonmeneu@eresa.com

[1] Cardiovascular Unit, ASCIRES Biomedical Group, C/ Marqués de San Juan, 6, 46015 Valencia, Spain

Regadenoson safety has been evaluated in nuclear stress studies, with favorable results compared to adenosine [10–12], and also in stress-CMR [13–15]. Thus, the aim of this study was to provide additional insight into the feasibility and safety of regadenoson stress-CMR in comparison with adenosine in a large referral population.

Methods

Study population

Between January 2016 and July 2019, a total of 6184 consecutive patients from 13 hospitals and 7 outpatient clinics within the Valencian Community area in Spain, were scanned with CMR. Of them, 2970 subjects were referred to stress-CMR with a clinical indication. Regadenoson was initially used only in patients with COPD or asthma of any degree of severity in which adenosine was contraindicated. Later, in several hospitals, its use was approved in all patients as a first-line vasodilator. Thus, finally 2285 subjects were scheduled for regadenoson and 685 for adenosine stress-CMR. Interestingly, 99.5% of stress-CMRs were performed in a hospital environment (four University Hospitals and three Community Hospitals) and only 0.5% in an outpatient CMR unit. All scans were performed on 1.5 T scanners (Sonata, Avanto, Symphony and Aera, Siemens, Erlangen, Germany; Signa HDxt, GE Healthcare, Waukesha, Wisconsin, US). All the CMR scans were performed and interpreted by five cardiologists with average 11 years of experience in stress-CMR. All the CMR units had adequate equipment, drugs, including bronchodilator therapy, and resuscitative measures to treat any potential stress-related cardiovascular complications.

Study protocol

The indications, contraindications, diagnostic criteria regarding test results, and reasons for termination of the tests were in accordance with the current recommendations [16]. All patients were required to be clinically stable for the scan to be performed. Absolute contraindications for regadenoson and adenosine stress testing included: (1) second or third-degree atrioventricular block or sinus node dysfunction without a functioning pacemaker, (2) known hypersensitivity (allergy) to adenosine or regadenoson, and (3) systolic blood pressure less than 90 mmHg. Importantly, there was no restriction for regadenoson stress in patients with moderate or severe bronchoconstrictive lung disease such as asthma or COPD.

Patients were previously instructed to avoid caffeine, theophylline and dipyridamole at least 24 h before the CMR scan. A resting 12 lead electrocardiogram was performed outside the scan room immediately before the CMR study in all cases. Heart rate (HR) and blood pressure (BP) were continuously monitored and a patient intercommunication system was available throughout the scan.

The CMR protocol included: (a) Rest study with acquisition of black blood HASTE sequences and steady-state free precession (SSFP) cine sequences in the usual views for quantification of ventricular dimensions and function. (b) Stress study which included administration of intravenous regadenoson (Rapiscan®, GE Healthcare Bio-Sciences, S.A, Madrid, Spain) at a fixed dose of 400 µg in 10 s, or adenosine (Adenocor®, Sanofi-Aventis S.A, Barcelona, Spain) at a dose of 140 µg/kg body weight/min, (with increase up to 210 µg/kg body weight/min if after 2–3 min HR does not increase by 10 bpm and or BP does not drop by > 10 mmHg) followed 60–90 s later by infusion of 0.15 mmol/kg gadoteric acid (Dotarem®, Guerbet, France) at a flow of 5 mL/s during simultaneous acquisition of first pass saturation-recovery sequences in one long-axis and three ventricular short-axis views. Images were sampled every RR in most cases and only if the fast HR avoids it, they were sampled every second RR. In all the sites the myocardial perfusion sequence was similar, with TR = 135–160 ms, TE = 1 ms, flip angle = 12 degree; acceleration factor = 2; voxel size $\leq 2.8 \times 2.2$ mm; slice thickness 8 mm and receiver bandwidth 790 Hz/pixel. This was followed by acquisition of stress cine sequences in two long-axis and three ventricular short-axis views. Finally, aminophylline 200 mg was administered intravenously if regadenoson was used. We did this to accelerate the disappearance of symptoms and promote rapid recovery of heart rate before acquiring late gadolinium enhancement (LGE) images and rest perfusion if necessary. (c) Segmented inversion recovery SSFP sequences were acquired at least 10 min after gadolinium injection, for detection of myocardial LGE. (d) Whenever considered necessary, rest perfusion sequences were acquired to rule out artifacts in stress perfusion images. Reasons for termination of the stress test were: presence of severe symptoms or side effects, technical reasons and patient refusal. Subsequently, the images were visualized and studies with artifacts or poor image quality that prevented adequate image analysis were excluded from the analysis.

Ventricular dimensions and function were eventually quantified with the Simpson´s method (Medis, The Netherlands). Stress myocardial perfusion, regional contractility and LGE were assessed by visual analysis.

Study variables

Relevant clinical and demographic data were prospectively collected in a database along with previous stress tests undergone, need for pharmacologic sedation, history of kidney failure. Variables obtained from the CMR scan included cardiac rhythm, left (LV) and right ventricular (RV) dimensions and function, presence and extent of myocardial ischemia, necrosis, and focal fibrosis, type of contrast used and contrast dose. A perfusion defect was considered ischaemic if ≥ 2 consecutive segments in at least three consecutive phases were affected, as previously described [17]. Inducible wall motion abnormalities are considered as a criterion of severity in cases with perfusion defects, not for diagnosis of ischaemia. HR and BP were measured at baseline, peak of stress, and then monitored every 2 min until the end of the test [18]. The increase in HR during stress was calculated as a percentage ([Peak stress HR−Resting HR/Resting HR] × 100). The change in BP was calculated accordingly.

In order to classify complications, we have established the severity criteria based on the absence of improvement in the CMR unit and the need for hospitalization. Thus, we considered severe complications death, myocardial infarction, unstable angina, severe or persistent arrhythmias or arrhythmias requiring continuous monitoring, second degree atrioventricular block, significant dyspnoea or severe chest pain, severe bronchospasm requiring bronchodilators and hospital admission, and new hospital admissions by any other cause. Non-severe complications were defined as those moderate in intensity, responding to aminophylline or specific management in the CMR unit and not requiring hospital admission. We also recorded minor symptoms as those mild in intensity, that disappeared immediately or shortly after administration of aminophylline.

After completing the study, we performed a subjective assessment of the overall quality of the study. Studies of optimal quality were those without artefacts of any type and in which contractility, first-pass perfusion, and LGE could be analyzed reliably. Studies with some artefact that did not prevent a correct interpretation of images were considered of suboptimal quality. Finally, those with artefacts that prevented reliable interpretation of images were considered of poor quality. Likewise, stress test was considered non diagnostic only when the image quality was poor.

Statistical analysis

Statistical analyses were carried out with SPSS 17 for windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were presented as absolute values and percentages. Continuous variables were expressed as mean ± standard deviation and categorical variables as proportions. Two-tailed unpaired Student's *T*-test was used for intergroup comparisons and χ^2 test for comparisons of proportions. A p value < 0.05 was considered statistically significant.

Results

Feasibility and baseline characteristics

Between January 2016 and July 2019, consecutive patients were selected to perform stress-CMR (Fig. 1). Finally, regadenoson stress-CMR was performed in 2253 patients (98.6% of requested) and adenosine stress-CMR in 655 patients (97.5% of requested). Importantly, 1948 patients (86.5%) underwent regadenoson stress as first line vasodilator according to their hospital policy. The reasons have been mainly based on its ease of use and time savings. In the remaining 305 patients (13.5%) regadenoson was used since contraindication to adenosine was present due to COPD or asthma by clinical criteria. None of the patients referred to our unit reported a history of hypersensitivity to adenosine or regadenoson.

The clinical characteristics of the study population are shown in Table 1. It was a population with an intermediate prevalence of risk factors, in which approximately a quarter or a fifth of patients had a known coronary artery disease (CAD). There were no significant differences in the main clinical variables between the regadenoson and adenosine subgroups, except in the prevalence of COPD or asthma (logically). In 24.8% of patients, a previous exercise tolerance test was available that was non-conclusive in 465 (64%). Sinus rhythm was reported in 89.8% of patients. There were 31 patients (1.1%) who had one or more previous stress-CMR. Also, 32% of subjects were inpatients at the time of the study. Mild sedation was administered with midazolam (1–3 mg intravenous) in 123 patients (4.2%).

