Adenosine vs. regadenoson for stress induction in dynamic CT perfusion scan of the myocardium: A single-center retrospective comparison

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Abstract. Cardiac computed tomography (CT) angiography offers several approaches to determine the hemodynamic severity of coronary artery obstruction. Dynamic myocardial perfusion is based on serial CT imaging of contrast flow into the myocardium and calculation of absolute myocardial perfusion rates. East-Slovak Institute of Cardiovascular Diseases has been the first center in Slovakia intensively using this modern technique to increase the quality level of non-invasive diagnosis of symptomatic patients with a low to moderate pre-test probability of ischemic heart disease. The present study included 46 patients with a mean age of 64 years (33 men and 13 women). Prior to the CT study, myocardial stress was pharmacologically (adenosine, n=15 and regadenoson, n=31) induced by vasodilatation of the coronary arteries. Hemodynamic parameters (myocardial blood flow) were evaluated in all patients following successful CT perfusion without complications, allergic reaction or other severe side effects. The present study revealed that regadenoson increased the heart rate following infusion with a higher magnitude compared with adenosine. Moreover, the effect of regadenoson was independent of patient's body mass index and was associated with a lower incidence of mild adverse effects. The present study provided further clinical evidence for a more wider use of regadenoson over adenosine.

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Introduction

Non-invasive coronary computed tomography angiography (CCTA) detects significant (≥50%) lumen reduction associated with coronary artery disease (CAD) (1). In particular, high sensitivity and negative predictive value (NPV) of ≥95% highlight the diagnostic technique since its introduction into the clinical practice two decades ago (2). Of note, clinical limitation of CCTA is associated with the presence of extensive coronary calcification, which may lead to false-positive findings; thus, current guidelines consider CCTA inappropriate in high-risk populations (3). Those patients may benefit from the complex approach combining CCTA and myocardial CT perfusion (CT-MPI) examination to reduce the number of patients undergoing invasive coronary angiography due to a false-positive non-invasive approach (4).

In the past, adenosine and dipyridamole were used as standard pharmacologic stress agents inducing vasodilatation during CT-MPI (5). However, their use was associated with frequent adverse events (mild events with higher frequency: Flushes, chest pain, dyspnea, dizziness and nausea; serious events with lower frequency: Bronchospasm, atrioventricular block, and peripheral vasodilation) in ≤80% of patients (6,7). Therefore clinicians have begun to use regadenoson (selective A_{2A} receptor agonist) (8) that is associated with improved safety and tolerability profile when compared with adenosine (non-selective A_1, A_{2A}, A_{2B} and A_3 receptor agonist) (9). Another major advantage of regadenoson over adenosine and/or dipyridamole is that it is administered as a single bolus (0.4 mg) whereas adenosine (10) and dipyridamole (11) must be administered as weight-adjusted infusions. Despite the advantages of regadenoson over adenosine, clinicians should be aware of potential side effects. Even though the majority of adverse effects are short, benign, and spontaneously terminate, they rarely may also graduate to more serious events (e.g., symptomatic myocardial ischemia, infarction, atrioventricular block, asystole and/or seizures) (12). Regadenoson had been approved by the Food and Drug Administration in 2008 as the next stress agent for CT-MPI examination (13,14) whereas the approval in the Slovak Republic came over a decade later

in 2019. The present study presents first experiences from the East-Slovak Institute of Cardiovascular Diseases with the administration of regadenoson (with direct comparison to adenosine) for myocardial perfusion scans.

Materials and methods

The present study retrospectively analyzed 46 patients (Table I) with varying degrees of coronary artery disease, from nonspecific chest pain to patients after stent implantation following coronary bypass surgery to confirm/exclude myocardial perfusion defects.

A stress-rest protocol was used in all patients. Of the total patient sample, 32 were men and 14 were women in the age categories between 43 and 84 years. Two types of stress-inducing drugs were administered to the patients: Adenosine (Adenocor) or reganedoson (Rapiscan). Adenocor was administered to 15 while Rapiscan was administered to 31 patients.

The East-Slovak Institute of Cardiovascular Diseases has the latest CT Somatom Force device (Siemens Healthcare GmbH). This is a third generation dual source CT. The critical features of this CT device for successful performance of myocardial perfusion scan are: i) Scan parameters: 2x96x0.6-mm collimation resulting in a 105-mm z-axis coverage by shuttle mode, ii) rotation time ≤250 msec, iii) temporal resolution ≤66 msec, iv) spatial resolution 0.24 mm, v) tube voltage 70-80 kV with automated exposure control (300 mAs/rotation at 80 kV as reference), vi) 3.0-mm-thick slices reconstructed with 2.0-mm overlap and vii) maximum speed of 73 cm/sec with Turbo Flash.

