11 November 2021
EMA/CHMP/18475/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Rapiscan

International non-proprietary name: regadenoson

Procedure No. EMEA/H/C/001176/II/0038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3D	3-Dimensional
82Rb	Rubidium-82
82RbCl	Rubidium-82 Chloride
AE	Adverse Event
AF	Atrial Fibrillation
APV	Average Peak Velocity
AS	Aortic Stenosis
AUC	Area Under the Curve
BMI	Body Mass Index
bpm	Beats Per Minute
CAD	Coronary Artery Disease
CBF	Coronary Blood Flow
CFR	Coronary Flow Reserve
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance
CT	Computed Tomography
CTA	Computed Tomography Angiography
DECT	Dual-Energy Computed Tomography
EF	Ejection Fraction
ECG	Electrocardiogram
FBP	Filtered Back Projection
FFR	Fractional Flow Reserve
GLS	Global Longitudinal Strain
HC	Hypertrophic Cardiomyopathy
HR	Heart Rate
IR	Iterative Reconstruction
IV	Intravenous
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LCX	Left Circumflex Artery
LV	Left Ventricle
LVD	Left Ventricular Dysfunction
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
MBF	Myocardial Blood Flow
MBV	Myocardial Blood Volume
MCR	Motion-Compensated Back-Projection Reconstruction
MDCT	Multidetector Computed Tomography
MFR	Myocardial Flow Reserve
MPI	Myocardial Perfusion Imaging
MPR	Myocardial Perfusion Reserve
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MVD	Multi-Vessel Disease
OHT	Orthotopic Heart Transplantation
PCBV	Perfused Capillary Blood Volume
PET	Positron Emission Tomography
PV	Peak Value
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SDS	Summed Difference Score
SLR	Systematic Literature Review
SPECT	Single Photon Emission Computed Tomography
SSS	Summed Stress Score
TAVR	Transcatheter Aortic Valve Replacement
TPD	Total Perfusion Deficit
TTP	Time To Peak

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GE Healthcare AS submitted to the European Medicines Agency on 6 April 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to modify the existing indication to allow use in line with new imaging technologies that have evolved since initial approval of Rapiscan; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Jayne Crowe

Timetable	Actual dates
Submission date	6 April 2021
Start of procedure:	24 April 2021
CHMP Co-Rapporteur Assessment Report	18 June 2021

Timetable	Actual dates
CHMP Rapporteur Assessment Report	28 June 2021
CHMP members comments	9 July 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 July 2021
Request for supplementary information (RSI)	22 July 2021
CHMP Rapporteur Assessment Report	18 October 2021
CHMP members comments	29 October 2021
Updated CHMP Rapporteur Assessment Report	04 November 2021
CHMP Opinion	11 November 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Non-invasive myocardial imaging is being used in coronary artery disease (CAD) to:
• Detect obstructive CAD and assess its location, extent and severity
• Guide medical therapy and monitor the treatment effect after revascularization procedures
• Risk stratify patients and provide prognostic information
• Assess myocardial viability
European and North American medical societies have conducted appropriate use review of common clinical presentations in CAD to consider use of diagnostic procedures. The current available procedures are transthoracic echocardiography (TTE), transesophagic echocardiography (TEE), stress echocardiography, radionuclide ventriculography (RVG), myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) or positron emission tomography (PET), cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (CT) (ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease). The most appropriate imaging modality should be chosen according to the clinical question, patient characteristics, strengths, limitations, risks, costs and availability. The traditional gold standard test for the diagnosis of CAD is invasive coronary angiography via cardiac catheterization. SPECT MPI is the type of myocardial perfusion imaging most widely used in the management of patients with CAD. It provides important information on the extent and severity of myocardial perfusion abnormalities, including myocardial ischaemia, left ventricular cavity size and function. Moreover, it can deliver miscellaneous prognostic imaging data. It is based on the pathophysiological principle that stenosed coronary arteries cannot increase blood flow by vasodilation in response to stress to the degree that normal vessels can (coronary flow reserve is decreased), whereas at rest blood flow in stenosed arteries is comparable to that in normal arteries until stenosis is far advanced (over 90% of luminal area) (Lezaic et al. 2014). Regional uptake of radiopharmaceutical is dependent on regional blood flow, and therefore radiopharmaceutical uptake is greater in areas perfused by normal, relative to stenosed, arteries. Interpretation of SPECT MPI studies has been primarily qualitative or semiquantitative in nature, assessing regional perfusion defects in relative terms

(Paganelli et al. 2017).
Stress is commonly induced in two ways: by exercise (on a stationary bicycle or treadmill) or by pharmacological agents (Lezaic et al. 2014). The available pharmacological agents differ in terms of the mechanism by which they simulate changes induced by exercise: vasodilators (such as adenosine, dipyridamole and regadenoson) induce vasodilation, while dobutamine induces an increase in heart rate and contractility.
Pharmacological stress testing is included in the European and North American guidelines for SPECT (Verbene 2015, Dorbala 2018). In this imaging modality, they are indicated for patients who cannot reach an adequate endpoint with physical exercise stress testing (Paganelli et al. 2017). Vasodilators are adenosine receptor agonists. There are four known types of adenosine receptors: A1, A2A, A2B, and A3. Activation of the A2A receptors results in the desired effect, coronary artery vasodilation. Activation of the others results in less desirable effects. Activation of the A1 receptor results in decreased atrioventricular conduction. Activation of the A2B and A3 receptors can result in bronchospasm.
Dipyridamole was the first vasodilator used for myocardial perfusion stress testing (Paganelli et al. 2017). Dipyridamole is an indirect coronary artery vasodilator, whose mechanism of action is the building up of adenosine in tissues by blocking the cellular reuptake of endogenous adenosine. Adenosine is a direct coronary artery vasodilator and acts on the 4 known types of receptors. Regadenoson is another direct coronary artery vasodilator and it is a selective A2A receptor agonist. Regadenoson was approved for use for radionuclide MPI in 2010. Efficacy of regadenoson was demonstrated in two phase-3 prospective controlled trials to be non-inferior to adenosine for diagnosing reversible perfusion defects in patients undergoing SPECT MPI (EPAR). Even when the term “radionuclide” covers *de facto* the use with SPECT and PET, only data on SPECT MPI were presented and assessed at that time. In fact, the approval of the use of regadenoson for those three diagnostic techniques is the objective of the present variation.
Nevertheless, since the approval of Rapiscan its use has expanded beyond the area of radionuclide in clinical practice being its use also common with cardiac magnetic resonance (CMR) or CT.
The use of PET for MPI began in the 1980s (Sciagrà 2021). However, due to logistic constraints, myocardial perfusion PET was restricted to few research centres. Recently, the accessibility of PET has increased due to a major increase in the number of installed PET scanners and due to the availability of PET perfusion radiopharmaceuticals that do not require an on-site cyclotron, such as the (generator-based) Rubidium-82 (82Rb).
The North American speciality medical societies have issued appropriate use criteria for PET MPI (Schindler 2020). The high spatial and contrast resolution in concert with photon attenuation-free images of PET have led to high image quality associated with the highest sensitivity and specificity of PET/CT perfusion imaging in the detection and characterization of CAD. In addition, the noninvasive evaluation and quantification of global and regional myocardial blood flow (MBF) in milliliters per gram per minute during hyperemic stress and at rest, as well as the calculation of the resulting myocardial flow reserve (MFR), extends the scope of standard MPI from the detection of advanced and flow-limiting epicardial CAD to a comprehensive assessment of ischemic burden. Then, PET affords not only the assessment of relative differences in myocardial perfusion, but also, in conjunction with tracer kinetic modeling, the calculation of regional and global MBF of the left ventricle in absolute terms in milliliters per gram per minute. Dynamic acquisitions are performed to obtain perfusion data while static perfusion images, as well as ECG-gated images, are acquired for the evaluation of LV function and wall motion.
European procedural guidelines have recently been issued for PET MPI (Sciagrà 2021). Several PET myocardial perfusion tracers are available for clinical use in Europe, such as rubidium (82RbCl) chloride and nitrogen-13 (13N) ammonia and 15O-water. Rubidium (82RbCl) chloride is registered in Germany for use with positron emission tomography (PET) for the assessment of myocardial perfusion and is

indicated for the detection and localization of coronary artery disease in adult patients with known or suspected coronary artery disease. The other two radiopharmaceuticals are not registered and can only be used at hospitals with an on-site cyclotron due to their short physical half-life.
The visual assessment of relative differences in myocardial perfusion on PET MPI is based on similar arguments than in SPECT MPI. If the stress-induced regional perfusion defect persists on the corresponding paired rest images, it suggests the presence of an irreversible myocardial injury. Contrarily, if the defect on the stress images resolves completely or partially on the rest images, it suggests the presence of stress-induced myocardial ischemia (Dilsizian 2016).
Pharmacological stress testing has been included in the most updated European and North American guidelines for PET (Sciagrà 2020 and Dilsizian 2016). Stress testing is most commonly performed with pharmacological agents, and for quantitative MBF measurement stress by pharmacological agents is the sole possible option (Sciagrà et al. 2021). The stress test modalities do not differ for the various radiopharmaceuticals and are the same as for SPECT MPI, although the execution of the stress injection with the patient already positioned on the camera bed, together with the additional problem to avoid his/her motion, requires particular cautiousness (Sciagrà et al. 2021). The commonly used stressors are dipyridamole, adenosine and, most recently, regadenoson (Sciagrà et al. 2021). Dipyridamole has the longest history of use and has the most data available in the literature in relation to MPI; however, it is not approved for this indication in many European countries (Sciagrà et al. 2021).
Regadenoson has some advantages versus the other commercially available vasodilators, dipyridamole and adenosine, because it has fixed dosing (0.4 mg for all patients) and a simple intravenous bolus administration requiring no infusion system. However, questions have persisted about its accuracy for PET MPI because of its quick onset, short duration of action, and low degree of vasodilation compared with other vasodilators historically used for cardiac PET protocols (i.e. adenosine and dipyridamole). Myocardial uptake, clearance, and biodistribution of various radiopharmaceuticals can vary with the type of stressor used and affect diagnostic accuracy. The short physical half-life of PET radionuclides is another factor to take into consideration when optimising regadenoson PET MPI protocols.
Pharmacological stress testing has been included in the most updated European and American guidelines for Magnetic resonance imaging has rapidly developed into a versatile tool for investigating CAD, being able to evaluate cardiac structure and ventricular function and to detect myocardial perfusion defects or infarction scar. Cardiac magnetic resonance (CMR) stress protocols are very useful for evaluation of myocardial perfusion and wall motion. The main advantage of stress MRI is the ability to accurately evaluate cardiac morphology, function and tissue characteristics during the same test.
An expert committee from the French Society of Radiology and the French Society of Cardiology issued an opinion paper to define how cardiac stress MRI should be positioned in the management of patients suspected of/or having chronic CAD (Le Ven et al). This paper reflects that dobutamine and vasodilators are being used for the test. Although vasodilators are the preferred products, because they are simple and safe to use, their administration in this diagnostic modality remains off-label in some European countries. The committee considers that their use is justified by many articles in the literature, European recommendations, several randomized studies and the recommendations from international societies.
The recommended acquisition protocol is cine MRI sequences associated with first pass-perfusion and late enhancement ones. Perfusion MRI is based on a qualitative (visual) analysis of the enhancement of the myocardial signal during the first pass of a bolus injection of gadolinium-based contrast agents (GBCA); the acquisitions are performed under pharmacological stimulation. A perfusion acquisition at rest after injection of the vasodilator is optional. It could be superfluous if the result of the stress perfusion is unequivocal (normal, ischemia).
Coronary CT angiography (CCTA) has evolved into a robust and non-invasive tool for the assessment of CAD, being able to identify coronary anatomy, presence of obstructive and non-obstructive CAD and

plaque characteristics. Vasodilator stress computed tomography perfusion imaging is complementary to CCTA, used to determine the hemodynamic significance of CAD; however, it requires a separate image acquisition due to motion artifacts caused by higher heart rates during stress (Balaney 2019). Seitun et al. in a review article stated that stress CT perfusion imaging has good accuracy for detection of myocardial perfusion defects (Seitun et al. 2016). Dynamic stress myocardial perfusion CT is performed by acquiring a series of CT images after injection of a bolus of contrast medium during pharmacological hyperemia, similar to perfusion imaging technique by MRI or PET (Nieman and Balla, 2020).
Qualitative analysis of stress myocardial perfusion CT requires visual analysis of images obtained in stress and rest conditions, using a normalcy pattern based on the experience (Seitun et al. 2016). Interpretation of images is based on the presence, location and extension of perfusion defects. Similarly, for SPECT and MR, a perfusion defect in stress images which is partially or totally reversible at rest indicates ischemic but viable myocardium. Contrarily, a similar defect in stress and rest images is compatible with myocardial necrosis. Dynamic myocardial perfusion CT can be analysed either semi-quantitatively or quantitatively.

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2.1.2. About the product

Regadenoson is a selective A2A receptor agonist that produces hyperemia with rapid onset (30 seconds) for approximately two to four minutes.

Regadenoson is currently approved for use in adults as a pharmacological stress agent for:

- Radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.
- the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated (see sections 4.2 and 5.1).

This medicinal product is restricted to use in a medical facility where cardiac monitoring and resuscitation equipment are available. The single injection of regadenoson must be given strictly intravenously.

The recommended dose in adults is 5 ml (0.4 mg of regadenoson) with no dosage adjustment necessary for body weight. The way of administration is as a rapid, 10-sec injection into a peripheral vein using a 22-gauge or larger catheter or needle, followed by an immediate 5 ml saline flush into a peripheral vein, and with injection of a radionuclide for myocardial perfusion imaging into the same catheter as soon as 10-20 seconds after the saline flush.

It is not recommended for use in population younger than 18 years old due to lack of data on safety and efficacy. No dosage adjustments are necessary for neither elderly nor patients with renal impairment.

Regadenoson produces hyperemia with rapid onset (30 seconds) for a longer period (approximately two to four minutes) than adenosine, which permits more convenient administration (injection of 400 mcg over 10 seconds for regadenoson instead of 6-min infusion of a weighted-adjusted dose for adenosine). Straightforward dosing (no weight adjustment) facilitates use and reduce errors due to dose calculations in comparison to adenosine.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application concerns a variation of Rapiscan, to modify an existing indication to allow use of the product for myocardial perfusion imaging not only with SPECT but using other imaging modalities. Rapiscan is currently approved for use in adults as a pharmacological stress agent for:

- Radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.
- the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated (see sections 4.2 and 5.1).

The present variation request modification of the first indication to be

~~"Radionuclide~~ myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress."

No formal Scientific Advice has been given by the CHMP for this medicinal product. A pre-submission meeting was hold on October 6th, 2020.

2.1.4. General comments on compliance with GLP, GCP

No new non-clinical or clinical studies have been submitted. A systematic literature review of the use of regadenoson with other imaging modalities (PET, MRI, and cardiac CT) has been presented. Therefore, GLP or GCP compliance not applicable.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

The applicant submitted information for ERA of regadenoson, based on the changes to therapeutic indication indicated in this variation, and in accordance with the EMEA/CHMP/SWP/4447/00 guidance.

The CHMP agreed that the new information related to ERA does not modify the current SmPC.

2.2.2. Ecotoxicity / environmental risk assessment

The applicant presented data for the phase I assessment of ERA (log K_{ow} and PEC_{sw}).

- Persistence, bioaccumulation and toxicity

The octanol/water partition coefficient (pH 7.4) was calculated for regadenoson, resulted in a value of -0.46 (experimentally determined according to guideline OECD 117).

- Calculation of the Predicted Environmental Concentration (PEC)

PEC value was estimated in line with the formula provided in the ERA guideline.

$$PEC_{surface\ water} = \frac{DOSE_{ai} * F_{pen}}{WASTEW_{inhab} * DILUTION}$$

For the estimation of DOSEai parameter, the highest dose given according to the SPC is 400 µg regadenoson per patient contained in a 5 mL vial, equating to 0.4 $mg.inh^{-1}d^{-1}$. The $f_{pen\text{-}refined}$ was calculated according to the following formula:

$$f_{pen\text{-}refined} = \frac{p_{region} \times t_{treatment} \times n_{treatment}}{Nd}$$

p_{region} is the prevalence of disease (the highest prevalence is 4394 per 100000 in Lithuania (Wilkens et al., 2017), resulting in a P_{region} value of 0.044); $t_{treatment}$ is the duration of one treatment period (1 year); $n_{treatment}$ is the number of treatments per year (worst case scenario is 4 per year); and Nd are the number of days per year (365). Considering the values showed above, the final value of $f_{pen\text{-}refined}$ (0.044*1*4/365) is $4.8x10^{-4}$.

Maximum daily dose of active substance consumed per inhabitant ($DOSE_{ai}$).	0.4 $mg \cdot inh^{-1} \cdot d^{-1}$
Percentage of market penetration ($f_{pen\text{-}refined}$)	$4.8x10^{-4}$

Amount of wastewater per inhabitant per day ($WASTEW_{inhab}$)	200 $L \cdot inh^{-1} \cdot d^{-1}$
Dilution factor	10
$PEC_{SURFACEWATER}$	9.63×10^{-8} $mg \cdot L^{-1}$ = 9.63×10^{-5} µg/L

It is concluded that a Phase II environmental assessment of regadenoson is not required.

2.2.3. Discussion on non-clinical aspects

The new data presented in relation to the ERA for regadenoson show that no additional studies would be required. Phase I assessment was reported, resulting in a PECsw value below the action limit (9.63×10^{-5} µg/L) and an octanol/water partition coefficient value of 0.46 (pH 7.4).

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of regadenoson.

Considering the above data, regadenoson is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

No new clinical studies have been submitted.

The dossier is based on published scientific literature to demonstrate clinical efficacy for the use of regadenoson in adults as a pharmacological stress agent for MPI without restricting to any particular diagnostic modality. The MAH has performed a review of the literature of the efficacy of regadenoson in three different MPI techniques (that is using PET, CT and MR). A phase-2 sponsored study with cardiac CT was also presented. No scientific critical discussion performed by the MAH, but only individual summaries and full-text paper of the literature references that were part of the systematic literature review were provided. This was accepted by the CHMP.

With this application, the MAH seeks to modify an existing indication of Rapiscan to allow use of the product for myocardial perfusion imaging not only with SPECT but using other imaging modalities. Rapiscan is composed of regadenoson, a selective coronary vasodilator currently approved for use in adults as a pharmacological stress agent for:

- Radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.
- the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated (see sections 4.2 and 5.1).

The present variation requests modification of the first indication to be ~~"Radionuclide~~ myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress." The term radionuclide *de facto* includes both SPECT and PET, despite only data for SPECT were provided at the time of

approval, and the removal of this term would allow the use of Rapiscan with alternative diagnostic methods such as CMR or CT.

2.4. Clinical efficacy

It is argued that the perfusion assessment should be independent from the stress applied either physical or drug-induced in the sense that the stress has the objective to increase the local blood flow demand while the imaging modality has the objective to measure the relative changes in the blood flow response to this stress itself. That would mean that any imaging modality able to measure perfusion at the cardiac level would therefore be suitable to assess stress-induced perfusion changes related to the effect of regadenoson.

Regadenoson produces hyperemia with rapid onset (30 seconds) for a longer period (approximately two to four minutes) than adenosine, which permits more convenient administration (injection of 400 mcg over 10 seconds for regadenoson instead of 6-min infusion of a weighted-adjusted dose for adenosine). Straightforward dosing (no weight adjustment) facilitates use and reduce errors due to dose calculations in comparison to adenosine.

PET Literature Review

A literature search was performed in Medline via PubMed and Scopus databases from 01 January 2000 through 10 February 2021, supplemented by manual searches of reference lists in all accepted studies and recent reviews (past 2 years), using best methods in established, peer-reviewed science of systematic review research, such as PRISMA guidelines.

The abstracts and publications were screened by 2 independent reviewers, with discrepancies resolved by a consensus conference. Data extraction was done by 1 reviewer with 100% quality check by a second reviewer to ensure accuracy, completeness, and consistency.

MEDLINE search terms:
1) Regadenoson;
2) Myocardial Perfusion Imaging;
3) PET OR PET-CT;
4) Coronary Artery Disease;
5) 1 OR 2 OR 3 OR 4;
6) 1 AND 2 AND 3;
7) 1 AND 3 AND 4;
8) Case reports[Publication Type] OR editorial[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR letter[Publication Type];
9) Exclude the following publication types, editorials (ed), chapter books (ch), notes (no), short survey (sh), and a series of keywords in order to limit the results to studies of humans only.