Study quality was optimal in 2612 cases (90.0%), suboptimal in 276 cases (9.5%), and poor in 20 cases (0.5%). Suboptimal or poor-quality studies were associated with older age of the patients (72 ± 10 vs. 67 ± 12 years, p < 0.0001), history of COPD or asthma (23.2 vs. 12.3%, p < 0.0001), history of heart failure (13.7 vs. 7.5%, P = 0.008), in-patients (39.1 vs. 28.8%, p = 0.025), presence of rhythm other than sinus (49.8 vs. 7.1%, P < 0.0001), lower LV ejection fraction (57 ± 15 vs. 63 ± 14%, p < 0.0001), lower RV ejection fraction (58 ± 12 vs. 63 ± 8%, p < 0.0001), and administration of midazolam (9.6 vs. 3.9%, p = 0.002). All these factors can be associated with each other and influence a worse performance of apneas by patients, e.g. patients with right ventricular systolic dysfunction were associated with a higher presence of COPD or asthma and worse LVEF. We must emphasize that, although in patients with non-sinus rhythm (most of them in atrial fibrillation) the quality of the studies was significantly worse, only in one case was not possible to obtain diagnostic

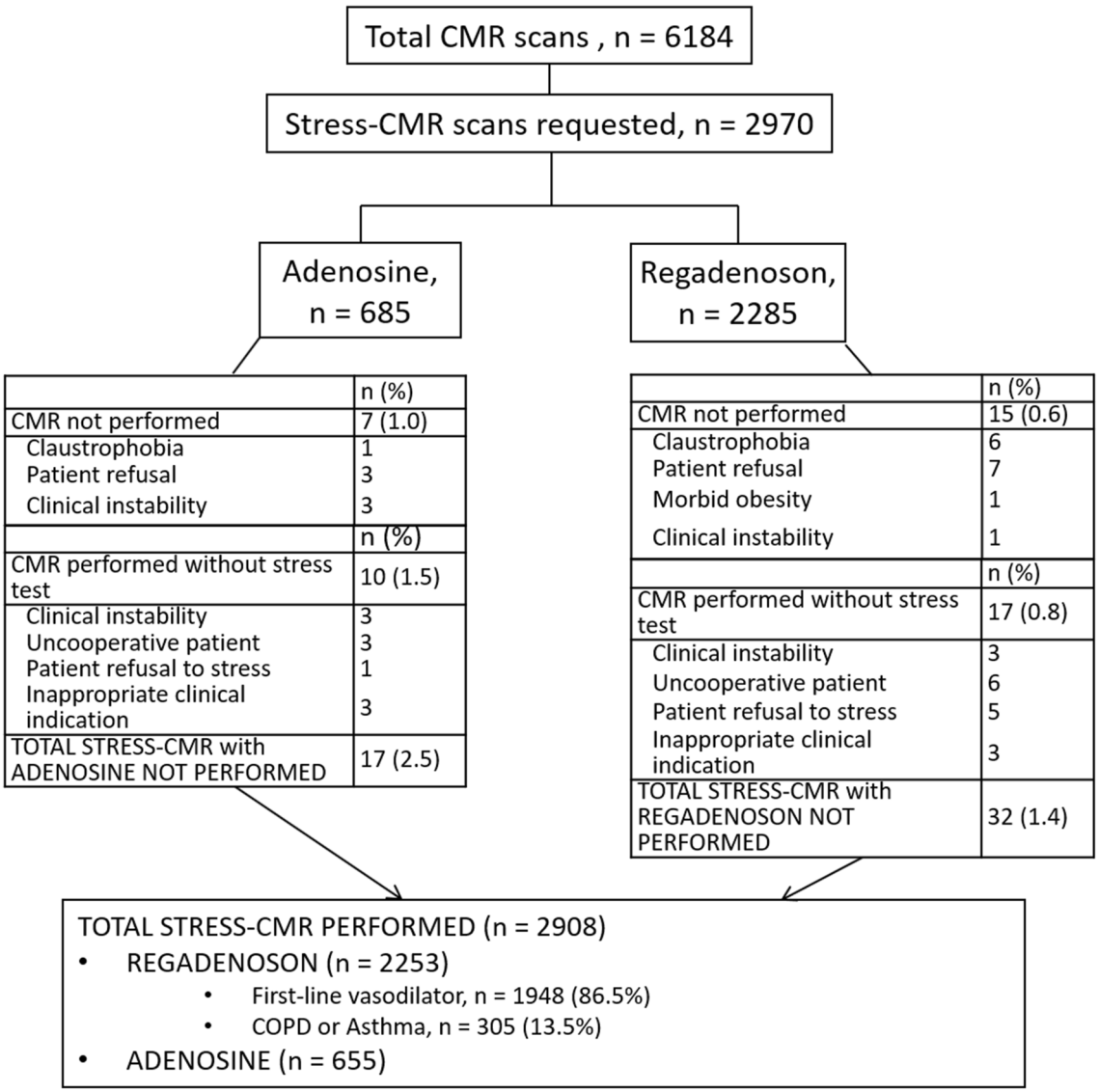


Fig. 1 Flow diagram showing patient selection for stress-CMR in this study. After excluding patients with general contraindications to CMR and with contraindications to pharmacologic stress we performed stress-CMR in 2908 patients

information about the function, presence of ischaemia or necrosis. There were no differences with respect to gender, vasodilator used, CMR unit in which the test was done or other stress-CMR parameters.

Stress-CMR data

Stress was performed in 2908 patients (97.9% of those requested). In a sample of 20 studies with each drug the average duration of the tests was 34 min with regadenoson compared to 42 min with adenosine. The stress tests provide diagnostic information in 2875 patients (98.9% of the tests performed). Table 2 shows the main findings of stress-CMR. Resting wall motion abnormalities were detected in 28.9% of the patients, inducible ischaemia was detected in 17.7% of cases and 25.4% had myocardial necrosis on LGE sequences. The subgroup of patients evaluated with adenosine had a slightly higher LV ejection fraction and a slightly higher percentage of ischaemia than the subgroup with regadenoson.

The haemodynamic response to regadenoson and adenosine was assessed (Fig. 2a and b). Resting HR and BP were similar between subgroups. Peak stress HR was higher with regadenoson than with adenosine (90 ± 15 vs. 86 ± 15, $p < 0.0001$). The subgroup of patients with atrial fibrillation ($n = 175$) had a higher baseline heart rate (77 vs. 66 bpm, $p < 0.0001$) and a lower systolic blood pressure at rest (137 vs. 141 mmHg, $p < 0.05$) as well as a lower HR increase than patients in sinus rhythm (19 vs. 23 bpm, $p < 0.0001$). These

Table 1 Clinical characteristics of the study population

	Regadenoson (n = 2253)	Adenosine (n = 655)	p
Age, years	67 ± 12	66 ± 12	< 0.001
Gender, male	1405/2253 (62.4)	426/655 (65.0)	n.s
Body surface area (m^2)	1.89 ± 0.2	1.90 ± 0.2	n.s
Body mass index (kg/m^2)	29.1 ± 4.7	29.2 ± 17.9	n.s
Abdominal perimeter (cm)	105 ± 30	102 ± 12	n.s
Type 2 diabetes mellitus	624/2253 (27.7)	188/655 (28.7)	n.s
Hypertension	1502/2253 (66.7)	420/655 (64.1)	n.s
Hypercholesterolemia	1246/2253 (55.3)	346/655 (52.8)	n.s
Smoking	345/2253 (15.3)	88/655 (13.4)	n.s
Ex-smoking	713/2253 (31.6)	144/655 (22)	< 0.0001
Family history of CAD	97/2253 (4.3)	16/655 (2.4)	0.016
Number of cardiovascular risk factors	1.8 ± 1.2	1.9 ± 1.3	0.04
Cocaine abuse	19/2253 (0.8)	2/655 (0.5)	n.s
Renal failure (eGFR 30–60 mL/min/1.73 cm^2)	59/2253 (2.6)	15/655 (2.3)	n.s
COPD or Asthma	305/2253 (13.5)	2/655 (0.3)	< 0.0001
Known CAD	583/2253 (25.9)	140/655 (21.3)	n.s
Q-Myocardial infarction	320/2253 (14.2)	114/655 (17.4)	
Non-Q-Myocardial infarction	266/2253 (11.8)	26/655 (4.0)	
Revascularisation. Stent	307/2253 (13.6)	80/655 (12.2)	
Revascularization. Bypass	96/2253 (4.3)	32/655 (4.9)	
History of heart failure	177/2253 (7.9)	55/655 (8.3)	n.s
Previous exercise test	542/2253 (24.1)	180/655 (27.4)	n.s
Previous SPECT	5/2253 (0.2)	2/655 (0.3)	n.s
Previous coronary angiography	583/2253 (25.9)	192/655 (29.3)	n.s
Cardiac rhythm			
Sinus rhythm	2021/2253 (89.7)	589/655 (89.9)	n.s
Complete LBBB	48/2253 (2.1)	12/655 (1.8)	n.s
AF-flutter	137/2253 (6.1)	38/655 (5.8)	n.s
PSVC	9/2253 (0.4)	3/655 (0.5)	n.s
PVC	33/2253 (1.5)	9/655 (1.4)	n.s
Pacemaker rhythm	4/2253 (0.2)	4/655 (0.6)	n.s