All subjects were kindly asked to refrain from caffeine-containing drinks for 12 h and nicotine (may act as a vasodilators) for 3 h prior the scan (15). The stress-rest protocol is shown in Fig. 1. The cardiac rhythm was continuously monitored, and the blood pressure was measured at regular intervals. Briefly, stress protocol (hyperemia) was induced by i) intravenous adenosine (140 μg/kg/min) over 3 min or ii) intravenous regadenoson (single bolus of 0.4 mg). The standard contrast injection protocol was a 50 ml in load phase and 50 ml in rest phase contrast bolus at 5.5 ml/s (iopromide; Ultravist; Bayer AG; 370 mg/ml), followed by 40 ml saline. The CT-MPI scan started 4 sec after contrast injection, using alternating table positions (shuttle mode) for complete myocardial coverage. Cardiac shuttle mode scan at CT SOMATOM Force is a dual source prospective ECG triggered sequence with shuttle move of the table. The 10.5 cm range is scanned in two slabs where each slab is scanned in separated R-R intervals (usually in systolic phase). Speed of the table is dynamic and is dependent on heart rate. Speed at start and end position is slower to avoid movement artifacts. Since each R-R interval is scanned in shuttle mode, the approximate table speed in patient with heart rate 60 beats/min is >50 mm/sec. The data set consisted of 10-15 CT data samples over 30 sec.

The rest protocol was performed 15-20 min after the first CT-MPI and included both the second CT-MPI and CCTA using prospective electrocardiogram-triggered axial or high-pitch spiral scans. Sublingual nitroglycerin was administered before CCTA and intravenous β1-blockers were given if the heart rate was >75 beats per min (BPM). Images were reconstructed with a medium-smooth kernel, 0.6-mm slice thickness and 0.4 mm increments.

All CT scans were examined by two experienced radiologists blinded to clinical history using syngo. CT Myocardial Perfusion (Siemens Healthcare GmbH), a widely used CTP post-processing software. Quality of the image was evaluated by a 4-point scale (Likert). Low quality CT-MPI images were omitted from the analysis. Discordant findings were reconciled during a consensus read. For qualitative analysis dynamic stress CT perfusion study was interpreted visually in conjunction with delayed enhancement CT viability scan. A myocardial segment was considered as showing reversible ischemia when hypoperfusion lasted >6 heart beats under adenosine/regadenoson stress without delayed enhancement on viability scans. Homogeneously perfused myocardium during adenosine/regadenoson stress that did not show delayed enhancement on viability studies was classified as normal (16).

Coronary stenosis were classified based on the Coronary Artery Disease Reporting and Data System (17). CT-MPI maps were compared side-by-side with the CTA images. The coronary anatomy based on the CTA scan was used to locate myocardial perfusion defects to the respective coronary artery. Based on the CCTA and CT-MPI scans, the presence of hemodynamically relevant CADs were determined (CT-MPI findings were superior to CCTA). The most severely affected coronary branch determined per-territory disease classification.

The myocardial blood flow (MBF; ml/100 ml/min) per-coronary artery territory was calculated from maximum slope of the fit model curve normalized to the peak arterial enhancement as follow: A region of interest (corresponding to 0.5 cm^3 of subendocardial myocardium) was sampled onto the MBF polar maps for each vessel territory (either in the area of suspected ischemia or centrally within territories without suspected ischemia). The reference MBF was defined as the 75th percentile of the automatically generated global endocardial MBF representing a robust measure of normal MBF in a specific patient/examination relatively unaffected by territorial ischemia or artifacts (18). Relative MBF was calculated (per vessel territory) as the absolute MBF divided by the reference MBF.

Statistical analysis was conducted with the MedCalc Version 12.5.00 (MedCalc Software Ltd.) software. Selected demographic data with relevant medical history (see Table I), MBF, calcium score and BPM values were expressed as mean ± standard deviation and compared (between adenosine and regadenoson group) with the unpaired t-test or non-parametric Kruskal-Wallis test. For correlation analysis (BMI correlation with MBF or BPM increase), the Spearman's rho coefficient was calculated. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A reliable perfusion examination could be performed in all patients (Fig. 2) Of note, 33 mild adverse effects were observed in patients treated with adenosine (shortness of breath, chest discomfort, nausea, palpitations, hypotension and bradycardia) and 12 in patients treated with regadenoson (shortness of breath, chest discomfort, palpitations and bradycardia) (Table II). No

Table I. Patient demographic data with relevant medical history.