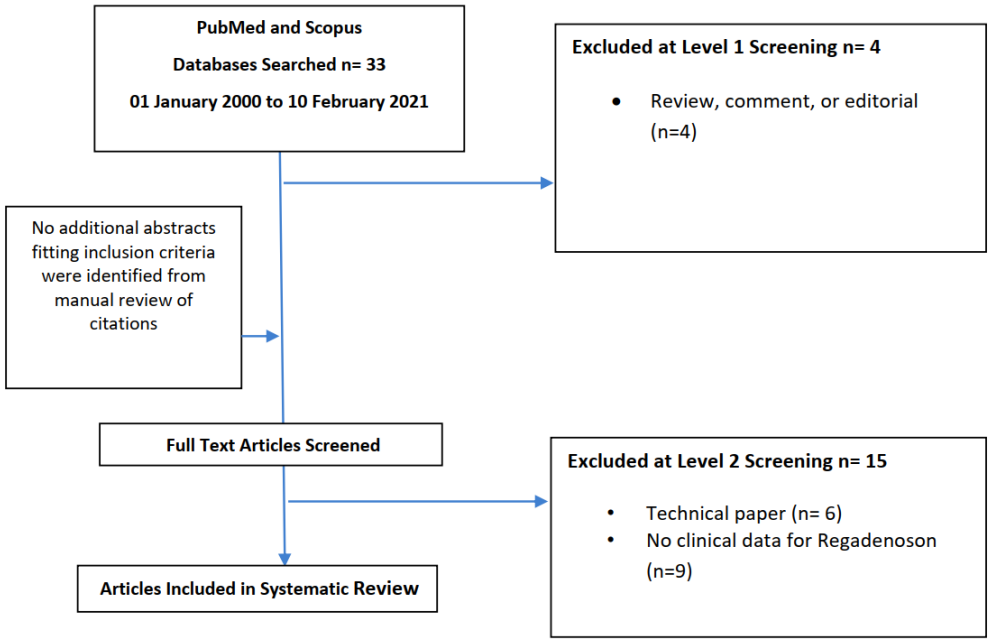


Figure 1 Flowchart of systematic literature review for use of regadenoson in PET imaging

Cardiac Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) Literature Review

A literature search in the National Library of Medicine – National Center for Biotechnology Information database (PubMed.gov) was performed using the following keywords:
Regadenoson AND (MRI OR CT).

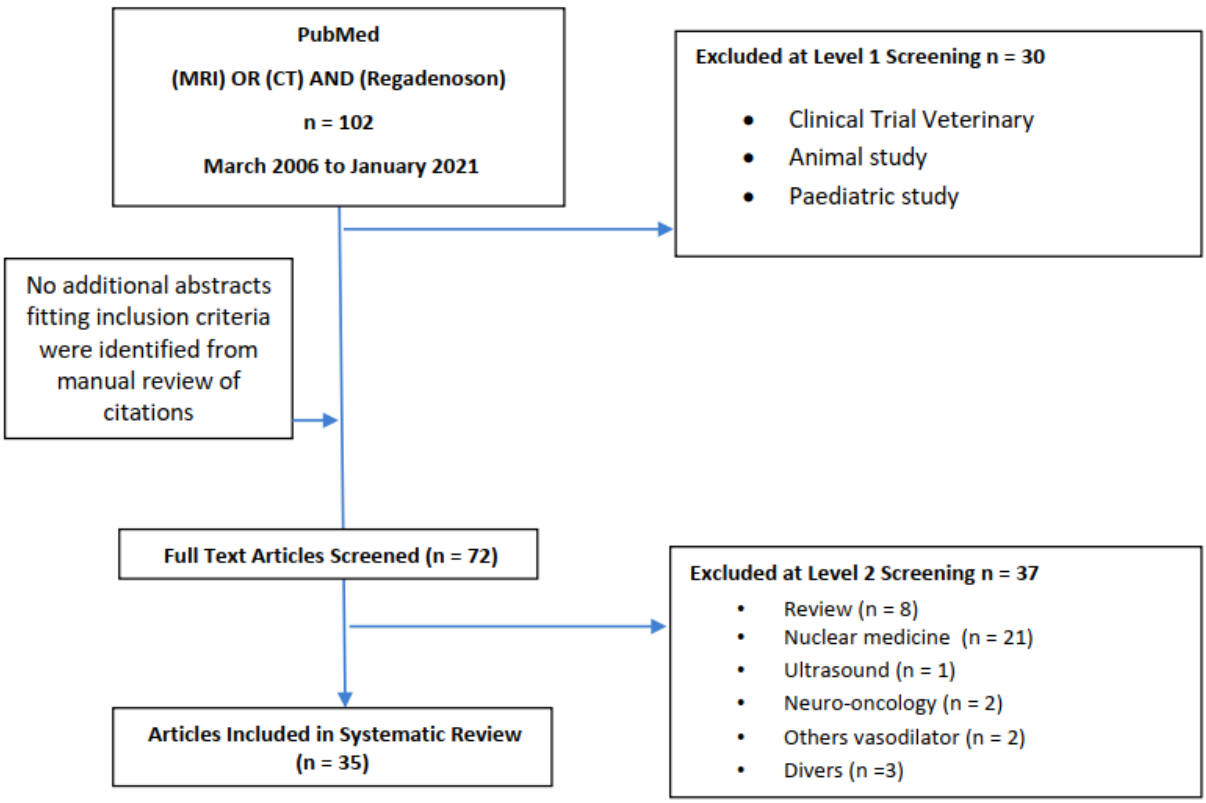


Figure 2 Flowchart of systematic literature review for use of regadenoson in cardiac MRI and CT imaging

Then, 14 articles of PET MPI and 35 articles of CT and MR MPI finally resulted from the systematic review. The Applicant has provided full-text papers, but no scientific critical discussion was presented. The CHMP has reviewed and assessed:

- From the 14 articles of the systematic literature review for PET MPI, 13 aimed to assess clinical efficacy are assessed in the efficacy section of the present report. The remaining article only assessed safety (Lazarus et al. 2020) and is then discussed in the safety part.

Regarding CMR and CT, 35 articles (22 for CMR and 13 for CT) resulted from the systematic review which were in fact 33, since two articles referred both to CRM and CT. Thirty of these papers are discussed in the efficacy section of the present report. There are two papers (Uhlig et al. 2019 and Nguyen et al. 2014) which referred only to safety and therefore discussed in the safety part of the present report.

POSITRON EMISSION TOMOGRAPHY (PET) MYOCARDIAL PERFUSION IMAGING (MPI)

The main source of clinical data to assess efficacy of regadenoson as a stress pharmacological agent in PET MPI are provided by the two prospective controlled studies:

- Vleeming et al. 2018 compared adenosine and regadenoson used as a stress agent on PET/CT images with ^{13}Nammonia (13NH3) in two parallel groups.
- Cullom et al. 2013 performed a within-subject comparison of dipyridamole and regadenoson used as a stress agent on 82RbCl PET/CT MPI in 26 patients who had a reversible perfusion defect (previously identified already on a clinically indicated dipyridamole-stress PET scan)

In both studies, stress was induced with 0.4 mg of regadenoson given intravenously over 10 s followed by 5-mL flush with normal saline. This corresponds to the proposed posology for PET MPI and is the currently approved one for SPECT MPI.

In addition, a number of non-comparative and retrospective studies have been provided by the MAH that are considered as supportive.

- *Vleeming et al. 2018*

A prospective single-center parallel controlled study was conducted to investigate differences in cardiac displacement during adenosine stress versus regadenoson stress in 13Nammonia (13NH3) MP PET/CT scans.

Study participants

61 patients, all referred for 13NH3 MP PET/CT, were prospectively included.

Treatments

Adenosine-stress ^{13}Nammonia (13NH3) myocardial perfusion PET/CT scans (n=30) and regadenoson-stress ^{13}Nammonia (13NH3) myocardial perfusion PET/CT scans (n=31).

A low-dose CT scan was acquired before a 25-min list-mode PET acquisition. Simultaneously with the initiation of the PET acquisition (t = 0 min), 305 ± 4 MBq of 13NH3 were rapidly injected intravenously to obtain PET images at rest. This scan was followed by the administration of the stressor using the second intravenous line, when available. In the case of adenosine, this was done after t=12 min with a dose of 140 mg/kg/min during 6 min. In the case of regadenoson, this was done after t=14:20 min using a single bolus of 400 mg (5 mL in 10 s) followed by a 10-mL saline flush (in 10 s). At t=15 min, a second dose of 394 ± 3 MBq of 13NH3 was administered.

Objectives/endpoints

For both groups, cardiac displacement during rest and stress was measured 3-dimensionally by a commercial specific algorithm, relative to either a fixed reference frame or the previous frame, in each 1-min frame of a list-mode PET acquisition of 25 min. All stress scans were additionally evaluated for the presence of motion artifacts.

Results

Significantly larger cardiac displacement during stress was detected in the adenosine group than in the regadenoson group, reflected by both maximal cardiac displacement (mean±SD, 8.1±3.7 vs. 6.1±2.3 mm; P=0.022) and mean cardiac displacement (median, 2.7 mm [interquartile range, 2.1–3.2 mm] vs. 2.0 mm [interquartile range, 1.5–2.4 mm]; P=0.001. The duration of the movement was typically shorter in the regadenoson group. Compared with the adenosine group, the regadenoson group showed fewer motion artifacts on stress 13NH3 PET/CT: 14 of 30 patients (46.7%) versus 9 of 31 patients (29.0%) (P=0.192), respectively.

Patient baseline characteristics were similar in both cohorts. Risk factors differed between adenosine and regadenoson cohorts: diabetes mellitus (0 vs 6; p=0.12) and previous myocardial infarction (13 vs 5; p=0.21) and previous percutaneous coronary intervention (12 vs 6; p=0.080).

Outcomes and estimation

In this study, regadenoson and the comparator adenosine were evaluated for the extent of cardiac displacement on 13Nammonia (13NH3) MP PET/CT images compared in two parallel subgroups of patients (n=31 and n=30, respectively). The primary endpoint (i.e. cardiac displacement on PET images) refers to an image artifact that may lead to erroneous interpretation of images but is not part of the variables assessed on PET MPI images for routine clinical use. This study points out that cardiac displacement occurs more frequently when adenosine rather than regadenoson is used. However, it was not a within-subject comparison and, as the authors acknowledged, comparison between subgroups is limited due to small cohort size (n=31 for regadenoson group and n=30 for adenosine group) and heterogeneity of clinical characteristics within the cohorts (they differed about the risk factors).

Therefore, even if this is a controlled study comparing with adenosine was not designed to compare images visually and quantitatively, the support provided by this study to the efficacy of regadenoson for PET MPI is considered weak.

- *Cullom et al. 2013*

A prospective single-centre controlled study was conducted to address concerns that the timing of 82RbCl delivery may not be suitably matched to the period of peak regadenoson hyperaemia. A comparison was made with conventional dipyridamole PET in the same subjects.

Study participants

A total of 32 subjects (23 M) participated in this investigation. Twenty-six (26) were recruited as presenting with reversible perfusion defects identified on a clinically indicated dipyridamole-stress PET/CT scan with 82RbCl. Six (6) additional subjects were identified who met the criteria for <5% pre-test likelihood for coronary artery disease (CAD) based on their gender, age, and symptoms as described by Diamond and Forrester.

Treatments

A low-dose CT scan was acquired at rest for attenuation correction. Immediately following, approximately 60 mCi of 82RbCl was infused in 50 mL of saline over approximately 25 seconds. A 6-minute image acquisition with 8 temporal frames per R-R cycle was started 90 seconds after completion of infusion. With the patient in the same position, dipyridamole was administered using 0.57 mg/kg for 4 minutes followed by a 3-minute delay and then start of a 60 mCi 82RbCl infusion in 50 mL over approximately 25 seconds. The remainder of the protocol was the same as described above, followed by a second CT scan for attenuation correction of the stress images.

All subjects completed identical rest imaging as described for the dipyridamole study. 400 µg of regadenoson was then administered over 10 seconds followed by a 5-mL saline flush. An infusion of 60 mCi of 82RbCl in 50 mL of saline was started immediately after the saline flush. Image acquisition was started 90 seconds after completion of the 82RbCl infusion. A second low-dose transmission scan was then acquired for stress attenuation correction.

Objectives/endpoints

Images were compared both visually and quantitatively.

For the visual assessment, two independent blinded readers were presented with two sets of images, displayed side-by-side on calibrated monitors and labeled monitor A and monitor B. Image presentation was randomized to eliminate any bias. The readers were blinded to the purpose of the study, source of the data, clinical findings, results of any prior interpretation, and order of the images. This comparison focused on the extent and severity of ischemia (the number of segments with reversible defects) between two MPI PET images of the same patient; one using dipyridamole as the stress agent and the other using regadenoson.

For the quantitative comparison, the uptake in the myocardium was resampled into the 17-segment model. The uptake in each segment was then normalized to the maximum count value in the myocardium, with values in each segment ranging from 0% to 100% of the maximal value using the Quantitative Perfusion PET (QPS) program. Summed stress scores (SSS), SDS, total perfusion deficit (TPD) and the difference between stress and rest TPD was calculated using Q-PETTM by comparison of the perfusion images to a 82RbCl gender-independent normal database as described. LVEF, endsystolic (ESV), and end-diastolic (EDV) LV volumes were calculated within QGSTM.

Results

All twenty-six (26) subjects had reversible perfusion defects on dipyridamole PET images (which was an inclusion criteria), and no defects existed in six (6) subjects had <5% likelihood of CAD. Visual interpretation of images indicated no difference in the number of segments with reversible defects between both vasodilators for 30/32 image pairs. In one case, the readers indicated a subtle greater number on the dipyridamole PET, and in one case there was a subtle greater number on the regadenoson PET image.

Quantitation the SSS was 12.9 ± 7.0 and 14.1 ± 6.4 (P = 0.23) and SDS was 7.0 ± 6.8 versus 7.6 ± 6.2 (P = 0.40) for dipyridamole and regadenoson, respectively, in the group of 26 patients. The six (6) subjects had <5% likelihood of CAD and were normal by both.

All paired measurements showed a high positive correlation between regadenoson and dipyridamole; stress segmental perfusion Reg=0.93Dip + 4.4, r = 0.88; TPD Reg = 0.94Dip + 0.41, r = 0.93; LVEF Reg = 0.92Dip + 4.7, = 5 0.95; stress minus rest LVEF Reg = 0.87Dip - 0.99, r = 0.82.

Stress LVEF for the 26 ischemic subjects was 50 ± 11.9 (range 23-68) and 49.7 ± 13.4 (range 18-75) for dipyridamole and regadenoson, respectively (P = NS). For the six (6) subjects who had <5% likelihood of and, stress LVEF was 68.3 ± 6.0 and 66.7 ± 7.7, respectively (P = NS). The difference between the ischemic and low likelihood group LVEF values was significant (P<.005) for both dipyridamole and regadenoson stress.

Outcomes and estimation

This prospective study intra-individually compared regadenoson versus dipyridamole in patients who had presented with a reversible perfusion defect on a clinically indicated dipyridamole-stress PET MPI study. PET MPI with regadenoson was interpreted as in clinical practice with regards to the visual detection of perfusion defects and prospectively compared with PET MPI with another stress agent (dipyridamole in this case). A comparison was performed in 26 patients who had a reversible perfusion defect already identified on a previous clinically indicated dipyridamole-stress PET study with 82RbCl. Additionally, six (6) subjects with <5% pre-test likelihood for CAD were recruited. This is considered the main study to support the clinical efficacy of regadenoson as pharmacological stress agent in PET MPI. Dipyridamole can be considered a valid comparator and, although it is currently not approved for this indication in

many European countries (Siagrà 2021), it has extensively been used for many years as a stress agent in MPI.

This study showed that, when the 82RbCl infusion is started promptly after regadenoson injection (that is imaging started 2 minutes following start of 82Rb infusion), regadenoson-stress 82RbCl PET/CT is equivalent to dipyridamole-stress 82RbCl PET/CT regarding the number of segments with reversible defects (visually blinded detected) and cardiac function measurements (assessed quantitatively).

This study has some limitations:

- there were only 26 recruited patients, and their clinical characteristics are not reported. The study included patients with a mild-moderate degree of ischemia with a small proportion of patients having moderate to severe ischemia, and they had normal or near-normal left ventricular function.

- quantitation of either dipyridamole or regadenoson 82RbCl PET was done using a normal database from 82RbCl PET studies obtained with a 7-minute adenosine stress protocol. Expected normal distributions and abnormality criteria are typically dependent on imaging and stress protocols, stress agents, tracer, and processing methods.

- timing and duration of maximal hyperemia varies among different vasodilators and could present challenges to radiopharmaceutical uptake that could impact perfusion defect or cardiac function measurements. For this, results from the present study in which the radiopharmaceutical infusion started promptly after regadenoson injection may not be generalizable to patients with slowed circulation times associated with left or right heart failure, pulmonary hypertension, or morbid obesity, who may have a delay in transit of the tracer arriving after the peak phase.

Despite the above-mentioned limitations, the results can be considered as being supportive of the expected effect of regadenoson when used as a pharmacological stress agent in PET MPI.

There were also non-controlled studies and/or retrospective studies provided, which are being discussed below.

- *Hsiao et al. 2013*

A prospective, single-centre, non-comparative study was conducted to investigate the diagnostic value of vasodilator stress testing with regadenoson in conjunction with perfusion defects on ^{82}RbCl MPI to detect obstructive CAD.

Study participants

134 patients (mean age, 63 ± 12 years; mean body mass index [BMI], 31 ± 9 kg/m2) with clinically suspected CAD but not known CAD were enrolled. There were 96 consecutive stable patients who underwent invasive coronary angiography within 6 months after the PET/CT study and, during the same period, 38 patients with a low pretest likelihood of CAD.

Patients with a known history of angiographic CAD, pathologic Q waves on resting electrocardiography, or prior coronary revascularization were excluded. Patients with a left bundle branch block, haemodialysis, active wheezing, or oxygen-dependent lung disease who could not receive regadenoson were also excluded.

Treatments

Patients were referred for a rest–stress regadenoson 82RbCl PET/CT because of clinical findings. Patients received 1,480–2,220 MBq of 82Rb intravenously at rest, and emission images were acquired in 2-dimensional list mode. After rest imaging, patients remained in scanner gantry for stress imaging. Stress was induced with 0.4 mg of regadenoson given intravenously over 10 s followed by 10-mL flush with normal saline. Immediately after saline flush, second dose of 1,480–2,220 MBq of 82RbCl was administered intravenously approximately 30 s after regadenoson injection and emission images were acquired as previously described.

Coronary angiography was performed on the basis of clinical and imaging findings. The diagnosis of CAD was confirmed by angiography (standard of truth).

Objectives/endpoints

PET images were interpreted semi-quantitatively and independently by 4 experienced observers using a standard 17-segment model and a 5-point (0 to 4) scoring system (semi-quantitative relative regional uptake scores), without knowledge of the angiographic results, in 96 patients. Global summed stress score (reflecting the magnitude of scar and ischemia), summed rest score (reflecting the magnitude of scar), and summed difference score (reflecting the magnitude of ischemia) (the difference between summed stress score and summed rest score) were computed. A summed stress score of more than 0 was considered abnormal.

In coronarography, a visually determined stenosis diameter of at least 50% in the left main coronary artery or at least 70% stenosis in other coronary arteries were considered significant.

Results

Regadenoson PET with 82RbCl had a high sensitivity, 92% (59/64; 95% CI: 83%-97%), in detecting obstructive CAD, with a normalcy rate of 97% (37/38); 95% CI: 86%-99%), specificity of 53% (17/32 patients; 95% CI: 34%-71%).

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. Efficacy was based on the semiquantitative assessment of rest–stress regadenoson 82Rb PET/CT images with respect to the angiographic results in 96 patients without known CAD but clinically suspected CAD. The authors acknowledge that both pre- and post-test referral biases (as patients were referred for stress PET because of clinical findings, and coronary angiography was performed on the basis of clinical and imaging findings) may have artificially inflated the test sensitivity and deflated the test specificity.

- *Valenta et al. 2017*

A prospective single-centre non-controlled study was conducted to evaluate whether a PET-determined longitudinal decrease in myocardial blood flow (MBF) correlates with invasively measured fractional flow reserve (FFR) in coronary artery disease (CAD) patients.

Study participants

Twenty-nine patients (14 men, 15 women) with a median age of 68 (IQR: 55; 72) years and with stress-induced regional myocardial perfusion defects on 13N-ammonia PET images were included. Patients presented with suspected or known CAD.

Treatments

13Nammonia PET/CT during regadenoson stimulation and at rest was performed. A low-dose CT scan (120 kV,30 mA) for attenuation correction, PET emission data were measured during shallow breathing. PET image acquisition during regadenoson-stimulated hyperaemia (0.4 mg intravenous bolus injection over 10 and 20 s interval) was started immediately following injection of ≈370 MBq 13N-ammonia and also 45–60 min later at rest for a total duration of 18-min list-mode PET data acquisition, respectively.

Invasive quantitative coronary angiography was performed within 20 days of the 13N-ammonia PET study.