Values are mean ± SD or n (%)

AF atrial fibrillation; *CAD* coronary artery disease; *COPD* chronic obstructive pulmonary disease; *GFR* glomerular filtration rate; *LBBB* left bundle branch block; *n.s.* not significant; *PSVC* premature supraventricular complexes; *PVC* premature ventricular complexes; *SPECT* single-photon emission computed tomography

differences were similar in the group treated with regadenoson and in the adenosine group. In 37 patients there was a decrease in HR, less frequent with regadenoson than with adenosine (22 [1.1%] vs. 15 [2.3%], p = 0.03), but in no case was severe, with the maximum HR always being ≥ 44 bpm.

Safety

No patient died during the performance of the stress-CMR. Complications and minor symptoms after stress.CMR are shown in Fig. 3a and b. Two patients without previously known COPD or asthma had severe bronchospasm after adenosine (0.3%) while no severe immediate complications occurred after regadenoson, p = 0.05 (Table 3). Only 11 patients (0.5%) in the regadenoson subgroup and 5 (0.8%) in the adenosine subgroup had non-severe complications, p = n.s. All cases were resolved in the CMR unit with no need for further specific care. Tables 4 and 5 depicts the characteristics of the patients who had complications. Given the low number of complications, only a univariate analysis was performed, which showed that patients who presented complications had more prevalence of known COPD or asthma and ischaemia during the test (Fig. 4a) compared to the subgroup with no complications. There were only two cases of non-severe bronchospasm (0.088%) following the use of regadenoson, both with known COPD or asthma, which resolved in the CMR unit after administering inhaled beta-agonists and intravenous corticosteroids. We have

Table 2 CMR characteristics of the study population (n = 2908)

	Regadenoson (n = 2253)	Adenosine (n = 655)	p
LV end-diastolic volume (mL/m^2)	73.1 ± 27	71.2 ± 23	n.s
LV end-systolic volume (mL/m^2)	30.9 ± 24	26.6 ± 17	< 0.0001
LV ejection fraction (%)	61.3 ± 14	64.8 ± 12	< 0.0001
LV mass (g/m^2)	65.9 ± 20	63.9 ± 19	0.02
RV end-diastolic volume (mL/m^2)	64.0 ± 17	63.6 ± 18	n.s
RV end-systolic volume (mL/m^2)	24.3 ± 11	22.3 ± 9	< 0.0001
RV ejection fraction (mL/m^2)	62.6 ± 9	65.2 ± 8	< 0.0001
Abnormal wall motion at rest ≥ 1 segment	623 (27.7)	217 (33.1)	0.01
Inducible ischaemia ≥ 1 segment			0.03
Yes	373 (16.6)	136 (20.8)	
No	1869 (83.0)	518 (79)	
Equivocal	11 (0.5)	1 (0.2)	
Necrosis, ≥ 1 segment	569 (25.3)	170 (26.0)	n.s
Fibrosis, ≥ 1 segment	241 (10.7)	65 (10.1)	n.s

Values are mean ± SD or n (%)

LV left ventricular; *RV* right ventricular

analyzed separately, based on clinical history, the patients who received regadenoson with more severe reactive airway disease for being taking inhaled or oral corticosteroids or being on active treatment with bronchodilators in the last weeks (131/305–43%). There were not significant differences in the number of complications between patients with severe in comparison with less severe reactive airway disease (3/131 vs 3/174, p = ns). No patient presented high-grade atrioventricular block when regadenoson was used, compared to two patients who presented paroxysmal atrioventricular block after use of adenosine. The presence of inducible wall motion abnormalities in the patients with ischaemia were not associated with a higher rate of immediate complications. The resting HR, BP, haemodynamic response or presence of atrial fibrillation were not associated to presence of complications in the complete group nor according to the drug used.

Obese patients (body mass index, BMI > 30 kg/m^2, n = 1051) were shown to have no more complications than non-obese patients (BMI < 30 kg/m^2, n = 1803) (0.7% vs. 0.6%, p = ns). No other demographic, clinical, hemodynamic, and CMR-derived parameters including the presence of scar in LGE images were associated with the occurrence of immediate complications. Neither were any of the factors regarding CMR unit in which the study was performed, referral department, performing cardiologist, or patient type (inpatient vs. outpatient).

Chronic renal failure was present in 71 patients (2.4%), with glomerular filtration rate (GFR) figures between 30 and 60 mL/min. No complications occurred in these patients.

Gadolinium related non-severe adverse effects occurred in only 14 patients (0.5%), mostly nausea and vomiting and only three cutaneous allergic reactions (mild urticaria) that resolved using standardized treatment for allergic reactions.

Minor symptoms occurred in 847 patients (29.1%) and resolved in all cases after administration of aminophylline, self-limited dyspnoea being the most frequent with regadenoson and mild chest pain with adenosine (Table 6). Minor symptoms were more frequent with the use of adenosine and were associated with female sex, myocardial ischaemia in the stress-CMR and previous history of CAD (Fig. 4b). Although the presence of ischaemia was associated with a higher percentage of complications, most of the patients who had ischaemia did not present any complications. Figures 5 and 6 show two clinical examples of stress-CMR with adenosine and regadenoson.

Discussion

This multicentre prospective registry demonstrates the feasibility and safety of regadenoson in comparison to adenosine stress-CMR in a large referral population. This study confirms the safety of regadenoson in patients with reactive airway disease. Stress-CMR with regadenoson is easier and faster to perform than with other vasodilators or dobutamine since the dose is fixed and it does not require dose adjustment to patient´s weight, it is administered intravenously in 10 s, and there is no HR or BP target. Also, regadenoson is usually better tolerated by patients, allowing completion of the study with images of diagnostic quality in most patients. Actually, the percentage of diagnostic studies is higher with regadenoson than with other drugs [19, 20].

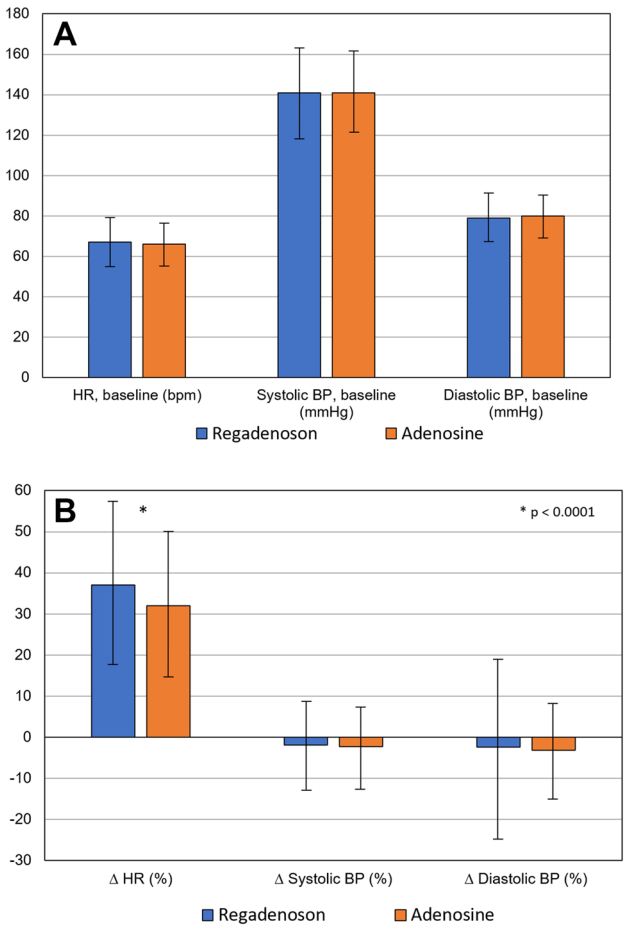


Fig. 2 Haemodynamic response with stress-CMR. **a** Absolute values of baseline heart rate (HR), systolic blood pressure (BP) and diastolic BP. **b** Percent changes in HR, systolic and diastolic BP with stress. Δ heart rate (%) = [(Peak stress heart rate − Resting heart rate)/Resting heart rate] × 100. Δ systolic blood pressure (%) = [(Peak stress systolic blood pressure − Resting systolic blood pressure)/Resting systolic blood pressure] × 100. Δ diastolic blood pressure (%) = [(Peak stress diastolic blood pressure − Resting diastolic blood pressure)/Resting diastolic blood pressure] × 100. Values reported are means. Error bars represent standard deviation