Population	Adenosine	Regadenoson	P-value
Number of patients	15	31	
Age	63.87±10.27 (F72.25±8.84/M60.81±9.26)	64.74±9.9 (F69.66±8.91/M62.72±9.75)	0.7825
Sex	4F/11M	9F/22M	
BMI	31.66±5.33 (F30.65±4.75/M32.02±5.70)	29.49±5.46 (F30.87±6.34/M28.91±5.11)	0.2097
History			
CAD	80.00% (F-75%/M-81.81%)	83.87% (F-77.77%/M-86.36%)	0.7520
Myocardial infarction	26.66% (F-0.0%/M-36.36%)	48.38% (F-22.22%/M-59.09%)	0.1679
PTCA without stent	40% (F-75%/M-27.27%)	25.81% (F-44.44%/M-18.18%)	0.6147
PTCA with stent	26.66% (F-0.0%/M-36.36%)	45.16% (F-11.11%/M-59.09%)	0.9152
Bypass	6.66% (F-0.0%/M-9.09%)	9.67% (F-0.0%/M-13.64%)	0.3829
Cardiovascular risk factors			
DM	33.33% (F50%/M27.27%)	32.25% (F11.11%/M40.90%)	0.9435
DLP	80% (F75%/M81.81%)	83.87% (F88.88%/M81.81%)	0.7520
HT	100% (F100%/M100%)	90.32% (F88.88%/M90.90%)	0.2178
FH	53.33% (F75%/M45.45%)	48.38% (F44.44%/M50%)	0.7596
S	40% (F25%/M45.45%)	35.48% (F11.11%/M45.45%)	0.7723

BMI, body mass index; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; DM, diabetes mellitus; DLP, dyslipidemia; HT, hypertension; FH, family history; S, smoker; F, female; M, male.

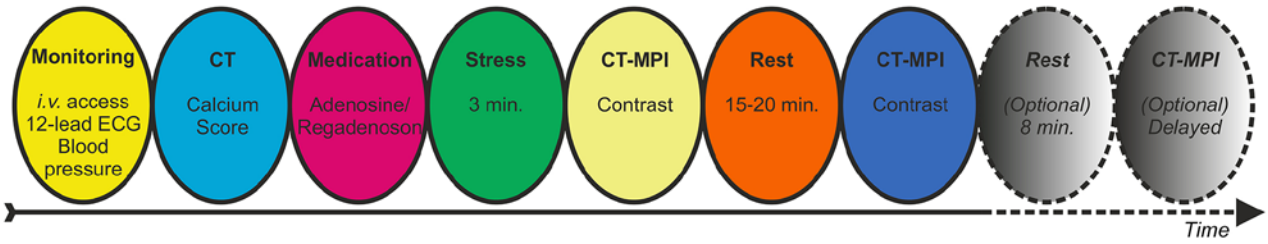

Figure 1. Schema of stress-rest protocol applied during CT-MPI examination. CT-MPI, myocardial computerized tomography perfusion.

severe adverse effects were observed. In 13 patients from adenosine group and 13 patients from regadenoson group, moderate to severe regional myocardial perfusion disorders were present, with MBF <75 ml/100 ml/min, of which three and eight patients had confirmed myocardial-scar necrosis after MI, respectively. Of note, no perfusion disorders or MBF values >75 ml/100 ml/min. were found in two and 18 patients from adenosine and regadenoson group, respectively.

Following CCTA, invasive coronary angiography was performed in nine patients with stent implantation (Fig. 2). Of note, no patient was assessed as false positive in the adenosine group whereas in two patients from the regadenoson group the invasive coronarography was performed and stents were not implanted.

The two studied agents were able to significantly increase the heart rate following infusion (Table III). Administration of adenosine led to an increase from 71.53±24.5 to 83.71±18.48 BPM while administration of regadenoson led to an increase from 62.42±11.91 to 93.83±32.1 BPM. Although regadenoson induced slightly higher BPM increase (compared with adenosine) in studied group of patients, the difference was not significant (P=0.1063; Fig. 3). On the other hand, the difference in MBF increase between regadenoson (104.43±54.52) and adenosine (57.08±31.67) was significant (P<0.01).