Objectives/endpoints

Myocardial perfusion and MBF in mL/g/min were determined with 13Nammonia PET/CT during regadenoson stimulation and at rest, and corresponding myocardial flow reserve (MFR=MBF stress/MBF rest) was calculated. A semiquantitative evaluation of 13N-ammonia PET perfusion images was performed with a standard 20-segment model and a five-point grading system by two expert observers. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were determined. An SSS <4 was considered normal, 4–8 mildly abnormal, 9–13 moderately abnormal, and >13 severely abnormal perfusion defect. In addition, an SDS ≥2 signified a reversible perfusion defect, whereas <2 was deemed as normal. According to this, the extent of regional reversible perfusion defects on 13N-ammonia PET images was scored according to the SDS value. An SDS of 2–4, >5–8, and >8 defined mild, moderate, and severe reversible perfusion defects, respectively.

Results

All patients had a history of effort-induced chest tightness: 19 with suspicion for CAD and 10 with known CAD. All patients presented with stress-induced regional myocardial perfusion defects on 13N-ammonia PET images (as an inclusion criteria). There were 24% (7 of 29) of patients with mild, 62% (18 of 29) with moderate, and 14% (4 of 29) with severe reversible perfusion defects.

There was a significant correlation between the hyperemic longitudinal MBF gradient and FFR (r=0.95; P= 0.0001), while this association was less pronounced for corresponding MFR (r=0.50; P=0.006).

Outcomes and estimation

Limited information is provided in this paper since no comparison versus another pharmacological stress agent is performed. This study evaluated whether myocardial blood flow quantitatively assessed on rest–stress regadenoson 13N-ammonia PET/CT images correlated with fractional flow reserve measured by invasive quantitative coronary arteriography in 29 patients with suspected/known CAD. There was a significant correlation. However, the relatively small sample size of a selected study population with severe and multivessel CAD is an important limitation of the study.

- *Van Tosh et al. 2020*

A retrospective single-centre non-comparative study was conducted to determine accuracy of PET for detecting CAD with quantitation of myocardial flow reserve.

Study participants

A total of 105 patients (age 69 ± 13 years; 42 females; 63 males) with known or suspected CAD, both symptomatic and asymptomatic, who had rest/regadenoson-stress 82Rb PET/CT data acquisition and arteriography at St. Francis Hospital, studied from January, 2010 through December, 2016 were retrospectively included.

Treatments

Coronary angiography was used as standard of truth.

82Rb PET/CT rest/regadenoson-stress: at rest, 0.94-1.22 GBq (35-45 mCi) of 82Rb was infused over 20-30 seconds from a 82Sr-82Rb generator. At peak pharmacologic stress, when hemodynamic steady state was achieved, usually 55-60 seconds after initiation of regadenoson injection, an activity similar to that used for rest imaging was infused for stress data acquisition. As noted in previous studies, about 10 seconds after initiation, the generator commenced infusion, which was complete at approximately 30 seconds.

Objectives/endpoints

PET images were interpreted quantitatively by a specific software to assess myocardial flow reserve. The coronarography images were interpreted quantitatively by software. Dichotomous rankings also were generated for quantified arterial territories, with ≥70% stenosis considered abnormal.

Results

65 vessels had stenoses ≥70%. 15 patients had multivessel disease (MVD). ROC area under curve (ROC AUC) for identifying patients with MVD was 83% for diastolic asynchrony (Asynch) and 73% for myocardial flow reserve (MFR). ROC AUC for identifying individual arterial territories with stenoses ≥ 70% was 81% and 72% for Asynch and MFR.

Outcomes and estimation

This was a retrospective non-controlled study. The dose of regadenoson administered was not mentioned. The test itself and the standard of truth were only quantitatively evaluated using specific software, to assess which quantitative parameters offer the best ROC curve to identify patients with coronary artery disease (stenosis ≥70%). However, visual/semiquantitative detection of reversible perfusion defects (as PET/CT images are interpreted in clinical practice) is missing.

- *Van Tosh et al. 2014*

A retrospective single-centre non-comparative study was conducted to determine the degree to which LV mass calculations obtained from 82Rb PET data are consistent from rest and stress imaging.

Study participants

205 consecutive patients (120 male, 85 female; age, 69 ± 12 years) referred for rest/regadenoson stress CT attenuation-corrected gated 82Rb PET MPI to evaluate known or suspected coronary disease. Studies were acquired between January 1, 2010 and June 30, 2011.

Treatments

82RbCl PET/CT rest/regadenoson-stress. At rest, 1.30 to 1.67 GBq (35-45 mCi) of 82Rb was infused over 20-30 seconds from a 82Sr-82Rb generator. At peak pharmacologic stress, when hemodynamic steady state was achieved, usually 55-60 seconds after initiation of regadenoson injection, an activity similar to that used for rest imaging was infused for stress data acquisition. CT scan transmission data were used to correct for attenuation.

Objectives/endpoints

Equilibrium gated myocardial perfusion PET data were analysed to calculate LV volumes, EF, and simultaneously mass values. Rest and stress LV EF, volume, and mass values were calculated using the Emory Cardiac Toolbox software. Polar perfusion maps using normal limits specific to 82Rb for relative perfusion distributions were generated using the Emory Cardiac Toolbox algorithms to compute summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS).

Results

Rest mass ranged from 62 to 284 g (median, 115 g), stress mass from 39 to 315 g (median, 120 g), and differences were -25 to +25 g (median, 1 g).
Rest and stress mass values were statistically similar (121±37 g vs 124±49 g, P = 0.45) and correlated strongly with one another (r = 0.94, P< 0.0001).

Outcomes and estimation

This was a retrospective non-controlled study, in which even the dose of regadenoson administered was not known. It aimed to study how left ventricular mass calculations using processing algorithms remain constant on rest and stress 82RbCl PET/CT. It is not an endpoint for diagnosis of a particular disease, or for interpretation of PET MPI images in clinical practice, but for quality control in LVEF calculations.

- *Brophey et al. 2017*

A retrospective single-centre non-controlled study to determine the clinical accuracy of 82Rb PET/CT MPI when performed with regadenoson stress in a U.S. Department of Veterans Affairs (VA) population of patients.

Study participants

480 patients presenting for a clinically indicated cardiac PET examination between January 2009 through July 2010. Ninety-seven percent were male, the average age was 61 y, and 38.9% had an established diagnosis of CAD at the time of the cardiac PET examination.

Clinical indications	
Chest pain	227 (47.5%)

Shortness of breath	30 (6.3%)
Risk factors	170 (35.5%)
Preoperative Abnormal ETT/ECG	6 (1.3%) 45 (9.4%)

Treatments

Coronary angiography was used as standard of truth.

PET/CT was performed before and after induction of pharmacologic stress using a rapid intravenous bolus of regadenoson, 0.4 mg, followed immediately by a 10-mL saline flush and stress tracer administration. Rest and stress imaging were both performed with 1,110 MBq (30 mCi) of 82RbCl (1,480 MBq [40 mCi] if patient weight>136 kg [300 lb]), and low-dose CT for attenuation correction was performed at rest and stress.

Objectives/endpoints

Perfusion images were independently interpreted by 4 experienced observers board-certified in nuclear medicine, who used a standard 17-segment cardiac model without knowledge of the catheterization results. The images were semi quantitatively analysed using a 5-point scoring system. A summed stress score (SSS) of less than 4 was considered normal; 4–8 was considered mildly abnormal; 9–13, moderately abnormal, and more than 13, severely abnormal.

Coronary cine angiograms were considered positive for significant CAD if the visually determined stenosis of the left main coronary artery was more than 50% or if the left anterior descending, circumflex, or right coronary arteries or their major branches had more than 70% stenosis.

Results

PET stress results were which were based on SSS, transient dilation, and systolic function evaluation, were normal (SSS<4) in 223 patients (46.5%), mildly abnormal (SSS 4–8) in 134 (27.9%), moderately abnormal (SSS 9–13) in 55 (11.5%), and severely abnormal (SSS>13, transient dilation, drop in left ventricular systolic function) in 68 (14.2%).

Catheterization correlation demonstrated a sensitivity of 95%, a positive predictive value of 88.4% for significant coronary artery disease, and an overall accuracy of 86% for PET MPI with regadenoson stress when compared with invasive catheterization.

Outcomes and estimation

The paper published by Brophey et al. 2017 refers to a retrospective non-controlled study in 480 patients (mostly men) presenting for a clinically indicated cardiac PET examination. Efficacy was based on the semiquantitative assessment of rest–stress regadenoson 82Rb PET/CT images with respect to the angiographic results. The retrospective nature of the study is considered an important limitation to support efficacy of regadenoson for PET MPI.

- *Cremer et al. 2014*

A retrospective single-centre non-controlled study to investigate regadenoson stress PET in high-risk patients with aortic stenosis (AS) and CAD, particularly the safety and the potential to guide coronary revascularization.

Study participants

50 consecutive patients who were referred to our institution for consideration of transcatheter aortic valve replacement (TAVR) and underwent regadenoson stress cardiac PET from May 2010 through August 2013. Patients were high risk with a mean Society of Thoracic Surgeons mortality score of 11.4% and had severe AS with a moderately reduced left ventricular ejection fraction (EF) (mean aortic valve area of 0.78 ± 0.25 cm2 and mean EF of 39 ± 16%). The vast majority had known CAD (92%).

Treatments

Coronary angiography was used as standard of truth. Obstructive CAD was defined as a stenosis >50% as determined by the interventional cardiologist. The severity of stenosis was based upon the invasive coronary angiography report in the medical record.

STRESS/REST MPI PET and FDG PET: gated cardiac PET images using 82-Rubidium or 13N-Ammonia were acquired. Seven patients received 13N-Ammonia, and 43 patients received 82-Rubidium. Stress images were obtained after the administration of 0.4 mg of intravenous regadenoson, and viability was assessed with 18F-FDG.

Objectives/endpoints

The perfusion defects were quantified using semi-automated polar maps with a 5-point scoring system and a 17-segment model by experienced nuclear cardiologists. The PET test was considered abnormal if there was any perfusion defect not related to artifact or if the EF was less than 45%. Summed rest score (SRS), summed stress score (SSS), and summed difference score (SDS) were recorded. Jeopardized myocardium was calculated as SDS, the amount of ischemia present, plus the rest score for any segments deemed viable with this total divided by 68 and then expressed as a percentage by multiplying by 100. If a viability study was not performed, then the SDS alone was used to calculate jeopardized myocardium. Jeopardized coronary territories were determined prior to revascularization according to established guidelines. Global myocardial blood flow (MBF) at rest and during stress was calculated using a one-compartment model of 82Rb kinetics and a nonlinear extraction function as previously validated. A region of interest was positioned at the base of LV to obtain the arterial input function. Myocardial flow reserve (MFR) was obtained by dividing stress MBF by resting MBF. We were able to calculate MBF on 26 patients. Among our cohort, 9 patients were excluded as they had testing performed before we began routinely measuring MBF, and 15 patients were excluded because they had testing on a PET scanner that did not have dynamic capability. All tests were reviewed and scored by an experienced nuclear medicine physician or cardiologist. The percentage of jeopardized myocardium was determined by combining ischemic and hibernating myocardium.

Coronary angiography was performed after PET MPI in 37 (74%) patients, and 36 (95%) of these patients had obstructive CAD. Coronary angiography after PET MPI was not performed in 13 patients (26%), but these patients had their coronary anatomy defined in the past. These 13 patients had minimal to no jeopardized myocardium (median of 0% with interquartile range of 0-3%). One patient with a normal PET study had a coronary angiogram that showed no obstructive CAD. All but one patient with an abnormal PET study had obstructive CAD upon coronary angiography.

Results

Most PET studies were abnormal. An assessment for viability with FDG was performed in 38 (76%) patients. Of these patients, 11 (28%) had hibernating myocardium with a median (interquartile range)

of 4% (3%,10%) hibernating myocardium. Regadenoson PET without FDG was performed in 12 (24%) patients. Of these patients, 7 had no or a minimal resting perfusion defect (SRS B4), and 3 of the remaining 5 patients had an ejection fraction [35%. The median amount of jeopardized myocardium, defined as ischemic plus hibernating myocardium, for all patients was 12.5%.

Outcomes and estimation

The paper published by Cremer et al. 2014 refers to a retrospective non-controlled study to investigate regadenoson stress PET in high-risk patients with AS and CAD, particularly the safety and the potential to guide coronary revascularization. Regarding efficacy, the percentage of jeopardized myocardium in patients was determined by combining ischemic and hibernating myocardium. Therefore, more than one PET examination was required: one MPI PET and one FDG-PET. MPI PET was done using two different radiopharmaceuticals in different patients.

Given the study design (retrospective study from a single centre involving patients referred specifically for TAVR – for whom the authors considered that PET is not clinically indicated) and the sample size, results are considered of little support.

- Goudarzi et al. 2011

A retrospective single-centre controlled study to determine whether the global flow response to regadenoson is comparable to that with the previous standard dipyridamole.

Study participants

This study retrospectively analysed the records and images of 52 patients who had undergone PET/CT myocardial perfusion imaging with 82Rb-rubidium chloride:

- During the first year of use of regadenoson: 52 patients. Only subjects with no prior history of coronary artery disease, with normal regional myocardial perfusion and normal left ventricle (LV) function (left ventricular ejection fraction, LVEF,>45%) on PET scan were included.
- Using the same inclusion and exclusion criteria, a similar group of patients who had dipyridamole for stress testing were identified from among those subjects who had undergone 82Rb myocardial perfusion PET imaging during the 2 years prior to the introduction of regadenoson (Jan 2007 to Jan 2009). The dipyridamole group was selected to match the regadenoson group for clinical variables including age, sex distribution, weight and body mass index (BMI), coronary risk factors including hypertension, cigarette smoking, hyperlipidaemia, diabetes and obesity, and baseline haemodynamics including baseline heart rate and systolic and diastolic blood pressure.

Treatments

PET/CT before and after induction of pharmacologic stress: a low-dose CT scan for attenuation correction of PET data was acquired during shallow breathing. Using a large antecubital intravenous line, 40–50 mCi of 82Rb-rubidium chloride was infused, and a list-mode 2-D PET scan was acquired for 8 min.
Vasodilator stress was then started and a second dose of 40–50 mCi of 82Rb-rubidium chloride was infused, followed by acquisition of an 8-min list-mode scan. Quality control of PET and CT for attenuation correction was performed and datasets were realigned if necessary. List-mode data were resampled to provide attenuation-corrected static (90-s prescan delay) and electrocardiographically gated (eight bins) images for clinical analysis. For absolute quantification of MBF, list-mode data were also resampled to provide dynamic images.

Dipyridamole stress: after the rest acquisition, infusion of dipyridamole was started (0.56 mg/kg, 4 min), and 82Rb infusion was started 4 min after the end of the dipyridamole infusion. Heart rate and blood pressure were recorded at baseline and every 2 min during infusion, at the end of infusion and at the end of the test. Peak stress heart rate was defined as the highest heart rate at any time during dipyridamole stress. Stress systolic, diastolic and mean blood pressures were defined as the values at the time of peak heart rate.

Regadenoson stress: after the rest acquisition, one prepared syringe of regadenoson (0.4 mg regadenoson in 5 ml solution) was injected over approximately 15 to 20 s into a peripheral vein, followed by a 5 ml saline flush. 82Rb infusion was started 30 s after the saline flush.

Objectives/endpoints

Static images were reangled to create short-axis and long-axis slices for visual analysis to exclude regional perfusion defects. Previously validated commercially available software (CardIQ physio) was used for analysis of electrocardiographically gated datasets to exclude cardiomyopathy and to calculate stress/resting LVEF. Quantification of MBF Myocardial activity in the last frame of the dynamic datasets was volumetrically sampled and polar maps of the LV were generated.

Results

Global MBF at rest, and during pharmacological vasodilation was not different between the regadenoson and dipyridamole groups, and there was no difference in MFR between the groups.

Outcomes and estimation

This was a retrospective interindividual comparison of 82RbCl PET MPI with regadenoson and with dipyridamole. It was shown that regadenoson increases absolute MBF at a level similar to the prior standard dipyridamole. Two groups of patients with myocardial perfusion PET images who were stressed with either regadenoson or dipyridamole were compared, and the groups were matched to the best possible level according to clinical variables, baseline haemodynamic characteristics, cardiovascular risk factors and MBF at rest. With this design, however, it is impossible to control for every potential interfering factor. Secondly, the ideal comparison of the flow response to two stress agents would require healthy subjects, where all factors that may potentially interfere with flow are excluded. Selected subjects who were as healthy as possible were recruited, but some coronary risk factors had to remain because the subjects were referred for a clinical perfusion study with an appropriate indication. Despite this limitation, it should be noted that this study reflects the true clinical situation in which the stress agent will be applied. And thirdly, 82Rb was used as PET perfusion tracer. While 82Rb is the most frequently used agent for clinical perfusion PET, it may have limitations for absolute quantification of MBF in the high flow range. Subtle differences between regadenoson and dipyridamole may thus have been missed in this study.

- *Memmott et al. 2018*

A retrospective single-centre controlled study was conducted to investigate the effect on patient motion of two pharmacological stressing agents, adenosine and regadenoson.

Study participants

This study comprises a retrospective review of 30 consecutive patients attending for a clinically indicated 82Rb dynamic PET/CT study who underwent stress using regadenoson. Two comparison groups of 30 patients during the same period who underwent stress via adenosine or incremental adenosine were also randomly selected.

Treatments

All patients were administered with 1110 MBq (30 mCi) of 82Rb from a Cardiogen 82Sr generator (Bracco Diagnostics). Adenosine patients underwent pharmacological stressing via a 4.5-minute infusion at a rate of 140 lg/kg/min. Incremental adenosine patients followed our standard incremental protocol of a 1-minute infusion at 50 lg/kg/min, followed by 1 minute at 100 lg/kg/min and 4 minutes at 140 lg/kg/min. Regadenoson patients underwent an injection of 400 lg of Rapiscan over 20 seconds. Data acquisition began 2.5 minutes before the end of the adenosine infusion, 2 minutes before the end of the incremental infusion, or 40 seconds after the end of the Rapiscan injection. Data were acquired on a Siemens Biograph mCT (Siemens Healthcare, Knoxville, US) with TrueV extended field of view. List mode data acquisition was started at the same time as the 82Rb infusion and lasted 7 minutes. For the dynamic reconstructions, all data were reframed into 18 frames of varying lengths: 1 9 10 seconds, 8 9 5 seconds, 3 9 10 seconds, 2 9 20 seconds, and 4 9 60 seconds. Prior to the rest acquisition, a low-dose (0.4 mSv) CT acquisition was performed for purposes of attenuation correction. A static reconstruction based on the fourth minute of the acquisition was used to check and correct for any misregistration between the PET and CT data, and the correction applied to all frames.

Objectives/endpoints

Severity of motion was scored qualitatively using a four-point (0-3) scale and quantitatively using frame-to-frame pixel shifts. The type of motion, returning or non-returning, and the frame in which it occurred were also recorded.

Results

There were significant differences in both the qualitative and quantitative scores comparing regadenoson to adenosine (P 5.025 and P < .001) and incremental adenosine (P=.014, P=.015), respectively. The difference in scores between adenosine and incremental adenosine was not significant. Where motion was present, significantly more adenosine patients were classed as non-returning (P 5.018). The median frames for motion occurring were 12 for regadenoson and 14 for both adenosine cohorts.

Outcomes and estimation

This study was a retrospective review of previously acquired clinical data, and hence it was not possible to randomly allocate patients to different stressing protocols. Although all attempts were made to control bias due to demographics, it is still possible that some bias may remain.

- *Koenders et al. 2019*

A retrospective single-centre non-controlled study was conducted to determine the prevalence and the effect of correcting for this myocardial creep on myocardial blood flow (MBF) quantification.

Study participants

119 consecutive patients referred for MPI using Rb-82 PET/CT who underwent dynamic rest- and pharmacological-induced stress using regadenoson.

Treatments

Prior to MPI, a low-dose CT scan was performed. Next, 740 MBq Rb-82 was administered intravenously with a flow rate of 50 mL/min using a Sr- 82/Rb-82 generator (CardioGen-82, Bracco Diagnostics Inc.). After the first elution, we induced pharmacological stress by administrating 400 µg (5 mL) of regadenoson over 10 seconds. After a 5 mL saline flush (NaCl 0.9%), we administered a second dose of 740 MBq Rb-82. We acquired seven-minute PET list-mode acquisitions after both Rb-82 administrations. Attenuation correction was applied to all data on the PET system after semiautomatic registration of CT and PET data.

Objectives/endpoints

Both rest and stress MBFs were calculated for the original data and for the corrected data regarding the three vascular territories (LAD, LCX, and RCA) and for the whole myocardium.

Results

Myocardial creep was observed in 52% of the patients during stress. Mean MBF values decreased after correction in the RCA from 4.0 to 2.7 mL/min/g ($P < 0.001$), in the whole myocardium from 2.7 to 2.6 mL/min/g ($P = 0.01$), and increased in the LAD from 2.5 to 2.6 mL/ min/g ($P = 0.03$) and remained comparable in the LCX ($P = 0.3$).