Vasodilator stress-CMR has been traditionally done with dipyridamole, which inhibits the reuptake of adenosine, and with adenosine, which binds non-selectively to receptors A_1, A_{2A}, A_{2B} and A_3. A_{2A} receptors are responsible for the vasodilation required in the stress study, while A_1, A_{2B} and A_3 receptors may be responsible for serious side effects such as high-grade atrioventricular block (A_1) or bronchospasm (A_{2B} and A_3), which prevent adenosine and dipyridamole to be used in patients with COPD or asthma [8, 9]. Adenosine stress requires two intravenous lines, often in different arms, one for adenosine and the other for contrast administration. In recent years, regadenoson has been approved for use in myocardial stress testing [7]. Regadenoson is a modification of the adenosine molecule that selectively stimulates A_{2A} receptors with a minimal effect on the other receptors, thus avoiding some side effects derived from the use of adenosine [11, 21]. This drug has the advantage of being administered in a single intravenous bolus of 400 µg without the need for adjustment by weight or renal function of the patient. The peak plasma concentration of regadenoson is achieved within 1 to 4 min after injection and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2 to 4 min. An intermediate phase follows, if aminophylline is not given, with an average half-life of 30 min coinciding with loss of the pharmacodynamic effect. The last phase consists of a decline in plasma concentration with a half-life of approximately 2 h. The vasodilator efficacy of regadenoson is similar to that of adenosine and superior to dipyridamole, as demonstrated by quantitative perfusion CMR [22]. Also, the fractional flow reserve (FFR) is similar between intravenous administration of regadenoson or adenosine [23, 24]. Regarding the hemodynamic response, regadenoson produces a significant increase in HR, greater than the one produced by adenosine, without significantly affecting BP [11, 12, 22]. The mechanism seems to be a direct sympathetic stimulation rather than a pure baroreflex response [25]. Cases of severe bradycardia and asystole attributable to the intense vagal stimulation caused by the common route of A_{2A} stimulation of the nucleus tractus solitary or hypothalamus have been described [26]. However, in our study, no patient presented this side effect.

Safety

The safety profile of stress-CMR has been demonstrated, with published data regarding adenosine [27], dipyridamole or dobutamine stress-CMR [19, 28]. Safety of regadenoson has been evaluated mainly in nuclear studies, with favorable results compared to adenosine [10–12, 29], though reports on regadenoson stress-CMR are scarce [15]. Thus, in a study of regadenoson CMR in 728 patients, a very low incidence of adverse effects with no deaths, one hospitalization for decompensation of heart failure and a single case of bronchospasm were reported, although there were only ten patients with COPD or asthma in the study population. In particular, the safety of this drug has been evaluated in patients with COPD or mild or moderate asthma in randomized, double-blind, placebo-controlled studies [30–32]. Likewise, a very low profile of complications has been demonstrated in patients with severe lung disease [33]. In our study, which included a significant proportion of patients (305, 13.5%) with COPD or asthma in the regadenoson subgroup, there were only two cases of non-severe bronchospasm registered, this supports the safety of regadenoson stress-CMR in patients with reactive airway disease. This is, in our opinion, an important aspect since this population

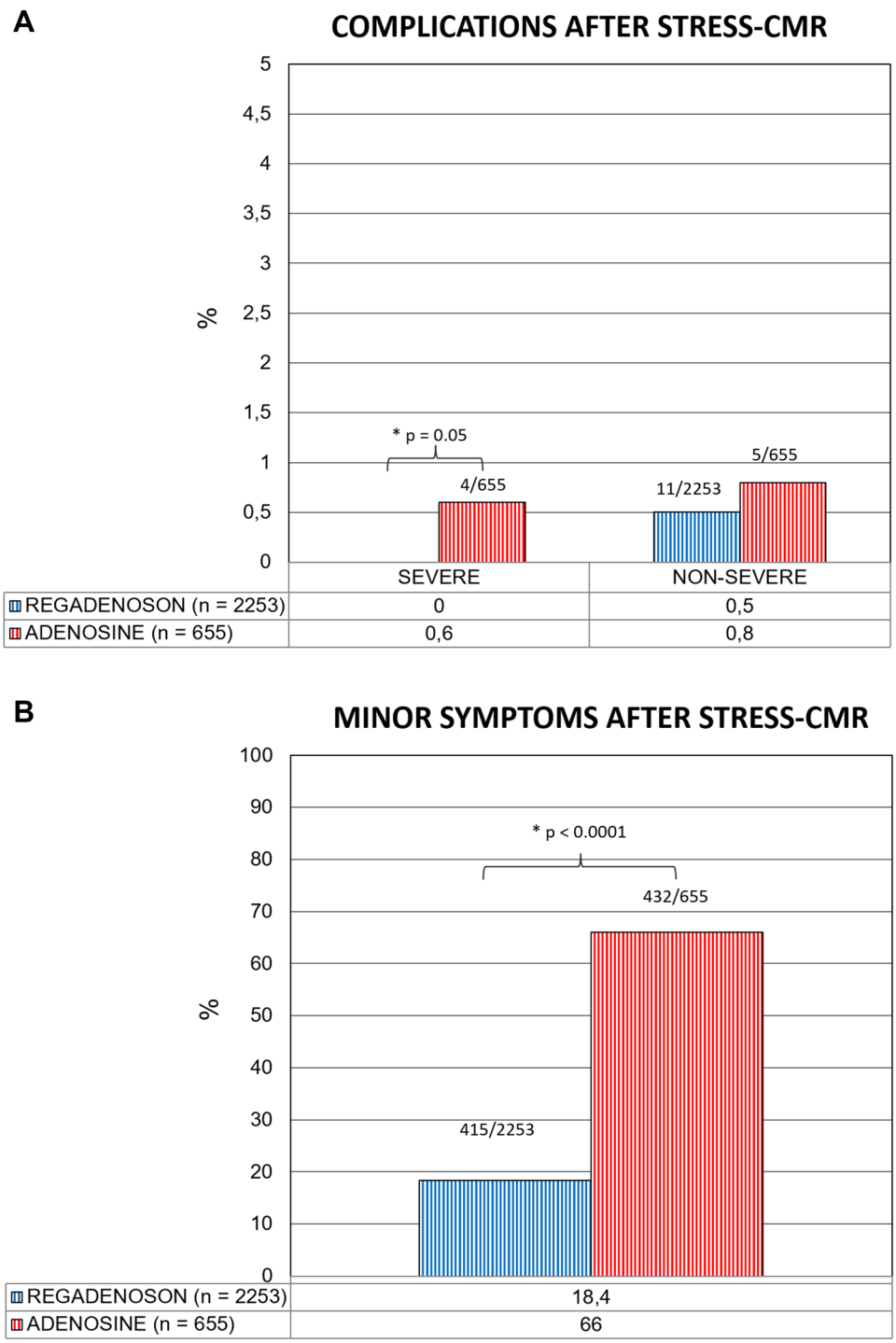


Fig. 3 Complications (**a**) and minor symptoms (**b**) during stress-CMR

has been routinely studied using dobutamine, which is significantly less clinically tolerated, as we have previously demonstrated [20]. The detection of ischaemia is associated with a greater number of complications, although this factor is of little use since we did not know it before performing the stress test. The presence of induced wall motion abnormalities is related to a worse prognosis and need to revascularization, as we previously demonstrated [5]. Although the presence of necrosis does not condition a greater number of immediate complications, it is an important factor since it has recently demonstrated its influence on prognosis, even in cases of unrecognized necrosis [34]. No differences were found in the presence of complications related to the presence of atrial fibrillation, which supports the safe use of regadenoson and adenosine in this patient population. Despite the limitation of ECG monitoring to