The analysis revealed no correlation (Fig. 4) between BPM increase (%) and BMI of patients subjected to adenosine- or regadenoson-induced stress CT-MPI.

Discussion

The analysis of clinical myocardial perfusion CT examinations in the present study revealed that regadenoson is comparable to adenosine in detecting myocardial perfusion defects. Clinically important, the selective A_{2A} receptor agonist regadenoson elicited an increase in MBF comparable to adenosine and/or dipyridamole (11) (of note, adenosine and dipyridamole doses were adapted to patient weight), while the flow response to regadenoson appeared to be largely independent of patient size, despite being administered as a bolus (fixed dose of 0.4 mg) (19). The equal bolus dose may theoretically result to a bodyweight-dependent attenuation

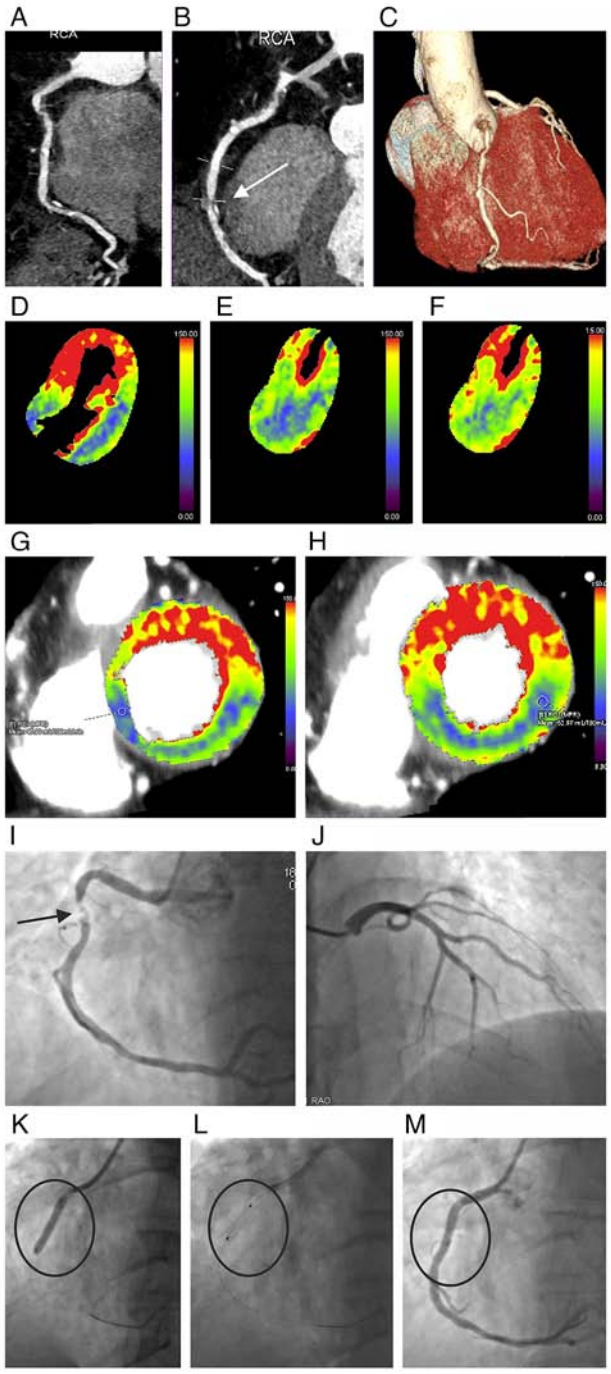

Figure 2. Myocardial perfusion imaging and invasive coronary angiography. CT (A-C) right coronary artery stenosis and (D-H) perfusion CT with hypoperfusion in examined region of right coronary artery images of representative patient subsequently indicated for (E-M) PTCA and (K-M) stent placement. CT, computerized tomography; PTCA, percutaneous transluminal coronary angioplasty.

Table II. Frequency and severity of side effects of studied agents.