Outcomes and estimation

This was a retrospective non-controlled study, in which it was assessed the impact of regadenoson-induced myocardial creep (which is an image artifact but not a finding/lesion to assess in clinical practice) on MBF quantification by 82Rb PET.

- Cremer et al. 2015

A retrospective single-centre controlled study was conducted to assess the relationship between heart rate and septal perfusion abnormalities in patients undergoing SPECT and PET MPI.

Study participants

A total of 440 consecutive patients with left Bundle BrAnch Block (LBBB) from August 2012 through July 2014.

Treatments

Regadenoson-stress SPECT MPI and regadenoson-stress PET MPI.

Objectives/endpoints

No detailed data are provided.

Results

In a cohort of 440 patients (67 PET, 373 SPECT; 71 + 11 years), comorbidities were more common in patients undergoing PET compared to SPECT (CAD 60.6% v 40.0%, p = 0.003; ejection fraction 32 + 16% v 55 + 16%, p <0.001). Possible septal perfusion artefacts were less common in PET v SPECT (1.5% v 19.3%, p <0.001). When compared to SPECT, PET patients had increased resting HRs (76 + 14 v 69 + 12, p<0.001), but a blunted response to regadenoson (peak 90 + 18 v 95 + 18, p = 0.04; change 14 + 11 v 26 + 14, p < 0.001).

Outcomes and estimation

This study was a poster and detailed information is missing.

- Bravo et al. 2012

A retrospective single-centre controlled study was conducted to compare interindividually regadenoson to dipyridamole for regional myocardial perfusion (rMP) and quantification of myocardial blood flow (MBF) with PET in hypertrophic cardiomyopathy (HC) patients.

Study participants

A total of 57 consecutive patients with a history of HC diagnosed by echocardiography, who were referred for cardiac PET for clinical indications between January of 2009 and February of 2012. Subjects with history of coronary artery disease (CAD), prior surgical myectomy or alcohol septal ablation were excluded. The diagnosis of HC was based on echocardiographic criteria by demonstrating left ventricular (LV) hypertrophy with wall thickness ≥ 15 mm.

Treatments

Nitrogen-13 ammonia PET was performed in 57 patients at rest and during vasodilator stress (peak), with either dipyridamole (0.56 mg/kg during 4-minute infusion) or regadenoson (0.4 mg fixed bolus dose), using a same day rest/stress protocol. Dipyridamole was the drug of choice at the beginning of our PET protocol for HC in 2009; however, as of May of 2011, all HC patients were stressed with regadenoson.

Objectives/endpoints

Electrocardiographic findings, rMP (17-segment American Heart Association summed difference score), MBF, and CFR. An SDS equal to or greater than 2 was considered abnormal. The Munich Heart package was used for absolute flow quantification. Coronary flow reserve (CFR) was determined as the ratio of stress MBF to rest MBF (unitless).

Results

A total of 57 individuals with HC were included in this cohort: 28 were stressed with dipyridamole and 29 patients with Regadenoson. Baseline and echocardiographic characteristics, including maximal wall thickness, were highly comparable between both groups.
The prevalence of abnormal rMP (71 vs. 83%, P = 0.3) and severity of reversible perfusion defects (SDS of 5.5 ± 5.5 vs. 5.8 ± 6.7, P = 0.8) were similar in patients undergoing dipyridamole and regadenoson vasodilator stress. At baseline, global MBF was similar between the dipyridamole and regadenoson group. After pharmacologic administration, the hyperaemic-MBF achieved in the entire LV with Dipyridamole was similar to that obtained with Regadenoson. As a result, global CFR was not significantly different between HC patients stressed with Dipyridamole or Regadenoson (2.02 ± 0.53 vs. 2.12 ± 0.12; P = 0.5). After correction for baseline differences in heart rate and systolic blood pressure, the resting MBF (0.99 ± 0.26 vs. 0.88 ± 0.22 ml/min/g; P = 0.1) and CFR (1.90 ± 0.52 vs. 2.19 ± 0.74; P = 0.1) remained comparable between the Dipyridamole and Regadenoson group. Regionally, no significant differences between Dipyridamole and Regadenoson in hyperaemic-MBF were observed in any myocardial wall.

Outcomes and estimation

The authors already acknowledged the retrospective nature of the study and the small sample size as important limitations of this study. The results show similar values of peak MBF and CFR following infusion of Dipyridamole or Regadenoson in this cohort of HC patients with similar baseline clinical and echocardiographic characteristics.

They observed a high prevalence of abnormal rMP (n=44/57) in the HC cohort. The presence and severity (evaluated by SDS) of myocardial perfusion abnormalities elicited by Regadenoson and Dipyridamole were similar.

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

Three prospective comparative single-centre published studies on CMR MPI, that are considered the main source of data for this application:

- Vasu et al. 2013 performed a within-subject comparison of regadenoson versus adenosine versus dipyridamole for stress CMR in 20 young healthy male volunteers
- DiBella et al. 2012 compared intraindividually regadenoson versus dipyridamole used as a stress agent on CMR MPI across a range of body sizes
- Thomas et al. 2017 compared intraindividually adenosine and regadenoson for stress CMR in healthy volunteers

• Vasu et al. 2013

A prospective single-centre controlled study was conducted to determine the relative potency of regadenoson, adenosine, and dipyridamole by quantifying stress and rest myocardial perfusion in humans using cardiovascular magnetic resonance (CMR).

Study participants

50 healthy subjects (Framingham score <1%) were recruited.

Treatments

CMR at rest and during stress was performed. Pharmacological stress with each of the products (regadenoson, 400 µg in bolus), dipyridamole (0.56 mg/kg over 4 minutes) and adenosine (140 µg/kg/min over 5 to 6 minutes) was carried out within a few-minutes days apart. Rest perfusion imaging was performed initially. Twenty minutes later, stress imaging was performed at peak vasodilation, i.e.70 seconds after regadenoson, 4 minutes after dipyridamole infusion and between 3–4 minutes of the adenosine infusion.

Objectives/endpoints

Myocardial blood flow (MBF) in ml/min/g and myocardial perfusion reserve (MPR) were quantified using a fully quantitative model constrained deconvolution.

Results

Regadenoson produced higher stress MBF than dipyridamole and adenosine (3.58±0.58vs.2.81±0.67vs.2.78±0.61ml/min/g, p=0.0009 and p=0.0008 respectively). Regadenoson had a much higher heart rate response than adenosine and dipyridamole respectively (95±11vs.76±13vs.86±12beats/minute). When stress MBF was adjusted for heart rate, there were no differences between regadenoson and adenosine (37.8±6vs.36.6±4µl/sec/g, p=NS), but differences between regadenoson and dipyridamole persisted (37.8±6vs.32.6±5µl/sec/g, p=0.03). The unadjusted MPR was higher with regadenoson (3.11±0.63) when compared with adenosine (2.7±0.61, p=0.02) and when compared with dipyridamole (2.61±0.57, p=0.04). Similar to stress MBF, these differences in MPR between regadenoson and adenosine were abolished when adjusted for heart rate (2.04±0.34vs.2.12±0.27, p=NS), but persisted between regadenoson and dipyridamole (2.04±0.34vs.1.77±0.33, p=0.07) and between adenosine and ipyridamole (2.12±0.27vs.1.77±0.33, p=0.01).

Outcomes and estimation

This prospective study intraindividually compared regadenoson versus adenosine and dipyridamole in young healthy normal volunteers. The CHMP considered this a main study to support the clinical efficacy of regadenoson as pharmacological stress agent in CMR MPI. The study showed regadenoson and adenosine having a similar efficacy on vasodilation (similar stress MBF adjusted for heart rate) and superior to dipyridamole.

This study has some limitations:

- the study population consisted predominantly of young, healthy male volunteers. Authors acknowledged that response of patients to vasodilators is influenced not only by coronary artery disease but concomitant risk factor. Patients might have different normal ranges of blood flow responses than young healthy volunteers.

- the protocol used in this study as rest-stress imaging which is different from currently used protocols.

- DiBella et al. 2012

A prospective single-center comparative study was conducted to demonstrate whether a single fixed size dose of regadenoson produces comparable coronary hyperemia than adenosine across the range

of body sizes seen in a clinical setting, and to explore the suitability of regadenoson for use during MRI.

Study participants

Thirty subjects (12 female, 18 male, mean BMI 30.3 ± 6.5, range 19.6–46.6) were imaged. Forty-three % of the subjects were obese based on World Health Organization Criteria. Twenty-five % had one or more known coronary risk factors.

Treatments

A 3T magnetic resonance scanner was used. Imaging with a saturation recovery radial turboFLASH sequence was done first at rest, then during adenosine infusion (140 lg/ kg/min) and 30 min later with regadenoson (0.4 mg/ 5 ml bolus). A 5 cc/s injection of Gd-BOPTA was used for each perfusion sequence, with doses of 0.02, 0.03 and 0.03 mmol/kg, respectively.

Objectives/endpoints

Analysis of the upslope of myocardial time-intensity curves and quantitative processing to obtain myocardial perfusion reserve (MPR) values were performed for each vasodilator.

Results

The tissue upslopes for adenosine and regadenoson matched closely ($y = 1.1x + 0.03$, $r = 0.9$). Mean MPR was 2.3 ± 0.6 for adenosine and 2.4 ± 0.9 for regadenoson ($p = 0.14$). There was good agreement between MPR measured with adenosine and regadenoson ($y = 1.1x - 0.06$, $r = 0.7$). The MPR values measured with both agents tended to be lower as BMI increased.

Outcomes and estimation

This prospective study intra-individually compared regadenoson versus adenosine in relation to the caused coronary hyperemia across the range of body sizes seen in a clinical setting. The CHMP considered this to be the main study to support the clinical efficacy of regadenoson as pharmacological stress agent in CMR MPI. The study showed regadenoson and adenosine having a similar efficacy on vasodilation (good agreement between MPR measured with adenosine and regadenoson).

This study has some limitations. Apart from several technical factors that could affect the interpretation of the study data, the main limitation is the relatively small sample size. The intent was not to prove the diagnostic accuracy of regadenoson in the evaluation of patients with possible coronary artery disease. Rather, the goal was to demonstrate whether a single fixed size dose of regadenoson produces comparable coronary hyperemia across the range of body sizes seen in a clinical setting, and to explore the suitability of regadenoson for use during MRI. In the recruited sample there were 45% of obese subjects, and 25% had one or more known coronary risk factor. The studied population with different body sizes would likely not include the broad spectrum of patients as might be seen in daily CMR MPI.

- Thomas et al. 2017

A prospective single-center study was conducted to evaluate the effects of vasodilators on CMR-derived ventricular volumes and function.

Study participants

25 healthy subjects

Treatments

Consecutive adenosine and regadenoson administration. Short axis CINE datasets were obtained on a 1.5 T scanner following adenosine (140mcg/kg/min IV for 6 min) and regadenoson (0.4 mg IV over 10 s) at baseline, immediately following administration, at 5 min intervals up to 15 min.

Objectives/endpoints

Hemodynamic response, bi-ventricular volumes and ejection fractions were determined at each time point.

Results

Peak heart rate was observed early following administration of both adenosine and regadenoson. Heart rate returned to baseline by 10 min post-adenosine while remaining elevated at 15 min post-regadenoson ($p = 0.0015$). Left ventricular (LV) ejection fraction (LVEF) increased immediately following both vasodilators ($p < 0.0001$ for both) and returned to baseline following adenosine by 10 min ($p = 0.8397$). Conversely, LVEF following regadenoson remained increased at 10 min ($p = 0.003$) and 15 min ($p = 0.0015$) with a mean LVEF increase at 15 min of 4.2 ± 1.3%. Regadenoson resulted in a similar magnitude reduction in both LV end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi) at 15 min whereas LVESVi resolved at 15 min following adenosine and LVEDVi remained below baseline values ($p = 0.52$).

Outcomes and estimation

This prospective study intraindividually compared regadenoson versus adenosine to evaluate the effects of vasodilators on CMR-derived ventricular volumes and function in 25 healthy subjects. They concluded that both vasodilators have significant and prolonged impact on ventricular volumes and LVEF. The main limitation of the study was young and healthy because hemodynamic responses may not be similar to individuals with cardiovascular disease and/or myopathic processes.

Below are included the non-controlled studies and/or retrospective studies provided.

- Romano et al. 2020

A prospective single-center study was to determine the prognostic value of feature-tracking global longitudinal strain measured during vasodilator stress cardiac magnetic resonance (CMR) imaging.

Study participants

535 consecutive patients undergoing stress perfusion CMR for evaluation of known or suspected CAD were prospectively enrolled.

Treatments

CMR images were acquired. 0,4 g of regadenoson were injected. Rest perfusion images were obtained after stress perfusion images with an additional contrast bolus.

Objectives/endpoints

Feature-tracking stress was measured immediately after regadenoson perfusion. Patients were followed for major adverse cardiac events.

Results

82 patients experienced major adverse cardiovascular event (MACE) over a median follow-up of 1.5 years. Patients with stress GLS ⩾ median (-19%) had significantly reduced event-free survival compared with those with stress GLS < median (log-rank p<0.001). Stress GLS was significantly associated with risk of MACE after adjustment for clinical and imaging risk factors (hazard ratio: 1.267; p<0.001).

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. Efficacy was based on the assessment of feature-tracking stress GLS measured during vasodilator stress CMR, which seems to be an independent predictor of MACE in patients with known or suspected CAD. The authors acknowledge that selection bias related to being able to undergo a CMR examination could exist. Moreover, results could not extrapolate to other centers using different methods to measure feature-tracking stress GLS (using other type of images, other software platforms) or were performed by not very experienced personnel.

- Bohnen et al. 2019

A prospective single-center non-comparative study was conducted to evaluate the performance of a segmental, truly non-contrast stress T1 mapping CMR approach to detect inducible ischemia.

Study participants

One-hundred patients with suspected/known coronary artery disease underwent CMR.

Treatments

T1 mapping CMR was performed using a 5s(3s)3s-MOLLI sequence before (=rest) and at400 µg regadenoson stress (before stress-perfusion CMR) on three representative short-axis slices (basal, midventricular, and apical).

Objectives/endpoints

T1 reactivity was defined as the change in native T1 from rest to stress (1) in the 16-segment AHA model independent from perfusion images and (2) in focal regions of interest that were copied from perfusion images to T1 maps. T1 reactivity was compared between segments/regions with inducible ischemia, scar, and remote myocardium for both approaches.

Results

Segmental T1 reactivity was significantly lower in segments including inducible ischemia [−1.15 (95%CI, −2.16 to −0.14)%] compared to remote segments [2.49 (95% CI, 1.87 to 3.11)%;p<0.001]. Focal T1 reactivity was also significantly lower [−2.65 (95% CI, −3.84 to −1.46)%] in regions with stress-perfusion defects compared to remote regions [4.72 (95% CI, 3.90 to 5.54)%;p<0.001]. However, the performance of segmental T1 reactivity to depict inducible ischemia was significantly inferior compared to the focal approach (AUCs 0.68 versus 0.85; p<0.0001). Stress T1 mapping did not enable a reliable differentiation between inducible ischemia and scar.

Outcomes and estimation

The authors concluded that myocardium with inducible ischemia is characterized by the absence of significant T1 reactivity and that the performance of a non-contrast segmental approach is not matured enough for clinical use so far. Limited information is provided in this paper since no comparison versus adenosine is performed. Another limitation is the sample size. Furthermore, this study does not provide intra-individual comparisons between different field strengths or T1 mapping sequences. Finally, stress-perfusion CMR was used as an accepted non-invasive reference technique for myocardial ischemia, but invasive coronary angiography and fractional flow reserve (FFR) were not systematically performed for ethical reasons in patients with a negative stress test.

- Zorach et al. 2018

A prospective single-center non-comparative study was conducted to evaluate whether fully quantitative CMR identifies reduced myocardial perfusion reserve (MPR) in patients with angina and risk factors for microvascular disease (MVD).

Study participants

Forty-six patients with typical angina and risk factors for MVD (females, or males with diabetes or metabolic syndrome) who had no obstructive coronary artery disease by coronary angiography and 20 healthy control subjects underwent CMR.

Treatments

Regadenoson stress CMR perfusion imaging using a dual-sequence quantitative spiral pulse sequence to quantify MPR. Subjects also underwent T1 mapping to quantify ECV and computed tomographic (CT) coronary calcium scoring to assess atherosclerosis burden.

Objectives/endpoints

Quantitative MPR and MBF T1 mapping and computed tomographic (CT) coronary calcium scoring.

Results

In patients with risk factors for MVD, both MPR (2.21 [1.95,2.69] vs. 2.93 [2.763.19], $p < 0.001$) and stress myocardial perfusion flow (2.65 ± 0.62 ml/min/g, vs. 3.17 ± 0.49 ml/min/g $p < 0.002$) were reduced as compared to controls. These differences remained after adjusting for age, left ventricular (LV) mass, body mass index (BMI), and gender. There were no differences in native T1 or ECV between subjects and controls.

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. It was concluded that Stress myocardial perfusion and MPR as measured by fully quantitative CMR perfusion imaging are reduced in subjects with risk factors for MVD with no obstructive CAD as compared to healthy controls. The authors acknowledged that, due to study enrolment after coronary angiography, invasive CFR and coronary reactivity testing were not acquired at the time of angiography to validate the diagnosis of MVD and to compare with the quantitative CMR findings.

- Bieging et al. 2017

A prospective single-center non-comparative study was conducted to investigate an approach of cardiovascular magnetic resonance (CMR) perfusion imaging with no ECG gating and a rapid rest/ stress perfusion protocol to determine its accuracy for detection of CAD in patients with AF.

Study participants

26 patients with a history of AF (age 69 ± 12 years, 15 males and 11 females) who were either being referred to X-ray coronary angiography or who had recently undergone clinically indicated X-ray coronary angiography without intervention within 30 days were included in this prospective study from January 2013 to November 2015.

Treatments

A rapid rest/regadenoson stress CMR perfusion imaging protocol.

Objectives/endpoints

CMR perfusion images were interpreted by three blinded readers as normal or abnormal. Diagnostic accuracy was evaluated by comparison to X-ray angiography

Results

21 of the CMR rest/stress perfusion scans were negative, and 5 were positive by angiography criteria. Majority results of the ungated datasets from all of the readers showed a sensitivity, specificity and accuracy of 80%, 100% and 96%, respectively, for detection of CAD.

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. An ungated, rapid rest/stress regadenoson perfusion CMR protocol appears to be useful for the diagnosis of obstructive CAD in patients with AF. Results showed a sensitivity, specificity and accuracy of 80%, 100% and 96%, respectively, for detection of CAD. However, the authors acknowledged that the prevalence of obstructive CAD was lower than expected (5 of 26 patients had obstructive CAD) and larger studies in populations with a higher prevalence of obstructive CAD are necessary to further validate the sensitivity of this novel approach to detect CAD in patients with AF.

- Abbasi et al. 2014

A prospective single-center non-comparative study was conducted to determine the prognostic association of presence of inducible ischemia by CMR with MACEs.

Study participants

A total of 346 patients with suspected ischemia who were referred for regadenoson CMR were studied.

Treatments

Regadenoson stress CMR MPI was used.

Objectives/endpoints

The prognostic association of presence of inducible ischemia by CMR with MACEs was determined.

Results

There were 52 MACEs during a median follow-up period of 1.9 years. Patients with inducible ischemia were fourfold more likely to experience MACEs (hazard ratio, 4.14, 95% confidence interval 2.37 to 7.24, p <0.0001). In the best overall model, presence of inducible ischemia conferred a 2.6-fold increased hazard for MACEs adjusted to known clinical risk markers (adjusted hazard ratio 2.59, 95% confidence interval 1.30 to 5.18, p = 0.0069). Patients with no inducible ischemia experienced a low rate of cardiac death and myocardial infarction (0.6% per patient-year), whereas those with inducible ischemia had an annual event rate of 3.2%. In conclusion, in patients with clinical suspicion of myocardial ischemia, regadenoson stress CMR MPI provides robust risk stratification. CMR MPI negative for ischemia was associated with a very low annual rate of hard cardiac events.

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. However, the study was quite large, with 346 patients undergoing stress MRI with regadenoson for the assessment of myocardial ischaemia. The authors conclude that data suggest that inducible ischemia on regadenoson CMR MPI can add incremental knowledge to clinically derived estimates of cardiovascular risk as regadenoson MRI allowed good risk stratification in patients with clinical suspicion of myocardial infarction. An important limitation is that there was not a control group.

- Dandekar et al. 2014

A prospective single-center non-comparative study was conducted to determine 1) the feasibility of MPR quantification during regadenoson stress CMR by measurement of Coronary Sinus flow, and 2) the role of aminophylline reversal on regadenoson stress-CMR.

Study participants

117 consecutive patients with possible myocardial ischemia were prospectively enrolled.

Treatments

Perfusion imaging was performed at 1 minute and 15 minutes after administration of 0.4 mg regadenoson. A subgroup of 41 patients was given aminophylline (100 mg) after stress images were acquired.