Table 3 Complications After Stress-CMR (n = 2908)

	Regadenoson (n = 2253)	Adenosine (n = 655)	p
Severe	–	2/655 (0.3)	0.05
Bronchospasm*	–	2 (0.3)	
Non-Severe	11/2253 (0.5)	5/655 (0.8)	n.s
Angina†	2 (0.1)	–	
Bronchospasm	2 (0.1)	2 (0.3)	
Hypotension‡	3 (0.1)	1 (0.2)	
Acute dispnoea	4 (0.2)	–	
Paroxysmal AV block	–	2 (0.3)	

Values are n (%)

*Requiring hospital admission

†Angina requiring specific treatment

‡Hypotension requiring specific treatment

Table 4 Complications After Regadenoson-CMR (n = 11/2253)

Patient	Complication	Age	Sex	Suspect drug	Concomitant diseases	Concomitant drugs
Non-severe						
1	Angina	73	Female	Regadenoson	Hypertension, Hyperlipidaemia, Smoking	Aminophylline, morfine clorure
2	Angina and Urticaria	51	Male	Regadenoson and Gadoteric acid	Hypertension, Hyperlipidaemia, COPD	Aminophylline, Dexchlorpheniramine, Methylprednisolone, Esmolol
3	Bronchospasm	74	Female	Regadenoson	Hypertension, Hyperlipidaemia, Diabetes, Paroxysmal AF, COPD	Aminophylline, Salbutamol
4	Bronchospasm	73	Male	Regadenoson	Hypertension, Hyperlipidaemia, Paroxysmal atrial fibrillation Asthma	Aminophylline, Ipratropium Hydrocortisone, Methylprednisolone
5	Hypotension	70	Male	Regadenoson	Hypertension, Hyperlipidaemia, Diabetes, Multivessel disease COPD	Aminophylline, Atropine
6	Hypotension	67	Female	Regadenoson	Hypertension, Hyperlipidaemia, LBBB, LV heart failure	Aminophylline, Intravenous fluids
7	Hypotension	50	Female	Regadenoson	–	Aminophylline, Intravenous fluids
8	Moderate dispnoea	64	Female	Regadenoson	Hypertension, Hyperlipidaemia, Smoking COPD	Aminophylline
9	Moderate dispnoea	75	Male	Regadenoson	Hyperlipidaemia, Diabetes Smoking	Aminophylline
10	Moderate dispnoea	69	Female	Regadenoson	Rheumatic mitral valvulopathy, AF, COPD	Aminophylline
11	Moderate dispnoea	75	Male	Regadenoson	Hypertension, Hyperlipidaemia, Myocardial infarction, LVEF depressed	Aminophylline

AF atrial fibrillation; *COPD* chronic obstructive pulmonary disease; *LBBB* left bundle branch block; *LV* left ventricular

detect advanced AV block in setting of CMR, we were able to obtain an adequate ECG recording during the test in the vast majority of patients. Thus, no patient in the regadenoson subgroup presented high-grade AV block (second or third degree), which shows that this complication is less frequent with regadenoson than with non-selective adenosine receptor agonists [35]. One of the concerns with the use of regadenoson is the intermediate phase of the stress agent, so we think that the use of aminophylline in all patients may have contributed to better tolerability, as described by Rangel et al. [36]. Likewise, no increased appearance of side effects has been demonstrated in patients with chronic kidney disease, as already described in nuclear tests [37], although this drug is eliminated in 57% unchanged by the renal route. Despite the elimination half-life of regadenoson is prolonged in chronic kidney disease, its maximal plasma concentration, severity and number of adverse side effects are not affected significantly, and its use can be safe even in patients with end-stage renal disease, as has already been demonstrated [38–40]. On the other hand, the use of certain gadolinium-based contrast agents can lead to nephrogenic systemic fibrosis (NSF). In spite of the risk factors

Table 5 Complications After Adenosine-CMR (n = 7/655)

Patient	Complication	Age	Sex	Suspect drug	Concomitant diseases	Concomitant drugs
Severe						
1	Severe Bronchospasm	69	Female	Adenosine	Hypertension, Hyperlipidaemia, Diabetes, ExSmoking Multivessel disease	Oxygen therapy, Methylprednisolone, Hydrocortisone
2	Severe Bronchospasm	39	Female	Adenosine	Chronic myocardial infarction. One vessel disease	Oxygen therapy, Salbutamole, Hydrocortisone
Non-severe						
3	Hypotension	78	Female	Adenosine	Hypertension, Diabetes, Subacute myocardial infarction. Two vessel disease	Intravenous fluids
4	Bronchospasm	75	Female	Adenosine	Hypertension	Aminophylline,
5	Bronchospasm	63	Male	Adenosine	Hypertension, LV heart failure	Aminophylline, Oxygen therapy, Hydrocortisone
6	Paroxysmal AV block	59	Male	Adenosine	Non-ST elevation myocardial infarction	–
7	Paroxysmal AV block	61	Male	Adenosine	Hypertension	–

AF atrial fibrillation; *AV* atrioventricular; *LV* left ventricular

for developing NSF include estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, the use of low-risk contrast agents, as gadoteric acid, remains approved in Europe and is fairly reasonable, even in patients with severely reduced renal function [41, 42]. Recently, a higher rate of acute adverse events of gadolinium-based contrast agents was found among patients receiving pharmacological stressors compared to non-stress imaging in a large registry [43]. Patients receiving regadenoson had higher event rates when compared to adenosine or dobutamine, but none of the events were severe. Moreover, adverse event rates were balanced between adenosine and regadenoson when gadoteric acid was used (as in our study).

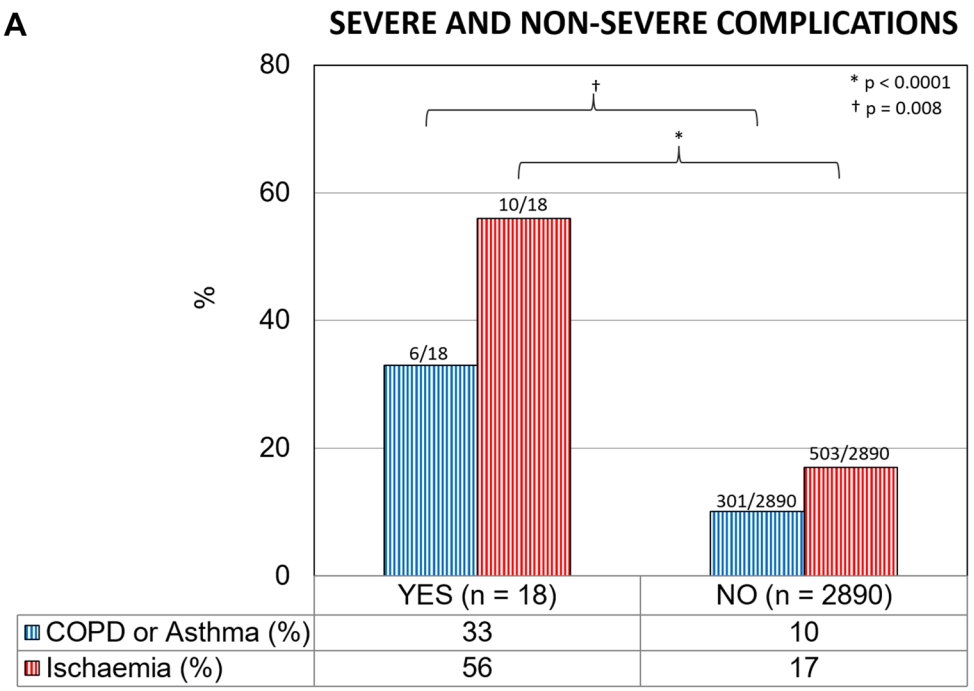
Although it has been postulated that women had a significantly higher rate of any side-effect [38, 44], we have only found this relation in the rate of appearance of minor symptoms. Recently, results from the European Society of Cardiovascular Radiology (ESCR) MRCT Registry have been published including 1151 patients with regadenoson stress-CMR reporting a percentage of complications (2.95%) which could be higher than with other drugs [39]. But in this study, with a significantly lower sample size than our work, most of the complications were moderate, mainly dyspnoea, and there were no severe complications, which is in concordance to our results. In addition, the authors did not mention the percentage of concomitant lung disease or the use of aminophylline after stress. Importantly, the authors suggest that there is a multiplicative association of adverse effects between stress drugs and gadolinium compounds, which would be significant with gadobutrol but not with gadoteric acid, the gadolinium compound we used in our study.