Symptom	Adenosine	Regadenoson	Severity
Shortness of breath	9	3	Mild/Mild
Chest discomfort	14	4	Mild/Mild
Vertigo	0	0	
Nausea	2	0	Mild
Palpitations	6	4	Mild/Mild
Headache	0	0	
Hypotension	1	0	Mild
Bradycardia	1	1	Mild/Mild
Hypertension	0	0	
AV block	0	0	
Cardiac arrest	0	0	

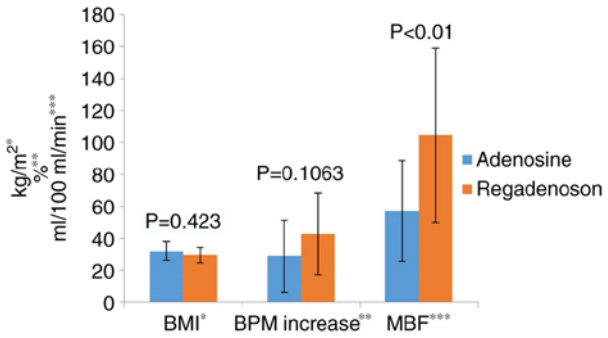

Figure 3. Statistical comparison (unpaired t-test) between adenosine and regadenoson treated groups. The analysis revealed no statistically significant difference between BMI and BPM increase whereas the difference in MBF was significant. BMI, body mass index; BPM, beats per minute; MBF, myocardial blood flow.

of the effect. However, as shown previously (19) the present study also did not observe a clinically relevant relationship between dose and BMI of the patient. Published data confirms that the bolus of 0.4 mg sufficiently saturates A_{2A} receptors independent on the BMI of the patient (19). Notably, the MBF increase was significantly higher following regadenoson compared with dipyridamole (11) or adenosine (observed also in the present study) which may result either from different application technique (bolus compared with infusion) or by more efficient stimulation of the sympathetic nervous system via the A_{2A} receptor (20).

Previously it was demonstrated that regadenoson increased blood flow >2.5-fold lasting 2-3 min, thus the effect is brief and easily tolerated (21). The study also demonstrated that the maximal coronary hyperemia induced by regadenoson appeared to be similar in magnitude to that induced by adenosine or dipyridamole. In another study, the MBF response to regadenoson was noninvasively measured using 15O-water and PET in healthy subjects. Notably, the work revealed a flow reserve of 2.97±0.16 that did not significantly change following caffeine application (22). Similarly, 82Rb myocardial perfusion PET examination revealed a flow response of 2.9 in the regadenoson-treated group (11). The flow response also appeared to be somewhat independent of the patient's body size.

Moreover, studies have demonstrated a lower incidence of side effects and patient's discomfort due to the receptor subtype selectivity of the agent (11,23), thus regadenoson can safely be administered as a fixed bolus regardless of age, gender, BMI and diabetes (24). Although, individuals <65 years of age and women had increased occurrence of side effects and benefit from aminophylline (bronchodilatator theophylline

Table III. Perfusion data, dynamic parameters and indicated procedures following CT perfusion examination.

MBF	Adenosine	Regadenoson
ml/100 ml/min	57.08±31.67	104.43±54.52
Calcium Score	1,323±1610	933±906
Heart rate (BPM)		
Baseline	71.53±24.5	62.42±11.91
Stress	83.71±18.48	93.83±32.1
Rest	61.54±10.65	65.46±13.91
Base to Stress increase (%)	21.50±28.27	50.33±38.49
Indicated procedure		
PTCA without stent	0.00% (F-0.00%/M-0.00%)	6.45% (F-11.11%/M-4.54%)
PTCA with stent	26.66% (F-0.00%/M-36.36%)	29.03% (F-44.44%/M-22.72%)

CT, computerized tomography; MBF, myocardial blood flow; BPM, beats per minute; PTCA, percutaneous transluminal coronary angioplasty; F, female; M, male.