Objectives/endpoints

CS flow was measured during phase-contrast imaging at baseline (pre-CS flow), an immediately after the stress (peak CS flow) and rest (post CS flow) perfusion images.

Results

CS flow measurements were obtained in 92% of patients. MPR was significantly underestimated when calculated as peak CS flow/post CS flow as compared to peak CS flow/pre CS flow (2.43±0.20vs.3.28±0.32, p=0.03). This difference was abolished when aminophylline was administered (3.35±0.44vs.3.30±0.52, p=0.95).

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. The authors conclude that regadenoson stress CMR with MPR measurement from CS flow can be successfully performed in most patients and this measurement of MPR appears practical to perform in the clinical setting. Residual hyperemia is still present event 15 minutes after regadenoson administration, at the time of resting-perfusion acquisition, and is completely reversed by aminophylline. However, there are important limitations in the study mainly technical errors and also that there was no direct head-to-head comparison with MPR obtained by a standard technique as PET.

- Freed et al. 2013

A prospective single-center non-comparative study was conducted to determine the prognostic value of a normal regadenoson perfusion CMR in patients with known or suspected CAD.

Study participants

Patients with known or suspected CAD were prospectively enrolled to receive perfusion CMR with regadenoson.

Treatments

First pass contrast CMR performed at 1 minute after injection of regadenoson (0.4 mg) and repeated 15 minutes after reversal of hyperemia with aminophylline (125 mg).

Objectives/endpoints

CMR was considered abnormal if there was a resting wall motion abnormality, decreased LVEF (<40%), presence of late gadolinium enhancement, or the presence of a perfusion defect during hyperemia. All patients were following for a minimum of 1 year for major adverse cardiovascular event (MACE).

Results

149 patients were included in the final analysis. Perfusion defects were noted in 43/149 patients; 49/149 had any abnormality on CMR. During the mean follow-up period of 24±9 months, 17/149 patients experienced MACE. The separation in the survival distributions for those with perfusion defects and those without perfusion defects was highly significant (log-rank p=0.0001). When the absence of perfusion defects was added to the absence of other resting CMR abnormalities, the negative predictive value improved from 96% to 99%.

Outcomes and estimation

Limited information is provided in this paper since no comparison versus adenosine is performed. The authors conclude that regadenoson perfusion CMR provides high confidence for excellent prognosis in patients with normal perfusion. However, sensitivity and specificity of regadenoson perfusion CMR for detection of CAD could not be assessed since only a small subgroup of patients underwent coronary angiography. Moreover, there was a low number of cardiovascular events although every patient was followed for a minimum of 1 year and had known or suspected CAD.

- Bhave et al. 2012

A prospective single-center non-comparative study was conducted to determine the optimal regadenoson CMR protocol for quantifying myocardial perfusion reserve index (MPRi).

Twenty healthy subjects underwent CMR perfusion imaging during resting conditions, during regadenoson-induced hyperemia (0.4 mg), and after 15 min of recovery. In 10/20 subjects, recovery was facilitated with aminophylline (125 mg). Myocardial time-intensity curves were used to obtain left ventricular cavity-normalized myocardial up-slopes. MPRi was calculated in two different ways: as the up-slope ratio of stress to rest (MPRi-rest), and the up-slope ratio of stress to recovery (MPRi-recov).

Results

In all 20 subjects, MPRi-rest was 1.78 ± 0.60. Recovery up-slope did not return to resting levels, regardless of aminophylline use. Among patients not receiving aminophylline, MPRi-recov was 36 ± 16% lower than MPRi-rest (1.13 ± 0.38 vs. 1.82 ± 0.73, P = 0.001). In the 10 patients whose recovery was facilitated with aminophylline, MPRi-recov was 20 ± 24% lower than MPRi-rest (1.40 ± 0.35 vs. 1.73 ± 0.43, P = 0.04), indicating incomplete reversal. In 3 subjects not receiving aminophylline and 4 subjects receiving aminophylline, up-slope at recovery was greater than at stress, suggesting delayed maximal hyperemia.

Outcomes and estimation

Limited information was provided in this paper since no comparison versus adenosine was performed. The authors conclude that MPRi measurements from regadenoson CMR are underestimated if recovery

perfusion (MPRi-recov was 36±16% lower than MPRi-rest) is used as a substitute for resting perfusion (MPRi-rest was 1.78±0.60).

- McGraw et al. 2016

A prospective single-center non-comparative study was conducted to determine overall rates of active clinical change resulting from stress CMR in the outpatient setting.

Study participants

350 consecutive outpatients referred for CMR stress testing.

Treatments

Regadenoson (0.4 mg)-Stress CMR was performed: cine sequences, perfusion sequences (stress and rest) and late gadolinium enhancement sequences

Objectives/endpoints

Clinical impact of the stress CMR findings.

Results

In the overall cohort, 243 (69.5%) of stress CMRs resulted in an active change in care, and 107 (30.5%) led to no change. The most common active changes were discharge from cardiology clinic (21.1%) or medication change (18.3%). The majority of active changes were non-invasive (65.5%) as opposed to invasive (8.6%) in nature. A significant minority (4.6%) underwent both a non-invasive and invasive change in management.

Outcomes and estimation

This study assessed the rates of active clinical change resulting from stress CMR in 350 outpatients referred for CMR stress testing. There was no comparison versus adenosine, but the study concluded that stress CMR made a significant impact on clinical management, resulting in active change in clinical care in about 70% of patients. This result is considered relevant despite the mentioned limitations.

- Ta et al. 2018

A retrospective single-center non-comparative study was conducted to evaluate whether quantitative myocardial blood flow (MBF) can differentiate dark rim artifacts from true perfusion defects in CMR perfusion.

Study participants

76 patients.

Treatments

Regadenoson perfusion CMR was performed.

Objectives/endpoints

MBF was quantified

Results

In a NonCAD subgroup with dark rim artifacts, stress MBF was lower in the subendocardial than midmyocardial and epicardial layers (2.17 ± 0.61 vs. 3.06 ± 0.75 vs. 3.24 ± 0.80 mL/min/g, both $p < 0.001$) and was also 30% lower than in remote regions (2.17 ± 0.61 vs. 2.83 ± 0.67 mL/min/g, $p < 0.001$). However, subendocardial stress MBF in dark rim artifacts was 37–56% higher than in true perfusion defects (2.17 ± 0.61 vs. 0.95 ± 0.43 mL/min/g, $p < 0.001$). Absolute stress MBF differentiated CAD from NonCAD with an accuracy ranging from 86 to 89% (all $p < 0.001$) using pixel-level analyses. Similar results were seen at a sector level.

Outcomes and estimation

This is a retrospective non-controlled study. It showed that quantitative stress MBF is lower in dark rim artifacts than remote myocardium but significantly higher than in true perfusion defects. However, fractional flow reserve (FFR) was lacking, the study was single-center and with small sample size, and an independent validation dataset did not exist.

- Patel et al. 2016

A retrospective single-center non-comparative study was conducted to determine whether chronic myocardial ischemia was associated with perfusion abnormalities at rest on CMR.

Study participants

31 patients who underwent vasodilator stress CMR, had myocardial infarct confirmed by late gadolinium enhancement (LGE), and coronary angiography within 6 months.

Treatments

Stress perfusion imaging during gadolinium first pass, rest perfusion, and late gadolinium enhancement imaging. The stress protocol involved administration of regadenoson (0.4 mg) in 22 patients or adenosine in 9 patients.

Objectives/endpoints

Resting and peak-stress time-intensity curves were used to obtain maximal upslopes, which were compared between infarcted and remote myocardial regions of interest.

Results

At rest, there was no significant difference between the slopes in the regions of interest supplied by arteries with and without stenosis >70% (0.31–0.16vs0.26–0.151/s), irrespective of LGE scar. However, at peak stress, significant differences existed (0.20–0.11vs0.30–0.221/s;$p<0.05$), reflecting the expected stress-induced ischemia. Similarly, at rest, there was no difference between infarcted and remote myocardium (0.27–0.14vs0.30–0.171/s), irrespective of stenosis, but significant

differences were seen during stress (0.21–0.16vs0.28–0.181/s;p<0.001), reflecting inducible ischemia.

Outcomes and estimation

This was a retrospective non-controlled study, in which not all patients received regadenoson as stressor agent but some of them received adenosine. It was concluded that abnormalities in myocardial perfusion at rest associated with chronic MI are not reliably detectable on CMR images. Accordingly, unlike SPECT, normal CMR perfusion at rest should not be used to rule out chronic myocardial infarction.

- Hojjati et al. 2014

A retrospective single-center non-comparative study was conducted to evaluate a novel protocol for assessing perfusion defects, wall-motion abnormality (WMA) and transient ischemic dilation (TID) in a single stress CMR session.

Study participants

29 consecutive patients who presented for clinically indicated regadenoson stress CMR.

Treatments

Immediately before and after the regadenoson (0.4 mg) stress perfusion sequence, baseline and post-stress cine images were obtained in the short-axis orientation to detect worsening or newly developed WMAs. This approach also allowed evaluation of TID. Delayed-enhancement imaging was performed in the standard orientations.

Objectives/endpoints

Perfusion defects, wall-motion abnormality (WMA) and transient ischemic dilation (TID)

Results

Thirteen patients (45 %) had perfusion abnormalities, and four patients developed TID. Seven patients had WMAs, and three of them also had TID.

Outcomes and estimation

This is a retrospective non-controlled study. It aimed to evaluate a novel protocol for assessing perfusion defects, wall-motion abnormality (WMA) and transient ischemic dilation (TID) in a single stress CMR session. However, the small number of subjects and the relatively high prevalence of CAD in the cohort are limiting factors.

- Reddy et al. 2013

A proof-of-concept single-center study was conducted to evaluate the feasibility of a ‘‘one-stop shop’’ in a magnetic resonance suite, performing assessment of cardiac structure, function, and viability, along with simultaneous evaluation of thoracoabdominal vasculature and liver anatomy for preoperative cardiovascular risk stratification in orthotopic liver transplantation candidates

Study participants

Over 2 years, 51 of 77 liver transplant candidates (mean age, 56 years; 35% female; mean Model for Endstage Liver Disease score, 10.8; range, 6Y40) underwent MRI.

Treatments

The patients underwent steady-state free precession sequences and stress cardiac magnetic resonance (CMR), thoracoabdominal magnetic resonance angiography, and abdominal magnetic resonance imaging (MRI) on a standard MRI scanner. Pharmacologic stress was performed using regadenoson, adenosine, or dobutamine. Viability was assessed using late gadolinium enhancement.

Results

All referred patients completed standard dynamic CMR, 98% completed stress CMR, 82% completed late gadolinium enhancement for viability, 94% completed liver MRI, and 88% completed magnetic resonance angiography. The mean duration of the entire study was 72 min, and 45 patients were able to complete the entire examination. Among all 51 patients, 4 required follow-up coronary angiography (3 for evidence of ischemia on perfusion CMR and 1 for postoperative ischemia), and none had flow limiting coronary disease. Nine proceeded to orthotopic liver transplantation. There were six ascertained mortalities in the nontransplant group and one death in the transplanted group. Explant pathology confirmed 100% detection/exclusion of hepatocellular carcinoma.

Outcomes and estimation

This was an observational/pilot non-controlled study with a small sample size. It appears feasible as a multi-imaging strategy in a CMR suite one-stop shop for the preoperative cardiovascular risk stratification in orthotopic liver transplantation candidates. However, not all patients received regadenoson but other stress agent, no comparison against any of the established modalities for effectiveness of the screening process was performed, and the incidence of postoperative cardiovascular complications was negligible.

- Tarroni et al. 2012

A study aimed to develop and validate a technique for near-automated definition of myocardial regions of interest suitable for perfusion evaluation during vasodilator stress cardiac magnetic resonance (MR) imaging.

The method was tested in 42 patients undergoing contrast material-enhanced cardiac MR imaging (at 1.5 T) at rest and during vasodilator (adenosine or regadenoson) stress, including 15 subjects with normal myocardial perfusion and 27 patients referred for coronary angiography. Contrast enhancement-time curves were near-automatically generated and were used to calculate perfusion indexes. The results were compared with results of conventional manual analysis, using quantitative coronary angiography results as a reference for stenosis greater than 50%.

Results

Analysis of one sequence required less than 1 minute and resulted in high-quality contrast enhancement curves both at rest and stress (mean signal-to-noise ratios, 17±7 [standard deviation] and 22±8, respectively), showing expected patterns of first-pass perfusion. Perfusion indexes

accurately depicted stress-induced hyperemia (increased upslope, from 6.7 sec (-1)±2.3 to 15.6 sec(-1)±5.9; P<.0001). Measured segmental pixel intensities correlated highly with results of manual analysis (r=0.95). The derived perfusion indexes also correlated highly with (r up to 0.94) and showed the same diagnostic accuracy as manual analysis (area under the receiver operating characteristic curve, up to 0.72 vs 0.73).

Outcomes and estimation

This was a study to develop a technique for definition of areas for assessment of CMR images.

- Rief et al. 2018

This was a two-center substudy of the prospective Combined Noninvasive Coronary Angiography and Myocardial Perfusion Imaging Using 320-Detector Row Computed Tomography (CORE320) multicenter trial to compare the diagnostic performance of stress myocardial computed tomography (CT) perfusion with that of stress myocardial magnetic resonance (MR) perfusion imaging in the detection of coronary artery disease (CAD).

92 patients (mean age, 63.1 years ± 8.1 [standard deviation]; 73% male). All patients underwent perfusion CT and perfusion MR imaging with either adenosine or regadenoson stress. The predefined reference standards were combined quantitative coronary angiography (QCA) and single-photon emission CT (SPECT) or QCA alone. Results from coronary CT angiography were not included.

Results

The prevalence of CAD was 39% (36 of 92) according to QCA and SPECT and 64% (59 of 92) according to QCA alone. When compared with QCA and SPECT, per-patient diagnostic accuracy of perfusion CT and perfusion MR imaging was 63% (58 of 92) and 75% (69 of 92), respectively (P = .11); sensitivity was 92% (33 of 36) and 83% (30 of 36), respectively (P = .45); and specificity was 45% (25 of 56) and 70% (39 of 56), respectively (P < .01). When compared with QCA alone, diagnostic accuracy of CT perfusion and MR perfusion imaging was 82% (75 of 92) and 74% (68 of 92), respectively (P = .27); sensitivity was 90% (53 of 59) and 69% (41 of 59), respectively (P < .01); and specificity was 67% (22 of 33) and 82% (27 of 33), respectively (P = .27).

Outcomes and estimation

In this substudy it was concluded that the diagnostic performance of perfusion CT is similar to that of perfusion MR imaging in the detection of CAD.

- Oleksiak et al. 2020

The purpose of this study was to assess the feasibility of low-dose dynamic regadenoson computed tomography perfusion (CTP) protocol, and to determine which parameters provide the best diagnostic yield for the presence and burden of ischemia in reference to the magnetic resonance myocardial perfusion imaging (MR MPI).

Fifty-six patients with ⩾1 intermediate (50-90%) coronary artery stenosis on CTA underwent dynamic stress CTP and MR MPI. The distribution of contrast agent in CTP was represented for each myocardial segment as either absolute or indexed: myocardial blood flow (MBF), myocardial blood volume (MBV), perfused capillary blood volume (PCBV), peak value (PV), time to peak (TTP), respectively.

Results

Of 56 patients (25 females, 63.5 ± 8.5y), 15 (27%) were diagnosed with reversible ischemia and 3 (5%) with fixed ischemia on the MR MPI. The median radiation dose for dynamic CTP scan was 352.00 [276.4-496.6] mGy*cm. The optimal cut-off point for the prediction of reversible ischemia on MR MPI for the absolute parameters were: MBF ⩽156.49 (AUC=0.899), MBV ⩽15.06 (AUC=0.901), PCBV ⩽ 7.90 (AUC=0.880), PV ⩽ 88.30 (AUC=0.766), TTP ⩾22.58 (AUC=0.595); and for the indexed: indexed MBF ⩽0.78 (AUC=0.926), indexed MBV ⩽0.81 (AUC=0.924), indexed PCBV ⩽0.70 (AUC=0.894); indexed PV ⩽ 0.79 (AUC=0.869), indexed TTP ⩽0.87 (AUC=0.685). The best parameters for ischemia detection were indexed MBF and indexed MBV, with sensitivities 91% and 89%, specificities 97% and 96%, NPV 99% and 99%, PPV 76% and 69%, and accuracies 96% and 95%, respectively. In per patient analysis, indexed MBF correlated significantly better with the ischemia burden than any of the absolute parameters ($p < 0.01$ for all comparisons).

Outcomes and estimation

This is a prospective single-center study aimed to establish the feasibility of a new protocol of cardiac CT with regadenoson, no comparison of regadenoson versus another stress agent was done.

- Kazmirczak et al. 2019

The purpose of this study was to evaluate the safety and the prognostic value of regadenoson stress CMR in heart transplant recipients.

Methods

Authors identified consecutive heart transplant recipients undergoing regadenoson stress CMR performed on at the University of Minnesota Medical Center, Minneapolis, Minnesota, USA between April 2012 and December 2017. To evaluate the prognostic value, they compared the outcomes of patients with abnormal vs. normal regadenoson stress CMRs using a composite endpoint of myocardial infarction, percutaneous intervention, cardiac hospitalization, re-transplantation or death.

All patients underwent a CMR protocol consisting of: 1) cine CMR at rest for assessment of left ventricular (LV) function; 2) gadolinium first pass perfusion imaging 1–2 min after regadenoson injection for assessment of stress perfusion; 3) gadolinium first-pass perfusion imaging without regadenoson for assessment of rest perfusion; and 4) late gadolinium enhancement (LGE) CMR 10–15 min later. Regadenoson 0.4 mg was injected over approximately 10 s into a peripheral vein followed by a 5 mL saline flush.

All stress CMR exams were interpreted blinded to patient outcomes by a consensus of two CMR physicians. Perfusion and LGE images were assessed in a qualitative fashion. A perfusion defect was identified as a regional dark area that: 1) persisted for > 2 beats while other regions enhanced during the first-pass of contrast through the LV myocardium; and 2) involved the subendocardium. LV systolic dysfunction was defined as an abnormality in global or regional systolic function on cine imaging. Ischemia was defined as a segmental stress perfusion defect without matching hyperenhancement (same location and size) on LGE imaging. A match between a perfusion defect and hyperenhancement on LGE was considered as fibrosis without ischemia. As in routine clinical practice, systolic dysfunction, ischemia and LGE images were interpreted in a binary fashion as normal or abnormal. A normal regadenoson stress CMR was defined as normal global and regional LV systolic function, no ischemia and no fibrosis.

Objectives/endpoints

Myocardial infarction, percutaneous intervention, cardiac hospitalization, re-transplantation and death. These events together formed the composite endpoint of major adverse cardiovascular events.

Results

To study the prognostic value of regadenoson stress CMRs, 20 heart transplant recipients with abnormal regadenoson stress CMRs were compared to 37 with normal regadenoson stress CMRs. At a median follow-up of 1.3 years (interquartile range 0.5–2.1 years), there were no instances of myocardial infarction, four percutaneous coronary interventions, four cardiac hospitalizations, three re-transplantations, and four deaths, accounting for 10 composite outcomes. On Kaplan-Meier analyses, the cumulative incidence estimates were significantly different between patients with abnormal regadenoson stress CMRs and those with normal regadenoson stress CMRs (3-year cumulative incidence estimates of 32.1% vs. 12.7%, p = 0.). Due to the small number of events, multivariable analysis was not performed.

Outcomes and estimation

This was a retrospective single-centre study aimed which findings highlight a potential role for regadenoson stress CMR as a non-invasive modality to identify heart transplant recipients at a higher risk for major adverse cardiovascular events.

This study is limited by the single-centre, retrospective design, relatively short follow up and a small number of events. Moreover, no comparison of regadenoson versus another stress agent was done.

COMPUTED TOMOGRAPHY (CT) PERFUSION TECHNIQUES

The main clinical data to assess efficacy of regadenoson as a stress pharmacological agent in cardiac CT are a company-sponsored phase 2 clinical study (Study 3606-CL-2001). Please refer to the section on the supportive study.

In addition, a number of published non-comparative studies have been submitted and the Rapporteur summarizes and commented below.

- Patel et al. 2019

A prospective study to measure the concordance between vasodilator-stress CT perfusion imaging and CT coronary angiography (CTCA) and their relationship to outcomes

Study participants

150 patients with chest pain, who underwent CTCA and regadenoson CT.

Objectives/endpoints

CTCA images were interpreted for presence and severity of stenosis. Fused 3D displays of subendocardial X-ray attenuation with coronary arteries were created to detect stress perfusion defects (SPD) in each coronary territory. In patients with stenosis > 25%, CT-FFR was quantified. Significant stenosis was determined by: (1) combination of stenosis >50% with an SPD, (2) CT-FFR $\leqslant$ 0.80.