The incidence of minor symptoms in our study was low compared to other series [11, 12, 45, 46]. This may be caused by differences in the subjective assessment of the importance of symptoms. The rate was also lower with regadenoson than with adenosine. Moreover, we found less symptoms with regadenoson stress-CMR than we have previously reported using dipyridamole or dobutamine [20].

Study limitations

We do not have long term prognostic data from the study cohort. We have not made a complete clinical long-term follow-up of patients for nephrogenic systemic fibrosis as a late complication. However, as far as we are aware, we have not had any documented cases.

All patients with COPD or asthma have been selected for regadenoson use without excluding any, so we suggest that the results can be applied to a non-selected population. However, we do not have information about respiratory tests that some patients had performed. In any case, the only pilot studies that were conducted to investigate the safety of regadenoson in COPD and asthma patients [30, 31] found no significant differences in bronchoconstrictive reactions, mean maximum decline in FEV1 or other parameters of pulmonary function tests between study and placebo groups. Furthermore, Husain et al. [47] found 0% incidence of clinical exacerbation of COPD or asthma after regadenoson MPI in 228 unselected patients with underlying lung disease. Therefore, we cannot analyze the relation between the severity of the reactive airway disease and the incidence of complications after regadenoson stress-CMR.



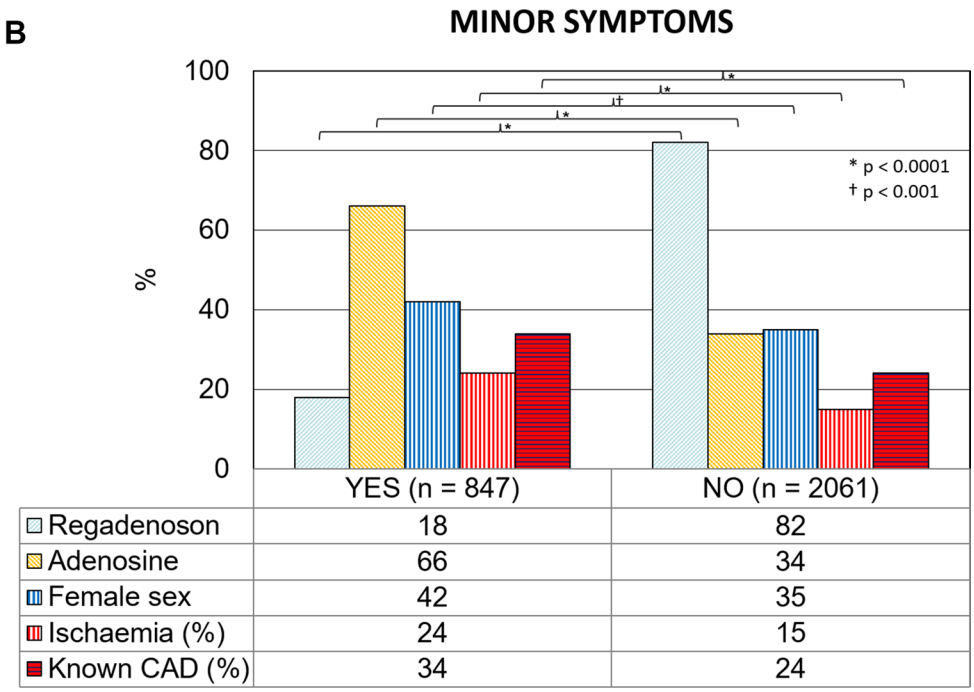


Fig. 4 Factors associated with the presence of complications (**a**) and minor symptoms (**b**) during stress-CMR. Bars represent the percentage of cases that each factor presents in the different categories

Importantly, all tests were carried out and interpreted by cardiologists with a high level of experience in performing stress-CMR, so the results in terms of image quality, diagnostic information, and presence of complications should not be extrapolated to other units with a different internal organization.

Although it has not been the goal of the study, we must note that the use of regadenoson and aminophylline represents a higher additional economic cost than adenosine, approximately 42 euros for each scan, although cost-effectiveness studies would be necessary for a complete analysis of this issue.

Conclusion

Stress-CMR with regadenoson and adenosine was evaluated in a large multicentre prospective registry of more than 2900 referral patients with known or suspected CAD.

Table 6 Minor Symptoms After Stress-CMR

	Regadenoson (n = 2253)	Adenosine (n = 655)	p
TOTAL	415/2253 (18.4)	432/655 (66.0)	< 0.0001
Headache	18 (0.8)	13 (0.2)	
Mild dyspnoea	143 (6.3)	93 (14.2)	
Abdominal pain	4 (0.2)	7 (1.1)	
Epigastric pain	2 (0.1)	2 (0.3)	
Mild chest pain†	105 (4.6)	155 (23.7)	
Left arm pain	–	1 (0.2)	
General discomfort	74 (3.3)	126 (19.2)	
Dizziness	27 (1.2)	8 (1.2)	
Palpitations	16 (0.7)	5 (0.8)	
Nausea/Vomiting	15 (0.7)	9 (1.4)	
Sweating	1 (0.0)	–	
Cough	1 (0.0)	–	
Other	9 (0.4)	13 (2.0)	

Values are n (%)

†Chest pain of < 20 min duration, alleviating in the CMR unit without specific management

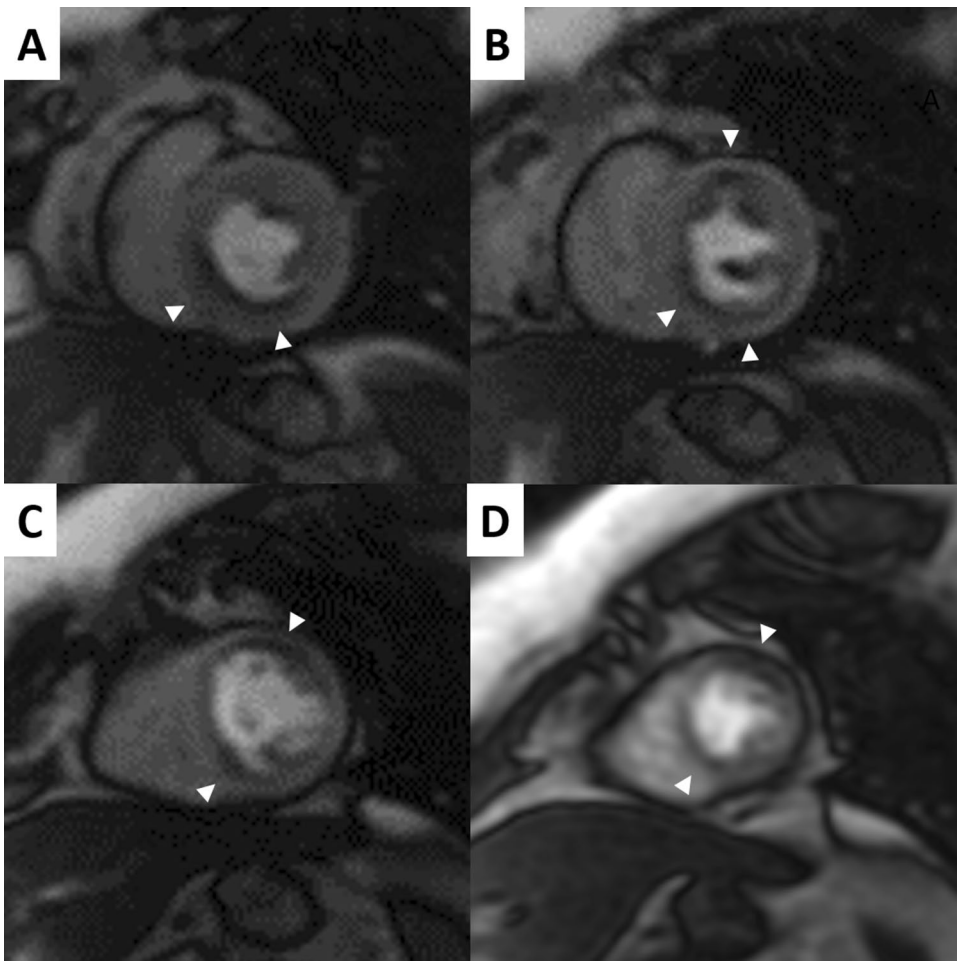


Fig. 5 Example of Adenosine stress first pass perfusion in a 69-year-old woman diagnosed with elevated blood pressure, hypercholesterolemia, diabetes, ex-smoker and multivessel coronary disease, with no history of reactive airway disease. Adenosine is administered at 140 mcg/kg/min, achieving an adequate vasodilator response at 4 min. Images are ordered from base to apex (**a** to **d**). A perfusion defect is evident at the inferior, inferoseptal and anterior segments (arrowheads). The patient has no angina during the administration of adenosine but increasing dyspnoea occurs with low O_2 saturation (85%) that requires the administration of oxygen therapy, methylprednisolone and hydrocortisone e.v. This patient presents a severe bronchospasm following the administration of adenosine