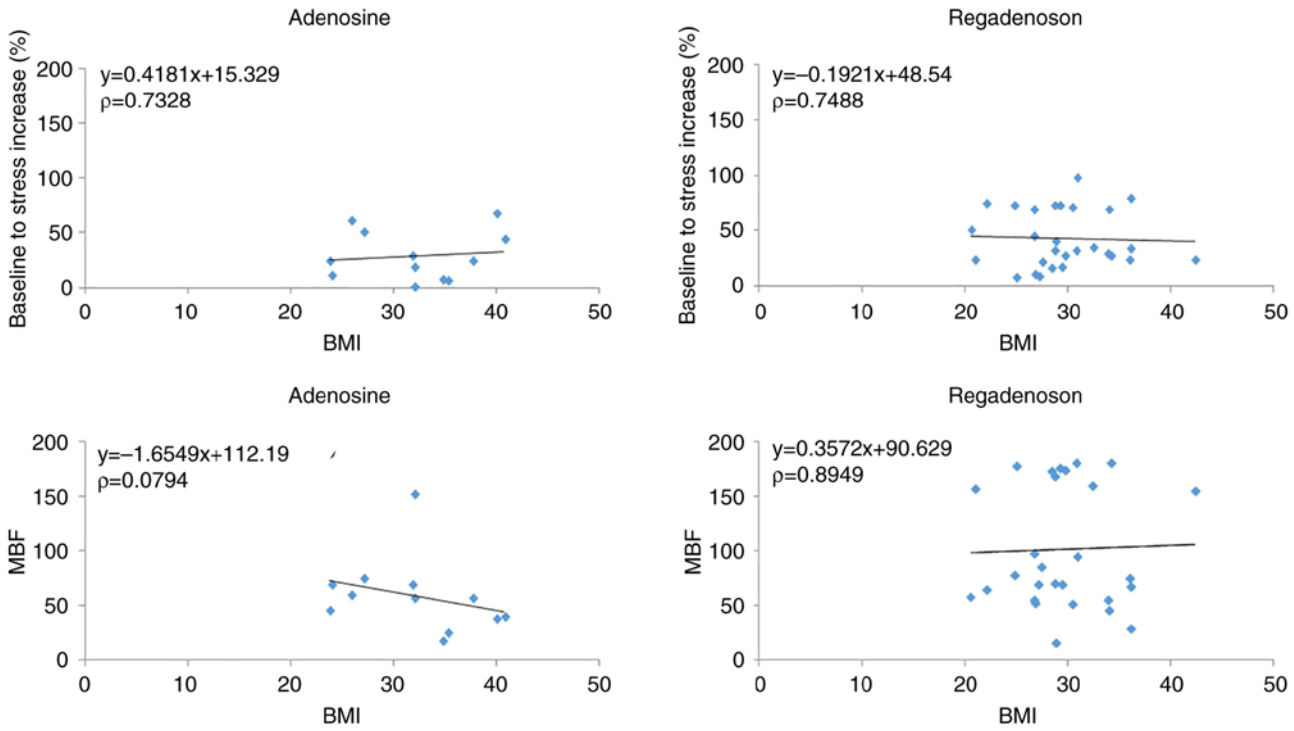

Figure 4. Correlation between BPM increase (baseline to stress increase %) and BMI as well as between MBF and BMI of patients subjected to adenosine- or regadenoson-induced stress CT myocardial perfusion scans. BPM, beats per minute; BMI, body mass index; MBF, myocardial blood flow; CT, computerized tomography.

and ethylenediamine 2:1) administration (25). Hence, further important parameters associated with side effects present with sex and age. Women demonstrate a higher median BPM associated with a significantly higher rate of side effects compared with men (26). Regarding the frequency of side effects, the present study was consistent with previously published work (21) where the presence of adverse events like chest pain, tachycardia, and hypotension was similar to those reported in the present study. Although occurrence of first-degree atrioventricular block were already noted upon regadenoson administration no significant heart rhythm disturbances were observed. These observations provided a rationale for a wider use of regadenoson, which is currently being explored; for example, in patients with asthma and obstructive airway disease, thus with dipyridamole and/or adenosine contraindication (27). However, a single-center retrospective cohort study reveals that the use of adenosine was associated with a lower occurrence of adverse effects and lower rate of rescue agent use (28). From this point of view, adenosine still presents a cost saving opportunity in direct comparison with regadenoson.

Although the present study did not provide entirely novel information, it should be seen as a further clinical evidence

for a more wider use of regadenoson over adenosine (in particular due to a lower occurrence of adverse effects and administration management). Nevertheless, it is necessary to consider three main limitations of this single-center study. First, presented data are summarized based on an observational retrospective analysis. The present study only compared two groups of patients with myocardial perfusion CT images who were administered either regadenoson or adenosine. Based on the current retrospective analysis, it is also impossible to control other potential interfering factors. From this point of view, a more complex prospective randomized study would be more appropriate albeit expensive and time-consuming. Second, the blood flow response to adenosine and regadenoson should be compared in healthy volunteers to exclude/reduce potentially interfering factors. Finally, the limited number of patients included in the present study was the third main limitation of the investigation. Nevertheless, in is considered that the present data reflect a realistic single-center clinical situation where the agents will be routinely administered for myocardial perfusion examination.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS and PG designed the present study. CG, PM, MH and RK performed the clinical part of the study. LU and PG analyzed data. PG wrote the first draft of the manuscript. CG and LU confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of East-Slovak Institute of Cardiovascular Diseases, Inc. (June 10 2022; approval no. A3062022).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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