Results

Patients were followed-up for 36 ± 25 months for death, myocardial infarction or revascularization. After excluding patients with normal arteries and technical/quality issues, in final analysis of 76 patients, CTCA depicted stenosis > 70% in 13/224 arteries, 50 – 70% in 24, and < 50% in 187. CT-FFR ⩽ 0.80 was found in 41/224 arteries, and combination of SPD with > 50% stenosis in 31/224 arteries. Inter-technique agreement was 89%. Despite high incidence of abnormal CT-FFR (30/76 patients), only 7 patients experienced adverse outcomes; 6/7 also had SPDs. Only 1/9 patients with CT-FFR ⩽ 0.80 but normal perfusion had an event. Fusion of CTCA and stress perfusion can help determine the hemodynamic impact of stenosis in one test, in good agreement with CT-FFR. Adding stress CT perfusion analysis may help risk-stratify patients with abnormal CT-FFR.

Outcomes and estimation

This is a prospective study to measure the concordance between vasodilator-stress CT perfusion imaging and CT coronary angiography (CTCA). No comparison of regadenoson versus another stress agent was done.

Invasive fractional flow reserve (FFR) was not used as reference standard for hemodynamic impact of stenosis, which is the main limitation of the study.

- Balaney et al. 2019

A prospective study to determine whether a novel motion correction algorithm applied to vasodilator stress computed tomography perfusion (sCTP) would improve the visualization of the coronary arteries to potentially allow coronary CT angiography (CCTA) + sCTP evaluation in a single scan.

28 patients referred for clinically indicated CCTA underwent sCTP imaging (retrospective-gating with dose modulation; 100 kVp and 250 mA; 5.2 ± 4.3 mSv) after regadenoson (0.4 mg). Stress images were reconstructed using standard filtered back-projection (FBP) and also processed to generate interaction-free coronary motion-compensated back-projection reconstructions (MCR). Each coronary artery from standard FBP and MCR images was viewed side-by-side by a reader blinded to the reconstruction technique, who graded severity of motion artifact by segment (scale 0–5, with 3 as the threshold for diagnostic quality) and to measure signal-to-noise and contrast-to-noise ratios (SNR, CNR).

Results

Visualization scores were higher with MCR for all coronary segments, including 14/86 (16%) segments deemed as non-diagnostic on FBP images. SNR (7 ± 2) and CNR (15 ± 8) were unchanged by motion-correction (7 ± 3, p = 0.88 and 15 ± 5, p = 0.94, respectively).

Outcomes and estimation

This pilot study tested the ability of a novel reconstruction algorithm applied to vasodilator stress computed tomography perfusion (sCTP) that compensates for cardiac motion to improve the visualization of the coronary arteries by alleviating motion artefacts. Since being a pilot study, the sample size was small. No comparison of regadenoson versus another stress agent was done.

- Mor-Avi et al. 2018

In this prospective study (combining 3-dimensional [3D] echocardiography with stress induced cardiac CT), resting myocardial strain (as obtained by echocardiography) was analysed to detect subclinical dysfunction in patients with CAD. Seventy-eight patients with chest pain referred to CT were studied. Two references were used; Standard A combined >50% stenosis on CT with perfusion defect in the same territory; Standard B combined >50% stenosis and FFRCT <80% in the same territory.

Results

Of the 99 arteries with no stenosis >50% and no stress perfusion defect, 19 (19%) had resting stress abnormalities. Conversely, with stenosis >50% and stress perfusion defect, resting stress abnormalities were more frequent (17 of 24 [71%]). The sensitivity, specificity, and accuracy of resting stress abnormalities were 0.71, 0.81, and 0.79, respectively, against reference Standard A and 0.83, 0.81, and 0.82 against reference Standard B. The authors concluded that combining 3D echocardiography with coronary CTA could be a means to detect hemodynamic significance of a stenosis with no additional radiation, vasodilator, or contrast medium.

Outcomes and estimation

This prospective study assessed fusion imaging of 3D echocardiography with coronary CTA in 93 patients. The sensitivity, specificity, and accuracy of resting stress abnormalities were 0.71, 0.81, and 0.79, respectively. No comparison of regadenoson versus another stress agent was done.

- Maffessanti et al. 2017

This study comes from the same team that conducted and also uses a fusion between 3D echocardiography and coronary CTA, including regadenoson stress perfusion.

This fusion software was applied in 28 patients with chest pain referred for coronary CTA.

Results

Coronary CTA showed 56 normal arteries, stenosis <50% in 17, and >50% in 8 arteries. Of the 81 coronary territories, stress perfusion defects were noted in 20 and rest strain anomalies in 29. Of the 59 arteries with no stenosis >50% and no stress perfusion defect, considered as normal, 12 (20%) had rest strain anomalies. Conversely, with stenosis >50% and splenopancreatic disconnections (hemodynamically significant), respiratory sinus arrhythmias were considerably more frequent (5/6 = 83%). Overall, resting strain and stress perfusion findings were concordant in 64/81 arteries (79% agreement). The authors suggest in conclusion that 3D echocardiograms could be used instead of stress cardiac CT in order to avoid radiation exposure and contrast medium injection.

Outcomes and estimation

This prospective study assessed fusion imaging of 3D echocardiography with coronary CTA. No comparison of regadenoson versus another stress agent was done.

- Mor-Avi et al. 2016

In this study, Mor-Avi et al. proposed to quantify myocardial perfusion from 3D cardiac CT acquisitions performed in patients stressed by regadenoson. Ninety-three patients referred for coronary CTA were studied. Parameters were as follows: mean X-ray attenuation, severity of defect and relative defect volume. Each index was averaged for myocardial segments, grouped by severity of stenosis: 0%, <50%, 50% to 70%, and >70%.

Results

With increasing stenosis, segmental attenuation showed a 7% decrease, defect severity increased 11%, but relative defect volume was 7-fold higher in segments with obstructive disease ($p < 0.001$). In the test group, detection of perfusion abnormalities associated with stenosis >50% showed sensitivity 0.78, specificity 0.54, accuracy 0.59. When compared to SPECT in a subset of 21 patients (14with abnormal SPECT), stress CT perfusion analysis showed sensitivity 0.79, specificity 0.71, accuracy 0.76 leading to modest performances in this subset of patients.

Outcomes and estimation

In this prospective study, no comparison of regadenoson versus another stress agent was done. According to the article, when compared to SPECT in a subset of 21 patients (14 with abnormal SPECT), stress CT perfusion analysis showed sensitivity 0.79, specificity 0.71, accuracy 0.76 leading to modest performances in this subset of patients.

- Baxa et al. 2015

This prospective study conducted by Baxa et al. included 54 asymptomatic high-risk patients who underwent coronary CTA and regadenoson-induced stress CT perfusion (Somatom Flash Siemens, second generation dual source CT). Diagnostic accuracy of significant stenosis ($\geqslant$50%) determination was evaluated for CTA alone and CTA +regadenoson-induced stress CT perfusion in 27 patients referred for invasive coronary angiography due to positive findings. Combined evaluation of CTA + regadenoson-induced stress CT perfusion had higher diagnostic accuracy over CTA alone (per-segment: specificity 96% vs 68%, $p = 0.002$; per-vessel: specificity 95% vs 75%, $p = 0.012$) and high overruling rate of regadenoson-induced stress CT perfusion was proved in intermediate stenosis (40% to 70%).

Results

They tend to demonstrate a significant additional value of regadenoson-induced stress CT perfusion in the assessment of intermediate coronary artery stenosis found with CTA.

Outcomes and estimation

In this prospective study, no comparison of regadenoson versus another stress agent was done. According to the article, combined evaluation of CTA + regadenoson-induced stress CT perfusion had higher diagnostic accuracy over CTA alone (per-segment: specificity 96% vs 68%, $p = 0.002$; per-vessel: specificity 95% vs 75%, $p = 0.012$) and high overruling rate of regadenoson-induced stress CT perfusion was proved in intermediate stenosis (40% to 70%).

- Cury et al. 2015

This Phase 2, open-label, randomized, cross over study was performed in 11 centers in the United States using 6 different CT scanners. Cury et al. [Cury et al. 2015] hypothesized that CT perfusion was not inferior to SPECT to detect ischemia. The main objective was the agreement rate between both techniques in detecting ischemia >2 segments as assessed by independent blinded readers. Complete interpretable examinations were obtained in 110 patients.

Agreement rate was 0.87 (95% CI: 0.77, 0.97). Sensitivity and specificity were respectively 0.9 (95% CI: 0.71, 1) and 0.84 (95% CI: 0.77, 0.91). The study's conclusion is that the hypothesis of non-inferiority of CT perfusion was confirmed with regard to SPECT.

In this prospective study, no comparison of regadenoson versus another stress agent was done. This seems to be the published paper of the phase II study sponsored by the Applicant.

- De Cecco 2014

De Cecco et al. aimed to prospectively determine the added value of stress dual-energy CT (DECT) MPI to coronary CTA for the assessment of CAD in a high-risk population. Twenty-nine consecutive patients who were referred for cardiac SPECT examinations underwent pharmacologic stress cardiac DECT (with either adenosine or regadenoson). Cardiac catheterization was available in 25 patients. Respective performances of CTA alone, dual energy myocardial perfusion CT alone and the association of both were evaluated. The combined approach yielded 100% sensitivity and 38% specificity if either was positive and 86% sensitivity and 75% specificity if both were positive. AUC values were highest for DECT alone (0.85) and when the 2 parts of the examination was positive (0.80).

No comparison of regadenoson versus another stress agent was done, but it is concluded that a combined analysis of coronary CTA and DECT myocardial perfusion reduced the number of false positives in a high-risk population for CAD and outperformed the purely anatomic test of coronary CTA alone for the detection of morphologically and hemodynamically significant CA.

- Bhave et al. 2014

As iterative reconstruction (IR) in cardiac CT has been shown to improve confidence of interpretation of non-invasive CTA, Bhave et al. made the hypothesis that IR could improve the quality of vasodilator stress coronary CT images acquired with low tube voltage to assess myocardial perfusion and the accuracy of the detection of perfusion abnormalities by using quantitative 3D analysis. Thirty-nine consecutive patients referred for coronary CTA underwent additional imaging at 100 kV with prospective gating and stress induced by regadenoson. Images were reconstructed using either FBP and IR (iDose; Philips). Then, FBP and separately IR images were analysed with custom 3D analysis software to quantitatively detect perfusion defects. Accuracy of detection was compared with perfusion abnormalities predicted by coronary stenosis >50% on coronary CTA. In the 34 evaluable patients, both signal-to-noise and contrast-to-noise ratios increased with IR. No comparison of regadenoson versus another stress agent was done, but the results show that in the 24 patients with stenosis, reduced noise levels in the IR images compared with FBP resulted in tighter attenuation distribution and improved detection of perfusion abnormalities.

- Patel et al. 2011

The capabilities of CT perfusion under regadenoson according to 2 technical protocols were compared; Group 1 using conventional parameters and contrast volume and Group 2 involving 100 kVp and low contrast volumes. In both groups, myocardial attenuation was equally reduced in segments supplied by diseased arteries (Group 1: 119 ± 19 vs 103 ± 14 HU, p <0.05; Group 2: 108 ± 20 vs 97 ± 16 HU, p <0.05), despite the 74% reduction in radiation (from 7.4 ± 2.8 to 1.9 ± 0.45 mSv) and the 28% reduction in contrast dose (from 84 ± 7 to 60 ±7 mL) (both p <0.05). Regadenoson stress MDCT imaging can detect hypoperfused myocardium even when imaging settings are optimized to provide a significant reduction in radiation and contrast doses.

No comparison of regadenoson versus another stress agent was done, but the study shows that the capabilities of CT equipment have improved since that period and allow scanning at very low voltage and high current allowing low radiations doses and low volumes of contrast media.

- Rief et al. 2018

Already mentioned for the CMR and it was concluded that the diagnostic performance of perfusion CT is similar to that of perfusion MR imaging in the detection of CAD.

- Oleksiaket al. 2020

This was a prospective single-center study aimed to establish the feasibility of a new protocol of cardiac CT with regadenoson, no comparison of regadenoson versus another stress agent was done.

Supportive study

A phase-2 sponsored study with cardiac CT was also presented.

This was a Phase 2, multicentre, open-label, randomized, cross-over study in subjects with typical angina to establish the noninferiority of myocardial perfusion imaging (MPI) using multidetector computed tomography (MDCT) with regadenoson as compared to SPECT with regadenoson in detecting the presence or absence of ischemia (defined by number of reversible defects). The secondary objectives of Study 3606-CL-2001 were to assess the image quality of regadenoson CT perfusion and SPECT MPI scans; to compare the agreement between and the presence of reversible defects associated with each coronary vessel (LAD,LCX, and RCA) identified by CT perfusion (CTP) as compared to SPECT MPI; to evaluate the sensitivity and specificity of diagnostic accuracy with CT perfusion as compared to SPECT for fixed defects; and to determine the percent of subjects who had 2 or more ischemic segments on SPECT, but less on CT (false negative CT).

Methods

Subjects were randomized to 1 of 2 imaging procedure sequences and to undergo both a rest and stress SPECT series and a rest and stress MDCT series. In the SPECT-MDCT sequence 1, subjects underwent a rest SPECT and a regadenoson stress SPECT procedure on Day 1 and a regadenoson stress CT perfusion and a rest coronary CTA/CT perfusion procedure on Day 2. In the MDCT-SPECT sequence, subjects underwent a regadenoson stress CT perfusion and a rest coronary CTA/CT perfusion procedure on Day 1 and a rest SPECT and a regadenoson stress SPECT procedure on Day 2. Subjects were administered open label regadenoson 0.4 mg in a 5 mL IV bolus as a pharmacological

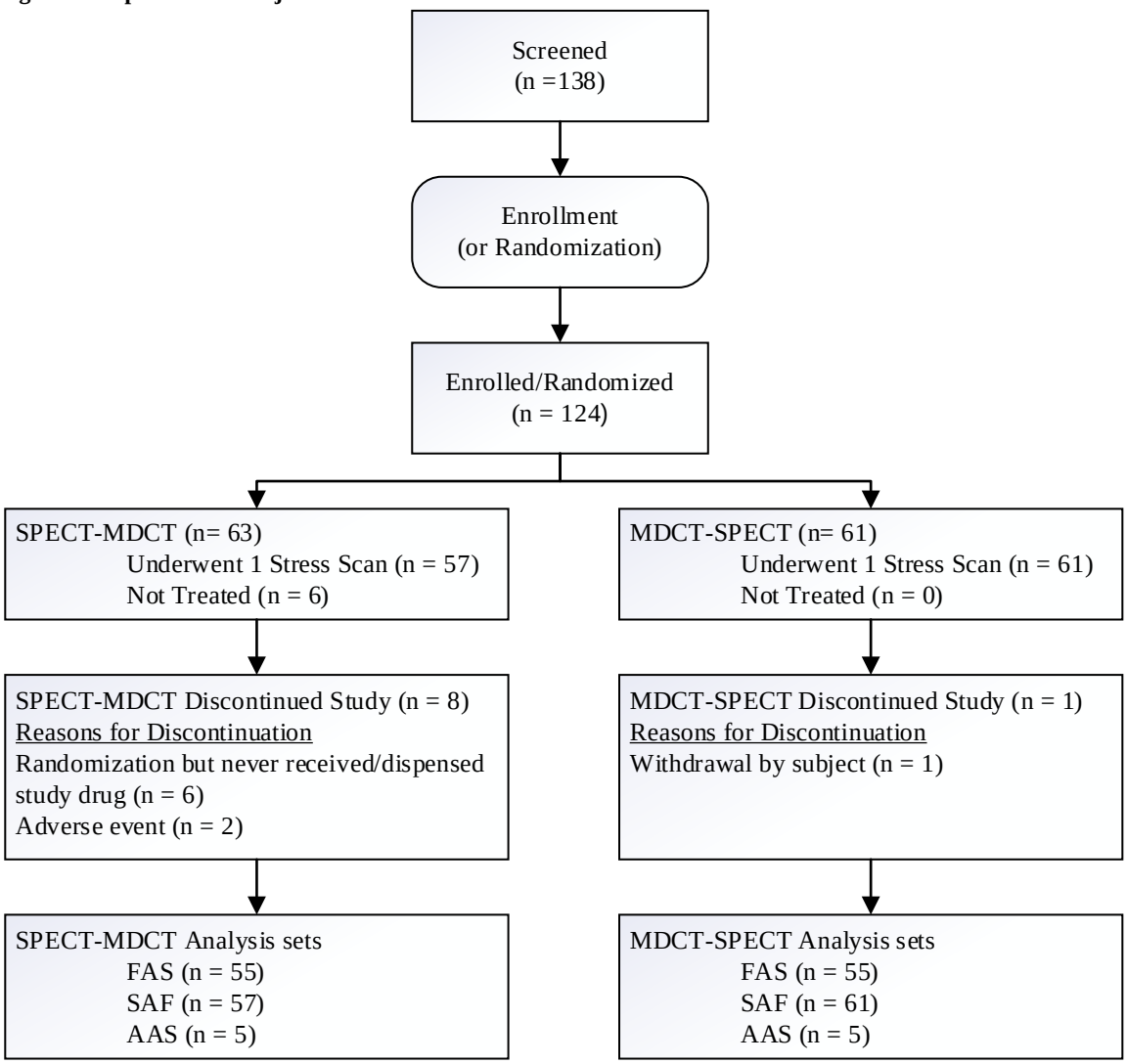
stress agent prior to each stress CT perfusion and stress SPECT procedure. At least 24 hours were stipulated between each dose of regadenoson.

Study participants

The planned number of subjects was 110. There were 124 subjects enrolled and randomized into the study: 63 subjects in sequence SPECT-MDCT and 61 subjects in sequence MDCT-SPECT.

Three analysis sets were used in the study. The Full Analysis Set (FAS) was composed of all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers. The Safety Analysis Set (SAF) was composed of all randomized subjects who received at least 1 dose of regadenoson. The Angiographic Analysis Set (AAS) was composed of all randomized subjects with interpretable SPECT, CCTA and CTP scans and interpretable ICA. The number of subjects in each treatment group for these analysis sets is presented in Figure 3.

Figure 3 Disposition of Subjects



FAS: Full Analysis Set composed of all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers.
SAF: Safety Analysis Set composed of all randomized subjects who received at lead 1 dose of regadenoson.
AAS: Angiographic Analysis Set composed of all randomized subjects with interpretable SPECT, CCTA and CTP scans and interpretable ICA.
MDCT: multidetector computed tomography; SPECT: single photon emission computed tomography

Diagnosis and Main Criteria for Inclusion: Subjects that were eligible to participate in this study were males ≥ 45 years of age and females ≥ 50 years of age with typical angina. Subjects with typical angina who met at least 1 of the 3 following criteria: suspected (clinical impression) or known diagnosis of coronary artery disease (CAD) with typical angina that had been referred from nuclear cardiology lab schedule or cardiac CT schedule; stable symptoms with possible elective catheterization procedure scheduled and where further imaging might be beneficial; or known CAD from a previous invasive coronary angiography (ICA) performed more than 12 weeks prior to screening who presented with new cardiac symptoms. Subjects had to have been referred for a clinically indicated myocardial perfusion imaging procedure or cardiac CT procedure for suspected moderate or high-risk CAD.

Criteria for Evaluation: The primary variable was the number of reversible defects categorized into absence or presence of ischemia (0 – 1 versus 2 or more), as assessed by the central imaging laboratory for both SPECT and MDCT. The secondary variables were overall image quality as assessed by independent blinded readers; the absence or presence of reversible defects (0 – 1 versus ≥ 2) in each of 3 regions of defect localization (LAD, RCA, LCX); the presence of 1 or more fixed perfusion defects as assessed by the central imaging laboratory; and the number of subjects who had 2 or more ischemic segments on SPECT, but less on CT (false negative CT).

Baseline data

The mean age of subjects included in the FAS was 61.7 years (range 45 to 85 years). This population was primarily white (90.0%) and male (70.9%). No significant differences were identified between the randomized treatment sequences in terms of any demographic variable or baseline weight and BMI.

Table 1 Demographic Characteristics

Parameter Category/Statistic	**Regadenoson** **SPECT-MDCT (n = 57)**	**Regadenoson** **MDCT-SPECT (n = 61)**	**Total (n = 118)**	**P Value**
Sex, n (%)				
Male	39 (68.4)	46 (75.4)	85 (72.0)	0.40†
Female	18 (31.6)	15 (24.6)	33 (22.0)	
Race, n (%)				
White	52 (91.2)	54 (88.5)	106 (89.8)	0.50†
Black or African American	2 (3.5)	5 (8.2)	7 (5.9)	
Asian	3 (5.3)	2 (3.3)	5 (4.2)	
Ethnicity, n (%)				
Non-Hispanic or -Latino	37 (64.9)	41 (67.2)	78 (66.1)	0.79†
Hispanic or Latino	20 (35.1)	20 (32.8)	40 (33.9)	
Age (years)				
Mean (SD)	60.8 (9.19)	62.3 (9.41)	61.6 (9.29)	0.67‡
Median	61.0	62.0	61.5	
Minimum - Maximum	47 – 79	45 – 85	45 - 85	
Weight (kg)				
Mean (SD)	85.54 (16.836)	88.85 (20.116)	87.25 (18.600)	0.63‡
Median	83.60	90.20	85.30	
Minimum - Maximum	49.4 – 144.1	50.5 – 159.1	49.4 – 159.1	
BMI (kg/m^2)				
Mean (SD)	29.03 (5.57)	30.02 (5.10)	29.54 (5.33)	0.60‡
Median	28.96	29.89	29.35	
Minimum - Maximum	18.3 – 45.1	21.0 – 45.0	18.3 – 45.1	
Enrolled Under, n (%)				
Original protocol	2 (3.6)	2 (3.3)	4 (3.4)	NC
Protocol amendment 1	55 (96.5)	69 (96.7)	114 (96.6)	

Safety Analysis Set (SAF): All randomized subjects who received at least 1 dose of regadenoson.
SPECT: Single Photon Emission Computed Tomography; MDCT: Multidetector Computed Tomography; BMI: body mass index; NC: Not calculated.