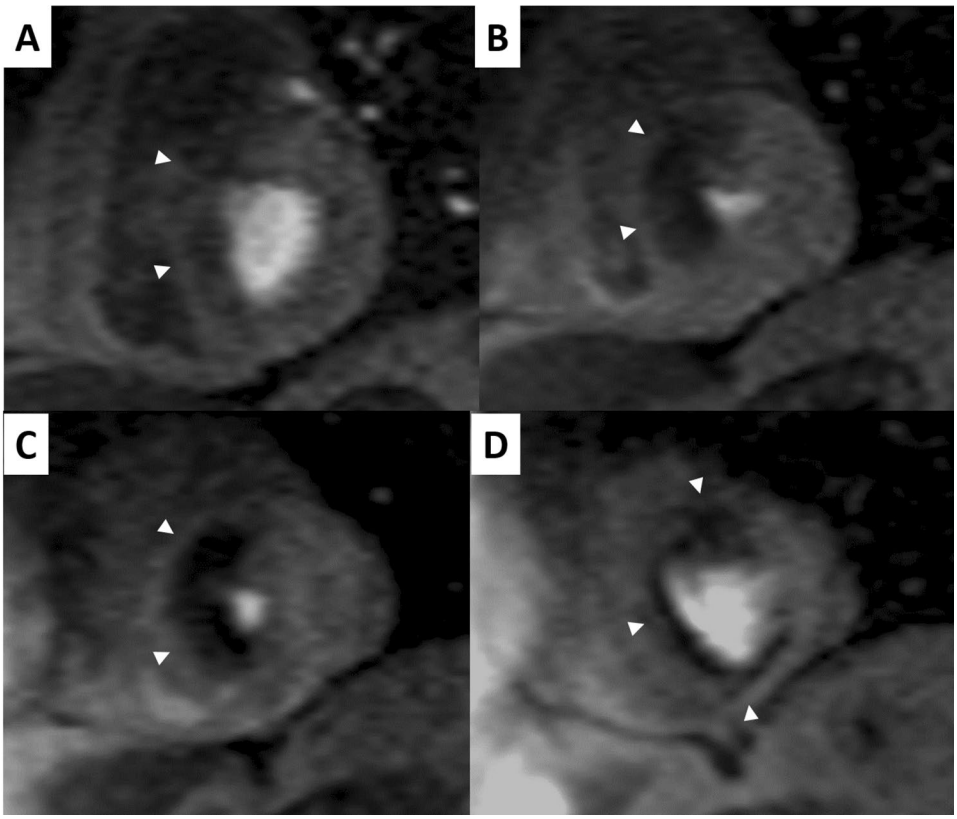


Fig. 6 Stress-CMR performed with Regadenoson 400 mcg in a 66-year-old woman diagnosed with elevated BP and moderate COPD. Images are ordered from base to apex (**a** to **d**). A perfusion deficit can be seen in the anteroseptal, anterior and apical wall (arrowheads). No symptoms or immediate complications arise following the administration of regadenoson

Stress-CMR with regadenoson is feasible, and in the vast majority of patients provides optimal image quality and useful diagnostic information for their diagnostic workup. Regadenoson stress-CMR showed an excellent safety profile with no serious immediate complications and a low incidence of non-severe complications and minor symptoms in comparison with adenosine.

Only inducible ischaemia and history of COPD or asthma were associated with complications. Nevertheless, the use of regadenoson stress-CMR is safe in this type of patients.

The registry was approved by the institutional review board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all the subjects included.

Authors contributions MMJV and MGAM conceived the study. MMJV analyzed data and drafted the manuscript. MMJV, MGAM, GGMP and LLMP revised the manuscript. All authors acquired data, read and approved the final manuscript.

Funding This study received no funding.

Data availability The data that supports the findings of this study is available from corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval consent to participate The registry was approved by the institutional review board, and written informed consent was obtained from all the subjects included.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C et al (2020) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 41(3):407–477. https://doi.org/10.1093/eurheartj/ehz425 (**PMID: 31504439**)
2. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC et al (2012) Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 379(9814):453–60. https://doi.org/10.1016/S0140-6736(11)61335-4
3. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Saskia Rutjes AW et al (2018) The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. Eur Heart J 39:3322–3330. https://doi.org/10.1093/eurheartj/ehy267
4. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R et al (2007) Prognostic value of cardiac magnetic resonance

stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 115(13):1769–1776. https://doi.org/10.1161/CIRCULATIONAHA.106.652016
5. Bodi V, Husser O, Sanchis J, Núñez J, Monmeneu JV, López-Lereu MP et al (2012) Prognostic implications of dipyridamole cardiac MR imaging: a prospective multicenter registry. Radiology 262(1):91–100. https://doi.org/10.1148/radiol.11110134
6. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST et al (2019) Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 380(25):2418–2428. https://doi.org/10.1056/NEJMoa1716734
7. Al Jaroudi W, Iskandrian AE (2009) Regadenoson: a new myocardial stress agent. J Am Coll Cardiol 54(13):1123–1130. https://doi.org/10.1016/j.jacc.2009.04.089
8. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ (2016) ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 23(3):606–639. https://doi.org/10.1007/s12350-015-0387-x
9. Pape M, Zacho HD, Aarøe J, Eggert Jensen S, Petersen LJ (2016) Safety and tolerability of regadenoson for myocardial perfusion imaging—first Danish experience. Scand Cardiovasc J 50(3):180–186. https://doi.org/10.3109/14017431.2016.1163415
10. Hendel RC, Bateman TM, Cerqueira MD, Iskandrian AE, Leppo JA, Blackburn B et al (2005) Initial clinical experience with regadenoson, a novel selective A2A agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. J Am Coll Cardiol 46(11):2069–2075. https://doi.org/10.1016/j.jacc.2005.05.097
11. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC et al (2007) Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol. 14(5):645–58. https://doi.org/10.1016/j.nuclcard.2007.06.114
12. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE (2008) Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. JACC Cardiovasc Imaging 1(3):307–316. https://doi.org/10.1016/j.jcmg.2008.02.003
13. Tarroni G, Corsi C, Antkowiak PF, Veronesi F, Kramer CM, Epstein FH et al (2012) Myocardial perfusion: near-automated evaluation from contrast-enhanced MR images obtained at rest and during vasodilator stress. Radiology 265(2):576–83. https://doi.org/10.1148/radiol.12112475
14. DiBella EV, Fluckiger JU, Chen L, Kim TH, Pack NA, Matthews B et al (2012) The effect of obesity on regadenoson-induced myocardial hyperemia: a quantitative magnetic resonance imaging study. Int J Cardiovasc Imaging. 28(6):1435–44. https://doi.org/10.1007/s10554-011-9949-4
15. Nguyen KL, Bandettini WP, Shanbhag S, Leung SW, Wilson JR, Arai AE (2014) Safety and tolerability of regadenoson CMR. Eur Heart J Cardiovasc Imaging 15(7):753–60. https://doi.org/10.1093/ehjci/jet278
16. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E (2013) Society for cardiovascular magnetic resonance board of trustees task force on standardized protocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 15(1):91. https://doi.org/10.1186/1532-429X-15-91
17. Cury RC, Cattani CA, Gabure LA, Racy DJ, de Gois JM, Siebert U et al (2006) Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients with coronary artery disease. Radiology 240(1):39–45. https://doi.org/10.1148/radiol.2401051161
18. Wahl A, Paetsch I, Gollesch A, Roethemeyer S, Foell D, Gebker R et al (2004) Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 25(14):1230–1236. https://doi.org/10.1016/j.ehj.2003.11.018
19. von Knobelsdorff-Brenkenhoff F, Bublak A, El-Mahmoud S, Wassmuth R, Opitz C, Schulz-Menger J (2013) Single-centre survey of the application of cardiovascular magnetic resonance in clinical routine. Eur Heart J Cardiovasc Imaging 14(1):62–68. https://doi.org/10.1093/ehjci/jes125
20. Monmeneu Menadas JV, Lopez-Lereu MP, Estornell Erill J, Garcia Gonzalez P, Igual Muñoz B, Maceira GA (2016) Pharmacological stress cardiovascular magnetic resonance: feasibility and safety in a large multicentre prospective registry. Eur Heart J Cardiovasc Imaging 17(3):308–315. https://doi.org/10.1093/ehjci/jev153
21. Golzar Y, Doukky R (2014) Regadenoson use in patients with chronic obstructive pulmonary disease: the state of current knowledge. Int J Chron Obstruct Pulmon Dis 22(9):129–137. https://doi.org/10.2147/COPD.S56879
22. Vasu S, Bandettini WP, Hsu LY, Kellman P, Leung S, Mancini C et al (2013) Regadenoson and adenosine are equivalent vasodilators and are superior than dipyridamole—a study of first pass quantitative perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 24(15):85. https://doi.org/10.1186/1532-429X-15-85
23. Edward JA, Lee JH, White CJ, Morin DP, Bober R (2018) Intravenous regadenoson with aminophylline reversal is safe and equivalent to intravenous adenosine infusion for fractional flow reserve measurements. Clin Cardiol 41(10):1348–1352. https://doi.org/10.1002/clc.23052
24. Lee JZ, Singh N, Nyotowidjojo I, Howe C, Low SW, Nguyen T et al (2018) Comparison of regadenoson and nitroprusside to adenosine for measurement of fractional flow reserve: a systematic review and meta-analysis. Cardiovasc Revasc Med 19(2):168–174. https://doi.org/10.1016/j.carrev.2017.07.004
25. Dhalla AK, Wong MY, Wang WQ, Biaggioni I, Belardinelli L (2006) Tachycardia caused by A2A adenosine receptor agonists is mediated by direct sympathoexcitation in awake rats. J Pharmacol Exp Ther 316(2):695–702. https://doi.org/10.1124/jpet.105.095323
26. Derbas LA, Thomas GS, Medina CA, Abdel-Karim AA, Saeed IM, Bateman TM (2019) Severe bradycardia and asystole following regadenoson in pharmacological myocardial perfusion imaging: cases and treatment recommendations. JACC Cardiovasc Imaging 12(7 Pt 1):1288–1290. https://doi.org/10.1016/j.jcmg.2019.01.017
27. Bruder O, Wagner A, Lombardi M, Schwitter J, van Rossum A, Pilz G et al (2013) European cardiovascular magnetic resonance (EuroCMR) registry–multi national results from 57 centers in 15 countries. J Cardiovasc Magn Reson 18(15):9. https://doi.org/10.1186/1532-429X-15-9
28. Kuijpers D, Janssen CH, van Dijkman PR, Oudkerk M (2004) Dobutamine stress MRI. Part I. Safety and feasibility of dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 14(10):1823–1828. https://doi.org/10.1007/s00330-004-2425-y
29. Hussain N, Chaudhry W, Ahlberg AW, Amara RS, Elfar A, Parker MW et al (2017) An assessment of the safety, hemodynamic response, and diagnostic accuracy of commonly used vasodilator stressors in patients with severe aortic stenosis. J Nucl Cardiol 24(4):1200–1213. https://doi.org/10.1007/s12350-016-0427-1
30. Thomas GS, Tammelin BR, Schiffman GL, Marquez R, Rice DL, Milikien D et al (2008) Safety of regadenoson, a selective adenosine A2A agonist, in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled

trial (RegCOPD trial). J Nucl Cardiol 15(3):319–28. https://doi.org/10.1016/j.nuclcard.2008.02.013
31. Leaker BR, O'Connor B, Hansel TT, Barnes PJ, Meng L, Mathur VS et al (2008) Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: a randomized, double-blind, placebo-controlled trial. J Nucl Cardiol 15(3):329–36. https://doi.org/10.1016/j.nuclcard.2008.02.009
32. Prenner BM, Bukofzer S, Behm S, Feaheny K, McNutt BE (2012) A randomized, double-blind, placebo-controlled study assessing the safety and tolerability of regadenoson in subjects with asthma or chronic obstructive pulmonary disease. J Nucl Cardiol 19(4):681–692. https://doi.org/10.1007/s12350-012-9547-4
33. Schiopu SRI, Zacherl M, Todica A, Bartenstein P, Milger K, Leuschner G et al (2020) Feasibility and accuracy of SPECT myocardial perfusion imaging in end-stage lung disease. J Nucl Cardiol 27(3):903–911. https://doi.org/10.1007/s12350-019-01851-4
34. Kwong RY, Ge Y, Steel K, Bingham S, Abdullah S, Fujikura K et al (2019) Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. J Am Coll Cardiol 74(14):1741–1755. https://doi.org/10.1016/j.jacc.2019.07.074
35. Andrikopoulou E, Morgan CJ, Brice L, Bajaj NS, Doppalapudi H, Iskandrian AE et al (2019) Incidence of atrioventricular block with vasodilator stress SPECT: a meta-analysis. J Nucl Cardiol 26(2):616–628. https://doi.org/10.1007/s12350-017-1081-y
36. Rangel MO, Morales Demori R, Voll ST, Wassouf M, Dick R, Doukky R (2015) 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. J Nucl Cardiol 22(5):1008–1018. https://doi.org/10.1007/s12350-014-0036-9
37. Gupta A, Bajaj NS (2018) Regadenoson use for stress myocardial perfusion imaging in advance chronic kidney disease and dialysis: safe, effective, and efficient. J Nucl Cardiol. 25(1):150–152. https://doi.org/10.1007/s12350-017-1038-1
38. Zoghbi GJ, Iskandrian AE (2012) Selective adenosine agonists and myocardial perfusion imaging. J Nucl Cardiol 19(1):126–141
39. Doukky R, Rangel MO, Wassouf M, Dick R, Alqaid A, Morales DR (2013) The safety and tolerability of regadenoson in patients with end-stage renal disease: the first prospective evaluation. J Nucl Cardiol 20(2):205–213
40. Ananthasubramaniam K, Weiss R, McNutt B, Klauke B, Feaheny K, Bukofzer S (2012) A randomized, double-blind, placebo-controlled study of the safety and tolerance of regadenoson in subjects with stage 3 or 4 chronic kidney disease. J Nucl Cardiol 19(2):319–329
41. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/European_Commission_final_decision/WC500240571.Pdf
42. ACR manual on contrast media version 10.3. ACR Comitee on drugs and contrast media. American College of Radiology, 2018
43. Uhlig J, Lücke C, Vliegenthart R, Loewe C, Grothoff M, Schuster A et al (2019) Acute adverse events in cardiac MR imaging with gadolinium-based contrast agents: results from the European Society of Cardiovascular Radiology (ESCR) MRCT Registry in 72,839 patients. Eur Radiol 29(7):3686–3695. https://doi.org/10.1007/s00330-019-06171-2
44. Katsikis A, Kyrozi E, Manira V, Theodorakos A, Malamitsi J, Tsapaki V et al (2019) Gender-related differences in side-effects and hemodynamic response to regadenoson in patients undergoing SPECT myocardial perfusion imaging. Eur J Nucl Med Mol Imaging 46(12):2590–2600. https://doi.org/10.1007/s00259-019-04463-9
45. Freed BH, Narang A, Bhave NM, Czobor P, Mor-Avi V, Zaran ER et al (2013) Prognostic value of normal regadenoson stress perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 21(15):108. https://doi.org/10.1186/1532-429X-15-108
46. Mahmarian JJ, Peterson LE, Xu J, Cerqueira MD, Iskandrian AE, Bateman TM et al (2015) Regadenoson provides perfusion results comparable to adenosine in heterogeneous patient populations: a quantitative analysis from the ADVANCE MPI trials. J Nucl Cardiol 22(2):248–261. https://doi.org/10.1007/s12350-014-9981-6
47. Husain Z, Palani G, Cabrera R, Karthikeyan AS, Dhanalakota S, Pathmanathan S et al (2012) Hemodynamic response, arrhythmic risk, and overall safety of regadenoson as a pharmacologic stress agent for myocardial perfusion imaging in chronic obstructive pulmonary disease and bronchial asthma patients. Int J Cardiovasc Imaging 28(7):1841–1849. https://doi.org/10.1007/s10554-011-0003-3