† Chi-squared test.
‡ One-way ANOVA.

Outcomes and estimation

Primary Efficacy Results

In the primary assessment of the presence of cardiac ischemia by the central imaging laboratory, regadenoson stress SPECT imaging identified 100 subjects as having 0 – 1 reversible defects (i.e. absence of ischemia) and 10 subjects as having ≥ 2 reversible defects (i.e. presence of ischemia). In comparison, regadenoson stress CTP imaging identified 85 and 25 subjects as having 0 –1 or ≥ 2 reversible defects, respectively. The agreement rate between regadenoson stress SPECT and regadenoson stress CTP was 87% (95% CI: 77%, 97%) [Table 2 below]. The lower boundary of this 95% CI was within 0.15 of 0.78 (defined as the threshold for noninferiority); therefore, regadenoson stress CTP was determined to be noninferior to regadenoson stress SPECT in the primary analysis.

Table 2 Primary Efficacy Criteria: Agreement Between SPECT and CTP with Respect to Presence of Ischemia Defined by the Number of Reversible Defects

	Number of Reversible Defects	**Regadenoson CTP**			**Agreement Rate ± SE (95% CI†)**
		0 - 1	**≥ 2**	**All**	
Regadenoson SPECT	**0 – 1**	84	16	100	0.87 ± 0.051 (0.77, 0.97)
	≥ 2	1	9	10	
	All	85	25	110	

FAS: Full Analysis Set composed of all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers.
Regadenoson SPECT: stress Single Photon Emission Computed Tomography; Regadenoson CTP: stress Computed Tomography Perfusion.
Scoring based on 17-segment model for standardized myocardial segmentation: 0 = normal perfusion; 1 = mild reduction in counts, not definitely abnormal; 2 = moderate reduction in counts, definitely abnormal; 3 = severe reduction in counts; absent uptake.
† Predefined non-inferiority criterion: If the lower boundary of the 95% CI was within 0.15 of 0.78, MDCT would be determined to be noninferior to SPECT.

Using SPECT as the reference standard for the presence of ischemia (number of reversible defects), the specificity for regadenoson stress CTP to detect ischemia was 84% and sensitivity was 90%.

Results of secondary objectives

The overall image quality of the scans was assessed by 3 independent blinded readers according to the 4-point scale (excellent, good, fair or poor). For SPECT images, 89% of images were rated as either excellent or good (88% for rest SPECT, 90% for stress SPECT) [Table 3]. For rest CCTA/CTP images, 78% of images were rated as either excellent or good. For regadenoson stress CTP, that percentage fell to 50%.

Table 3 Overall Image Quality of Scans by Modality and Reviewer

			SPECT (n = 110)		
			Reviewer 1	**Reviewer 2**	**Reviewer 3**
Rest or Stress	**Parameter**	**Category**	**n (%)**	**n (%)**	**n (%)**
Rest	Image Quality	Excellent	89 (80.9)	25 (22.7)	83 (75.5)
		Good	16 (14.5)	53 (48.2)	23 (20.9)
		Fair	4 (3.6)	31 (28.2)	4 (3.6)
		Poor	1 (0.9)	1 (0.9)	0
Stress	Image Quality	Excellent	89 (80.9)	35 (31.8)	78 (70.9)

		Good	16 (14.5)	51 (46.4)	27 (24.5)
		Fair	4 (3.6)	24 (21.8)	5 (4.5)
		Poor	1 (0.9)	0	0
			MDCT (n = 110)		
			Reviewer 1	**Reviewer 2**	**Reviewer 3**
Rest or Stress	**Parameter**	**Category**	**n (%)**	**n (%)**	**n (%)**
Rest (CCTA)	Image Quality	Excellent	30 (27.3)	40 (36.4)	56 (50.9)
		Good	56 (50.9)	37 (33.6)	43 (39.1)
		Fair	23 (20.9)	33 (30.0)	11 (10.0)
		Poor	1 (0.9)	0	0
Stress (CTP)	Image Quality	Excellent	5 (4.5)	15 (13.6)	37 (33.6)
		Good	48 (43.6)	24 (21.8)	36 (32.7)
		Fair	56 (50.9)	62 (56.4)	34 (30.9)
		Poor	1 (0.9)	9 (8.2)	3 (2.7)

Full Analysis Set (FAS): All randomized subjects with interpretable SPECT and CTP scans as determined by at least two to three blinded readers.
SPECT: Single Photon Emission Computed Tomography; MDCT: MultiDetector Computed Tomography; CCTA Coronary Computed Tomographic Angiography; CTP: Computed Tomography Perfusion.
If the image quality was good, fair or poor, the reason was to be provided.
Source: Table 12.3.2.1.1 and Table 12.3.2.1.2

Reasons cited for inadequate image quality for SPECT included subject motion, breast attenuation, diaphragmatic attenuation, inadequate myocardial statistics, and “other” reasons that were not further specified. Reasons cited for inadequate image quality for both regadenoson stress CTP and rest CCTA/CTP images included subject motion, beam hardening, reconstruction artifacts, image noise, incomplete anatomical coverage, inadequate contrast enhancement, misalignment artifacts, slab artifacts, and “other” reasons not further specified. Image quality was also described by each reviewer on a segment by segment basis. The grading of image quality for each segment was generally consistent with the grading provided for overall image quality, in that there was similar scoring for rest versus stress SPECT images, SPECT images had generally lower percentages of images rated as Fair or Poor compared to rest CTP image quality, and stress CTP scans had a marginally higher percentage of image quality rated Fair to Poor compared to rest CTP image quality.

Sub-analyses of ischemia within various coronary artery regions were performed. Cardiac scans were subcategorized into 3 coronary artery territories (LAD, RCA, LCX), and the results from SPECT and CTP scans are presented in Table 11 below. The number of subjects determined to have an absence of ischemia by regadenoson stress SPECT was consistent across the three arteries (ranging from n = 97 to 101). The number of subjects with an absence of ischemia was also consistent across the three arteries as assessed by regadenoson stress CTP (ranging from n = 90 to 93). The agreement rates for stress SPECT and stress CTP for the number of reversible defects (0 to 1 versus ≥ 2) ranged from 47% for the RCA to 79% for the LCX and 95% for the LAD. In the RCA images, SPECT scans identified n = 1 subject with ≥ 2 reversible defects, while CTP identified n = 5. Using SPECT as the reference standard, regadenoson stress CTP specificity for detecting ischemia ranged from 89 to 95%, sensitivity ranged from 0% (for RCA) to 100%.

Table 4 Agreement Between SPECT and CTP with Respect to Presence of Ischemia Defined by Coronary Artery Region

	Coronary Artery Region	**Number of Reversible Defects**	**Regadenoson CTP**			**Agreement Rate ± SE (95% CI)**
			0 - 1	**≥ 2**	**All**	
Regadenoson SPECT	LAD	0 - 1	90	11	101	0.95 ± 0.015 (0.92, 0.98)
		≥ 2	0	4	4	

		All	90	15	105	
	RCA	0 - 1	92	5	97	0.47 ± 0.011 (0.45, 0.50)
		≥ 2	1	0	1	
		All	93	5	98	
	LCX	0 - 1	90	9	99	0.79 ± 0.097 (0.60, 0.98)
		≥ 2	2	4	6	
		All	92	13	105	

Full Analysis Set (FAS): All randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers.
Regadenoson SPECT: stress Single Photon Emission Computed Tomography; Regadenoson CTP: stress Computed Tomography Perfusion. LAD: left anterior descending artery; RCA: right coronary artery; LCX: left circumflex coronary artery
Source: Table 12.3.1.2

When assessing the presence of ischemia by number of fixed defects, regadenoson stress SPECT identified 97 subjects with no ischemia, and 13 with ≥ 1 fixed defect, compared to 95 and 15 subjects for regadenoson stress CTP, respectively.

Regadenoson stress CTP detected n = 25 subjects with cardiac ischemia (≥ 2 reversible defects); n = 16 of these 25 subjects were classified with 0 – 1 reversible defects by regadenoson stress SPECT, and n = 9 subjects were classified as ischemic by both imaging modalities [Table 7]. Of the n = 10 subjects classified as ischemic by regadenoson stress SPECT, only 1 of those subjects was identified as non-ischemic by CTP.

Conclusion

The CHMP considers this as a main source of data to support the clinical efficacy of regadenoson as pharmacological stress agent in CT MPI.

This prospective study aimed to determine agreement rate between regadenoson stress SPECT and regadenoson-stress CT perfusion for detecting the presence of ischemia (defined as 2 or more reversible defects seen visually) in 110 patients with suspected or known CAD referred for one of these diagnostic tests as being clinically indicated. The phase II study did not involve comparison of regadenoson versus another pharmacological stress agent, but comparison of regadenoson-stress cardiac CT versus another MPI diagnostic technique for which regadenoson is approved (i.e. SPECT MPI).

While regadenoson stress SPECT imaging identified 100 subjects as having 0 – 1 reversible defects and 10 subjects as having ≥ 2 reversible defects, regadenoson stress CTP imaging identified 85 and 25 subjects as having 0 –1 or ≥ 2 reversible defects, respectively. The agreement rate between regadenoson stress SPECT and regadenoson stress CTP was 87% (95% CI: 77%, 97%). The study concluded that regadenoson-stress CT perfusion demonstrated to be non-inferior than SPECT MPI for detection of myocardial ischemia.

As SPECT MPI was considered as a reference standard for detection of myocardial ischemia (no for diagnosis of CAD), sensitivity and specificity were assessed for stress CT perfusion (which were 84% and 90%, respectively) for detection of myocardial ischemia not for any particular diagnostic objective of CAD.

2.4.1. Discussion on clinical efficacy

The proposed indication aims to widen the use of regadenoson as a pharmacological stress agent for any type of MPI technique. Regadenoson is currently approved for radionuclide MPI in patients unable

to undergo adequate exercise stress. At the time of the approval, the efficacy of regadenoson was demonstrated in two phase-3 prospective controlled trials to be non-inferior to adenosine for diagnosing reversible perfusion defects in patients undergoing SPECT MPI.

Despite the fact that the approved indication for Rapiscan refers to “radionuclide” and PET is a radionuclide-based imaging modality, only data on SPECT MPI were presented and assessed at registration. Taking this into account, the claim for PET MPI is seen as a particular case since from a formal point of view its use would be covered by the current indication. However, as no data on PET were available at the time of approval and some publications have been submitted by the MAH in support of the use of regadenoson with PET, the studies have now been reviewed.

In support of the claimed extension of the indication, it is argued that perfusion assessment by imaging techniques should be independent from the stress applied either physical or drug-induced in the sense that the stress has the objective to increase the local blood flow demand while the imaging modality has the objective to measure the relative changes in the blood flow response to this stress itself. This notion is supported from a theoretical point of view and additional clinical data was discussed during the assessment.

No clinical development programme has been conducted to support this. The submitted clinical documentation is based on data available in published literature and on a company-sponsored phase II study. Those published studies were obtained from two systematic reviews of the literature performed by the MAH for the use of regadenoson in MPI using PET, and using CRM and cardiac CT. The search terms and methods used outlined by the MAH were considered appropriate. The systematic review yielded 14 studies for PET MPI, from which 13 aimed to assess clinical efficacy of regadenoson. Regarding CMR and CT, 33 articles resulted from the systematic review, from which 30 assessed clinical efficacy of the vasodilatator. Overall, the difficulties inherent to the bibliographic nature of the dossier and the limited availability of prospective comparative data on clinical efficacy need to be highlighted. The varied endpoints for assessment of the clinical efficacy, the different recruited populations, the different imaging protocols may not contribute much for clarification. Anyhow, the use of regadenoson for PET MPI, cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (CT) is recognized in clinical/procedural guidelines of European speciality medical societies even if it is performed technically off-label.

No scientific critical discussion of the publications was provided and only individual summaries and full-text papers for some (not all) of the literature references that were part of the systematic literature review were provided. A critical discussion has been performed during assessment.

No experience in special populations is provided, but no particular precautions are to be taken in special populations for the use of this product in the approved indication of SPECT MPI.

Neither own nor published studies have been presented aimed to establish the optimal dose and optimal method of administration of regadenoson for PET, CT or MR MPI. Dose administered in the provided papers (in some this data is missing) is the same than the dose currently approved for SPECT MPI. After reviewing the provided papers, when adenosine or dipyridamole were used as comparators, their dose was consistent and similar to that usually administered for SPECT MPI.

It is important to establish imaging starting time and duration in MPI taking into consideration 1) the duration and onset of peak hyperaemia for the particular pharmacological stressor administered, 2) the efficiency of the specific image modality used and, for radiopharmaceuticals, 3) their physical half-life. This is crucial because perfusion images after pharmacological stress could be different if obtained at peak hyperaemic phase or post-peak phase, and therefore the image quality or test accuracy might be affected. This was properly reflected in the SmPC.

For this variation, the company has presented 43 published studies related to clinical efficacy of regadenoson and one company-sponsored study. For each imaging modality, a limited number of studies were comparative and prospective, most of them being non-comparative or retrospective. The number of publications retrieved would well reflect the interest/use of regadenoson with these imaging techniques in clinical practice.

Positron emission tomography MPI

Two prospective comparative studies of PET-MPI with regadenoson (Vleeming et al. 2018 and Cullom et al. 2013) were provided. As mentioned before, when regadenoson was registered, adenosine was considered as an appropriate reference standard against which to compare a pharmaceutical stress agent. Dipyridamole can also be considered as a valid comparator as it has been used in this setting for many years and it is still recommended in clinical guidelines. Prospective data of regadenoson versus adenosine comes from the study of Vleeming et al. 2018 in which the extent of cardiac displacement on 13Nammonia (13NH3) PET/CT MPI was compared in two parallel subgroups of patients (n=31 and n=30, respectively). The primary endpoint (i.e. cardiac displacement on PET images) refers to an image artefact that may lead to erroneous interpretation of images but is not part of the variables assessed on PET MPI images for routine clinical use.

As stated in the recent EANM procedural guidelines for PET/CT quantitative myocardial perfusion imaging (Sciagrà et al. 2021), clinical interpretation of PET MPI for assessment of CAD requires to perform the analysis of the myocardial radiopharmaceutical uptake in qualitative/semiquantitative term together with the quantitative measurement of myocardial blow flood (MBF). Visual semi-quantitative image analysis is performed on a regional basis, using 17 segments (AHA model), and each segment is scored using a 5- point scale ranging from 0 (normal perfusion), 1 (mildly reduced perfusion), 2 (moderately reduced perfusion), 3 (severely reduced perfusion), to 4 (absent perfusion). This yields a summed perfusion score for both stress and rest myocardial perfusion images. The reported cut-off values to discriminate abnormal from normal PET MPI are diverse. The most widely accepted threshold is to consider a summed stress score (SSS) ≥ 4 as abnormal.

In the study of Cullom et al. 2013, PET MPI with regadenoson was interpreted as in clinical practice with regards to the visual detection of perfusion defects and prospectively compared with PET MPI with another stress agent (dipyridamole in this case). Comparison was performed in 26 patients who had a reversible perfusion defect already identified on a previous clinically indicated dipyridamole-stress PET study with 82RbCl. Additionally, six (6) subjects with <5% pre-test likelihood for CAD were recruited. In the absence of prospective studies of regadenoson-stress PET MPI in comparison to adenosine, dipyridamole can be considered a valid comparator. Although it is currently not approved for this indication in many European countries (Siagrà 2021), it has extensively been used for many years as a stress agent in MPI. These data, although from a limited database, support the use of regadenoson with PET MPI.

In this study, quantitation of either dipyridamole or regadenoson 82RbCl PET was also done by comparison of the perfusion images to a 82RbCl gender-independent normal database obtained with a 7-minute adenosine stress protocol. This normal database has not been validated for regadenoson or dipyridamole.

Two additional prospective non-controlled published studies (Hsiao et al. 2013 and Valenta et al. 2017), did not provide data versus another pharmacological stress agent. The remaining nine provided papers involved a retrospective evaluation of data. Both the non-comparative and retrospective studies submitted provide limited information none raise any concerns from the efficacy point of view.

Overall, the clinical data provided by the MAH ~~just~~ support the use of regadenoson with PET MPI. Such review exercise supports this use already formally covered by the indication of Rapiscan.

Cardiac magnetic resonance (CMR) imaging

The MAH has not provided any studies demonstrating the non-inferiority of regadenoson in comparison to adenosine as an active comparator for CMR in the population in which the test is indicated, and in terms of visual analysis of myocardial perfusion (as CMR is interpreted in clinical practice).

Several of the submitted studies examining the use of regadenoson with CMR MPI are focused on differential MR sequences and protocols and are of limited relevance to this submission.

However, some studies provided are considered useful for the purpose of this variation. The results from DiBella study, a comparative and prospective trial, show that regadenoson and adenosine have a similar efficacy on vasodilation with good agreement between MPR measured with adenosine and regadenoson. The results from another comparative trial in young healthy volunteers (Vasu 2013) show that regadenoson and adenosine have a similar efficacy on vasodilation (similar stress MBF adjusted for heart rate) and superior to dipyridamole. In other comparative study with healthy subjects (Thomas et al. 2017) it was showed that vasodilators (regadenoson and adenosine) have significant and prolonged impact on ventricular volumes and LVEF. Some differences in terms of duration of response and change in LVEF from baseline related to the known t1/2 differences between the agents and the degree of HR increase (higher with regadenoson relative to adenosine) were noted. These three comparative studies are reassuring and support the use of regadenoson with CMR.

The study assessing the rates of active clinical change resulting from stress CMR in 350 outpatients referred for CMR stress testing (McGraw et al. 2016) found a change in clinical care in about 70% of patients is reassuring, despite the limitation related to the lack of comparison with adenosine.

Overall, the non-comparative trials (prospective or retrospective) submitted, although of limited value given the well-known limitations of these kind of studies, do not suggest any concerns regarding the efficacy of regadenoson used with CMR.

Finally, the use of regadenoson with CMR in clinical practice is reflected in the Position Paper on stress cardiac MRI in chronic coronary syndrome (Le Ven 2021) that has been recently published. This paper makes it clear that myocardial ischemia-inducing tests (including with agents such as regadenoson) can be conducted with MRI. The paper, based on published articles, European recommendations, several randomized studies and the recommendations from international societies, recommends that adenosine or regadenoson should be preferred for MRI stress tests products.

Computed tomography (CT) perfusion techniques

The main source of efficacy is Study 3606-CL-2001.

This was a Phase 2, multicenter, open-label, randomized, cross-over study to establish the non-inferiority of regadenoson-stress CT perfusion as compared to SPECT with regadenoson, for detecting the presence of ischemia (defined as 2 or more reversible defects seen visually), in 110 subjects with typical angina and suspected or known diagnosis of CAD. Only a summary of this study was provided.

This phase II study did not involve comparison of regadenoson versus another pharmacological stress agent but comparison of regadenoson-stress cardiac CT versus the MPI diagnostic technique for which regadenoson is approved (i.e. SPECT MPI).

According to the data provided, while regadenoson stress SPECT imaging identified 100 subjects as having 0 – 1 reversible defects and 10 subjects as having ≥ 2 reversible defects, regadenoson stress CTP imaging identified 85 and 25 subjects as having 0 –1 or ≥ 2 reversible defects, respectively. The

agreement rate between regadenoson stress SPECT and regadenoson stress CTP was 87% (95% CI: 77%, 97%). Even when invasive coronary angiography with fractional flow reserve, which currently is considered the gold standard to detect hemodynamic significance of a specific lesion, was not used as the reference standard, the results of this phase II trial suggest similar efficacy for regadenoson-stress CT perfusion demonstrated and SPECT MPI for detection of myocardial ischemia.

While the design of this study is not considered to be ideal, the results are sufficient to support the use of regadenoson with CT perfusion imaging. In addition, the results are consistent with those of the CORE 320 study that assessed the diagnostic accuracy of adenosine-stress CTP and adenosine- or exercise-stress SPECT for the diagnosis of obstructive CAD (>50% stenosis) (Rochitte CE, 2014). This study showed that CTP had greater diagnostic accuracy compared with SPECT for diagnosing obstructive CAD. The study also shows incremental improvement in diagnostic accuracy when adding CTP to CTA for diagnosing vessels with hemodynamically significant stenosis.

The company also presented 12 additional non-comparative published trials (prospective or retrospective), which provide some limited information since no comparison versus another pharmacological stress agent is performed, that contribute with limited information. Several of the submitted literature references related to the use of regadenoson with CT perfusion imaging modalities focus on the efficacy of different technical imaging protocols and are of questionable relevance to the current application. Nevertheless, the results do not suggest any concern regarding the efficacy of regadenoson used with cardiac CT.

2.4.2. Conclusions on the clinical efficacy

The data provided in this bibliographic variation have the usual limitations in this kind of applications. However, the submitted studies provide enough reassurance of the efficacy of regadenoson when it is used as a pharmacological stressor with the claimed imaging techniques. This is in line with the regadenoson use in clinical practice. No efficacy concerns have been raised in any of the studies.

2.5. Clinical safety

Introduction

There are no new clinical safety data from clinical studies in the existing indication. Therefore, the safety profile for the existing indication is based on 1,651 subjects dosed with regadenoson in the two Phase 3 studies (CVT 5131 and CVT 5132) from the data provided with the initial Marketing Authorisation Application, and the changes implemented in the post-authorisation phase, which were supported only by data from literature, no with data from new clinical studies.

The current safety profile for regadenoson includes mild and transient adverse reactions. During clinical development in a total of 1,651 patients/subjects, adverse reactions occurred in approximately 80% of patients. The most common adverse reactions reported were dyspnoea (29%), headache (27%), flushing (23%), chest pain (19%), electrocardiogram ST segment changes (18%), gastrointestinal discomfort (15%) and dizziness (11%).

The following cardiac events can occur and are captured as warnings: myocardial ischaemia (potentially associated with fatal cardiac arrest, life- threatening ventricular arrhythmias, and myocardial infarction), hypotension leading to syncope and transient ischaemic attacks, elevated blood pressure leading to hypertension and hypertensive crises, and SA/AV node block leading to first, second or third degree AV block, or sinus bradycardia requiring intervention.

For the current procedure, the company has only provided evidence from literature through a systematic literature review.

Data provided to support safety of regadenoson comes from 4 published papers obtained through a systematic literature review, 1 study for PET (Lazarus et al. 2020) and 3 studies for CMR (Uhlig et al 2019, Kazmirczak et al. 2019 and Nguyen et al. 2014); and data from a Sponsored phase 2 clinical trial study (Study 3606-CL-2001). Additionally, the company has incorporated safety data from the published literature provided to support clinical efficacy.

No new adverse events for regadenoson have been identified in the published literature provided by the MAH. Therefore, no safety changes to the product information (PI) or the RMP are required.

Patient exposure

The following table is a summary with the studies provided by the MAH to support safety when regadenoson is used for MPI with PET, CT and CMR:

Article	Design	Patients Methods	Imaging Modality	Results
Nguyen et al. 2014	Prospective, cross-sectional and single centre study.	728 patients with indications for vasodilator stress testing and 25 healthy volunteers. Administration: Regadenoson 0.4 mg by IV bolus over 10 seconds.	Cardiac Magnetic Resonance (CMR). Contrast: Gadopentetate Dimeglumine (Magnevist).	No serious adverse events (AEs). Only 1 bronchospasm case and 1 aggravation of heart failure case in patients group. AEs Patients group: dyspnoea (30%, n = 217), chest discomfort (27%, n= 200) headache (15%, n = 111) AEs Control group: more palpitations than patients group (60 vs. 8%; P = 0.652). Dyspnoea similar to patients group (P=0.525)
Uhlig et al. 2019	Retrospective, multinational and multicentre study.	> 70,000 patients. 1,151 patients with Regadenoson (6% of all stress studies). Rest of patients with adenosine or dobutamine.	Cardiac Magnetic Resonance (CMR) GBCAs: Gadobutrol Gadoteric acid Gadobenate Gadopentetate Gadoteridol Gadodiamide	AEs rate: Regadenoson (34/1,151; 2.95%) Adenosine (99/16,921; 0.59%) Dobutamine (7/482; 1.45%) (severe AEs only with Adenosine). Gadobutrol-associated AEs from 0.52% for adenosine to 4.56% for regadenoson.
Kazmirczak et al. 2019	Retrospective matched cohort and single centre study.	234 regadenoson stress CMR studies: 78 studies in 57 patients with orthotopic heart transplant (OHT) and 156 non-heart transplant (1 study each patient).	Cardiac Magnetic Resonance (CMR) Contrasts: gadobenate dimeglumine or gadobutrol.	There were no differences in the rates of AE between heart transplant recipients and non-heart transplant patients. Minor side-effects not requiring any interventions such as dyspnoea, nausea and headache occurred at similar rates in both groups. Serious AE were hypotension and chest pain.

		Administration: 0.4 mg regadenoson in 10 seconds.		
Lazarus et al. 2020	Retrospective single-center study.	123 orthotopic heart transplant (OHT) patients. Administration: 0.4 mg regadenoson in 5-10 seconds. After 8 minutes: 75 mg aminophiline.	Positron Emission Tomography (PET) with Rb-82.	No SAEs occurred. Dyspnoea was the most common symptom (66.7%), followed by nausea and flushing (12.2%), dizziness (4.9%), headache and chest discomfort (3.3%), and palpitations/fatigue (1.6%).
Phase 2 Study 3606-CL-2001	Multicenter, open-label, randomized, cross-over study with SPECT and MDCT.	118 subjects with at least 1 dose of regadenoson. Condition: typical angina/CAD (coronary artery disease).	MDCT: multidetector computed tomography. Contrast agent not specified.	Similar AE with both imaging modalities (SPECT and MDCT). The most frequently reported adverse events (≥5%) included headache, dizziness, flushing, nausea, chest discomfort, dyspnoea and angina pectoris, similar to those seen in previous studies and with mild intensity.

Additionally, the MAH has summarised safety data from the published literature provided to support clinical efficacy. Therefore, more information about these studies can be found in the efficacy section and are summarized in the following table:

Positron Emission Tomography (PET) Myocardial Perfusion Imaging (MPI)	
Study	Safety data
Brophey et al. 2017	Regadenoson was well tolerated. Minimal side effects in 38% of patients. 6 patients (1.2%) experienced side effects severe enough to require aminophylline reversal.
Cremer et al. 2014	50 patients underwent a stress PET study using either ^{82}Rb or ^{13}N-Ammonia. No major AEs during testing. Transient hypotension in 16% of the patients. No MACEs related to the stress test. 2 patients developed symptomatic hypotension that resolved spontaneously without IV fluid or aminophylline administration. 1 patient with a permanent pacemaker developed a brief non-sustained wide complex tachycardia. Significant decrease in systolic blood pressure in 8 of the 50 patients.
Goudarzi et al. 2011	A group of 52 patients stressed with regadenoson were compared with a group of 52 patients stressed with dipyridamole. Regadenoson group: 4 patients (8%) reported side effects which included headache, palpitation, and shortness of breath; 2 of them received aminophylline. Dipyridamole group: 32 patients (62%) reported side effects which included headache, nausea, abdominal pain, palpitation, and light-headedness. All of them received aminophylline. The difference in reported side effects was highly significant (p = 0.003). Patients in the regadenoson group reported less severe symptoms and required less aminophylline.
Vleeming et al. 2018	61 PET/CT MPIs were acquired using either adenosine (n = 30) or regadenoson (n = 31) as a stressor. Tolerability of the adenosine/regadenoson and the occurrence of side effects were compared between groups: Respiratory symptoms were reported by 16 patients (53.3%) in the adenosine group and 11 patients (35.5%) in the regadenoson group (P = 0.095). Typical chest pain, gastrointestinal side effects, vasodilatation-related side effects, and a variety of other side effects were reported by patients of both groups, and no significant differences were found. The overall patient experience with respect to the pharmacologic stressors was also similar between the adenosine and regadenoson groups (P = 0.428), as patients graded both test protocols as equally inconvenient. The patient survey did not show differences in side effects between the adenosine and regadenoson groups.
Bravo et al. 2012	The aim of this study was to evaluate whether PET quantification of regional myocardial perfusion (rMP), myocardial blood flow (MBF), and coronary flow reserve (CFR) are comparable between dipyridamole and the newer vasodilator regadenoson in hypertrophic cardiomyopathy (HC). An additional aim was to evaluate the association between vasodilator-induced ST-segment depression on electrocardiography and myocardial flow in HC. Nitrogen-13 ammonia PET was performed in 57 patients with symptomatic HC at rest and during vasodilator stress (peak) with either dipyridamole (0.56 mg/kg during 4-minute infusion) or regadenoson (0.4 mg fixed bolus dose) for assessment of electrocardiographic findings, rMP (17-segment American Heart Association summed difference score), MBF, and CFR. The dipyridamole and regadenoson groups consisted of 28 and 29 patients, respectively. Fewer patients exhibited side effects with regadenoson (2 vs 7, p = 0.06): 7 patients (26%) experienced side effects with Dipyridamole including chest tightness/pain (n=4), nausea (n=3), and hypotension (n=3) requiring Aminophylline in all occasions. In contrast, only 2 individuals (7%, p = 0.06) experienced side effects after Regadenoson administration (headache and chest pain). Aminophylline was given in one case (chest pain). Regadenoson is tolerated better than dipyridamole and is easier to administer.
Cardiac Magnetic Resonance (CMR) Imaging	
Study	Safety data

Freed et al. 2013	No case of death, arrhythmia or bronchospasm was noted. Two patients had infiltration around their IV line and returned on a later date to complete the exam. Benign symptoms were frequent and included shortness of breath in 32%, flushing in 23%, chest discomfort in 15%, and palpitations in 15%. There was no evidence of bronchospasm. The majority of symptoms were reportedly mild and diminished by the end of the study. One patient experienced persistent headache and abdominal pain after the injection of regadenoson despite the administration of 125 mg of aminophylline. This patient had stress-induced perfusion defects and subsequently underwent coronary revascularization.
Reddy et al. 2013	Pharmacologic stress was performed using regadenoson, adenosine, or dobutamine. Fifty-one of 77 liver transplant candidates underwent MRI (stress CMR was completed in 98% patients). Forty-five patients were able to complete the entire 72-minute examination, and no complication was encountered during CMR examination.
DiBella et al. 2012	30 obese patients (12 male; 18 female) underwent MRI perfusion studies during adenosine infusion (140 µg/kg/min) and 30 minutes later with regadenoson (0.4 mg/5 ml bolus). Regadenoson was shown to be well tolerated (regadenoson produced fewer side effects) and effective as a vasodilator in those pharmacologically stress induced MRI scans. There were no serious adverse events. Nineteen of the subjects felt regadenoson produced fewer side effects, five preferred adenosine and four felt they were equivalent.
Dandekar et al. 2014	This prospective study included 117 patients with suspected myocardial ischemia. Forty-nine percent of patients experienced at least one side effect after administration of regadenoson. The most commonly reported symptoms were shortness of breath (24%), followed by chest pain (18%), headache (14%), flushing (13%), nausea (12%), and dizziness (8%). There were no life-threatening AEs and no instances of atrio-ventricular block or bronchospasm. In addition, there was no incidence of hypotension, contrast reactions, heart failure events, unstable angina or patients requiring antianginal treatment.
Computed Tomography (CT) Perfusion Techniques	
Study	Safety data
Baxa et al. 2015	54 asymptomatic high-risk patients who underwent coronary CTA and regadenoson-induced stress CT perfusion. No SAEs were observed.
Cury et al. 2015	This is the published paper of the phase II study sponsored by the MAH (Study 3606-CL-2001). The adverse events observed are consistent with the known safety and tolerability profile of regadenoson and captured in the current labelling. The safety profiles were overall similar across imaging modalities. No new safety issues have emerged with submission of the CSR.
Cardiac Magnetic Resonance (CMR) Imaging and Computed Tomography (CT) Perfusion Techniques	
Study	Safety data
Rief et al. 2018	Ninety-two patients ~~were~~ underwent perfusion CT and MRI with either adenosine or regadenoson stress. No SAEs occurred during or after either test.
Oleksiak et al. 2020	56 patients received regadenoson for both CT and MRI perfusion. No severe adverse reactions to regadenoson were observed. 1 patient developed allergic reaction to the contrast agent (gadobutrol) during MR MPI.

Adverse events

Cardiac Magnetic Resonance (CMR) Imaging

- Nguyen et al. 2014

Prospective and cross-sectional study conducted in US.

Objective

The aim was to assess the safety and tolerability profile of regadenoson during stress magnetic resonance imaging (MRI).

Methods

728 patients with indications for vasodilator stress testing and 25 healthy volunteers were included (between August 2009 and March 2012). Patients were asked to abstain from caffeine intake and to refrain from taking anti-anginal medications including beta-blockers 24 h prior to the exam. All of these patients received a fixed dose of regadenoson 0.4 mg by IV bolus over 10 seconds.

CMR imaging was performed using a 1.5 Tesla imaging system. Gadolinium (Magnevist, Gadopentetate Dimeglumine, Bayer Healthcare, Wayne, NJ, USA) 0.05 mmol/kg body weight was given at 5 mL/s for both stress and rest image acquisition.

Within 5 min after acquisition of first-pass perfusion images, aminophylline 100 mg iv was given to reverse the effects of regadenoson.

Results

In the following table is shown the frequency of adverse events associated with regadenoson CMR:

Adverse events	Patient cohort (n=728)
Death	0
VT/VF	0
Myocardial infarction	0
Hospitalization	1
Bronchospasm	1
High-grade AV block	0
Stress-induced atrial fibrillation	0
Nephrogenic systemic fibrosis	0
Stress-induced ectopies (PACs/PVCs)	46 (6%)
Bigeminy	2 (<1%)
Symptomatic hypotension	2 (<1%)
Contrast extravasation	2 (<1%)
Minor reaction to gadolinium (rash/hives)	1 (<1%)
Thrombophlebitis	0
Chest pain requiring NTG	9 (1%)
Chest pain requiring iv metoprolol	6 (<1%)

AV, atrioventricular; iv, intravenous; NTG, nitroglycerine; PACs, premature atrial contractions; PVCs, premature ventricular contractions; VF, ventricular fibrillation; VT, ventricular tachycardia.

No deaths, myocardial infarction, arrhythmias (such as tachycardia or ventricular fibrillation), high-grade atrio-ventricular block or stress-induced AF (atrial fibrillation) were observed in this series. The most notable/important AEs reported were a case of bronchospasm (in a patient known to have CAD but no chronic obstructive pulmonary disease or asthma) and a case of aggravation of heart failure (in a patient known to have multivessel coronary heart disease), which required hospitalization. The most common symptoms found in these patients were: dyspnoea (in 30% of patients, n = 217), chest discomfort (27%, n = 200), and headache (15%, n = 111). Chronotropic response to regadenoson was moderate in patients with BMI ≥30 kg/m2 (p <0.001) and in diabetes (p = 0.001).

There was minimal change between baseline and peak systolic and diastolic blood pressure in both patients and volunteers (P = 0.05). Systolic and diastolic BPR (blood pressure response) among patient subgroups and normal volunteers was not statistically significant (P = 0.05).

Frequency of symptoms: Dyspnoea, chest pain, and headache were the three symptoms most frequently reported by patients. More normal volunteers experienced palpitations when compared with the patient cohort (60 vs. 8%; P = 0.652), while dyspnoea was experienced at a similar frequency (P = 0.525).

The authors concluded that regadenoson in cardiac stress MRI is well tolerated and can be performed safely with a frequency of side events similar to those reported in the literature for use in scintigraphy.

Conclusions

This study is prospective and with a control group. However, it does not compare regadenoson with another cardiac stress agent and it is a single-centre study. Patients were recruited if a vasodilator stress testing was indicated, and their disease was unfortunately not characterized.

The study does not discuss a possible interference between regadenoson and the gadolinium-based contrast agent (GBCA) used for cardiac magnetic resonance imaging. Moreover, the GBCA safety profile shares some similarities with the regadenoson safety profile. It was therefore assessed which part of the adverse effects are due to regadenoson or to the contrast when both medicinal substances are used in conjunction and it was suggested that this aspect can be reviewed in the PSURs.

It should be noted that the contrast (gadopentate dimeglumine) is no longer authorised in the European Union, therefore, the results of this study should be taken with caution.

Regadenoson used for CRM is well-tolerated and the frequency of adverse events is low. The most common adverse events reported were dyspnoea (in 30% of patients, n = 217), chest discomfort (27%, n = 200), and headache (15%, n = 111), which are in line with the regadenoson safety profile in the approved indication.

- Uhlig et al 2019

Objective

This very large register (> 70,000 patients) conducted by the European Society of Cardiac Radiology, was a retrospective, multinational and multicentre study to analyse acute AEs observed during CMR examinations performed with gadolinium-based contrast agents (GBCA) including 18,554 stress studies performed with vasodilator agents (adenosine, dobutamine or regadenoson).

The aim was to assess the likelihood of gadolinium-associated acute adverse events in cardiac MR imaging.

Methods

The data source of this study is the multinational, multicenter ESCR MRCT Registry, which includes imaging studies submitted between 2013 and 2016. Only CMR scans with intravenous administration of GBCA were included. The largest GBCA subgroup of patients receiving gadobutrol was chosen as reference. The second more used GBCA was gadoteric acid until a total of 6 more GBCA used in this study.

Most imaging studies were performed without pharmacological stressor (74.5%). Older patients and those with known or suspected coronary artery disease (CAD) as the main imaging indication were more likely to receive pharmacological stressors (adenosine, dobutamine or regadenoson).

Results

In comparison to gadobutrol, patients receiving gadobenate, gadopentetate, and gadoteridol were more likely to develop acute adverse events, and those receiving gadodiamide and gadoteric acid were less likely to develop acute adverse events.

Considering the 3 stress agents, the most frequent acute adverse event was dyspnoea (n = 88, 33.8%), followed by hypersensitive reactions (n = 61, 23.5%) and emesis (n = 17, 6.5%). Regarding only regadenoson, the AE were back pain, heating, anxiety, angina pectoris, dyspnoea, symptomatic bradycardia and hypersensitive reaction.

The overall rate of acute events in this large multinational, multicenter study was 0.36%. Regadenoson had been used in 1,151 patients (6% of all stress studies). As expected, the AEs rate was higher among patients receiving pharmacological stressors but remained extremely low (140 cases in total; 0.75%). Across different pharmacological stressor subgroups, patients receiving regadenoson had higher AEs rate (34/1,151; 2.95%) when compared to adenosine (99/16,921; 0.59%) or dobutamine (7/482; 1.45%). However, the only severe AEs (arrhythmia 13 cases; renal failure 1 case; resuscitation 3 cases) occurred with adenosine. It should be added that even if that is not mentioned in the paper, patients who received regadenoson could have been more fragile and contraindicated to adenosine; it is a frequent situation in many centers who use preferably adenosine and switch to regadenoson in patients with respiratory conditions. Finally, this study showed that gadobutrol-associated AEs differed based on the function of the vasodilator agent used, ranging from 0.52% for adenosine to 4.56% for regadenoson. Event rates were balanced for gadoteric acid (0.3% vs 0.47%).

Conclusions

It appears that patients who received regadenoson had a higher rate of adverse reactions than when adenosine or dobutamine were used, but such adverse reactions were milder than with adenosine.

This study addresses the possibility of interference between cardiac stress and gadolinium-based contrast agents. No firm conclusions can be drawn regarding potential interference either, but it appears that there may be a potentiation between the vasodilator agent and the contrast medium used.

GBCA-associated adverse events varied across pharmacological stressors. For example, gadobutrol associated adverse event rates ranged from 0.52% for adenosine to 4.56% for regadenoson, while event rates were balanced for gadoteric acid (0.3% versus 0.47%). This might be explained by a potentiation of contrast media–associated acute events, depending on different pharmacological stressors, but has not been described in the literature so far. Although not statistically significant, subgroup analyses suggest that higher GBCA volume might contribute to the findings. For example, higher GBCA volumes were evident in the regadenoson subgroup with high AAE incidence. However, there is a limitation to draw conclusion since the GBCA volume and concentration reporting was not mandatory in the study.

Moreover, limitations regarding the high heterogenicity on methodology i.e., the gadolinium-based contrast agents (GBCA) used (until 8 different GBCA), 3 stressor agents, reporting methods and population, prevents the possibility to drawn solid conclusions. Of note, some of the GBCA with linear molecular structure used in this study are no longer authorised in the EU.

In conclusion, the regadenoson safety profile in this study is aligned with what it is already known when it is used in the currently approved indication and the type of contrast received will be reviewed in the PSURs.

- Kazmirczak et al. 2019

Retrospective matched cohort and single centre study of consecutive heart transplant recipients who underwent regadenoson stress CMR matched in a 2:1 ratio to age- and gender-matched non-heart transplant patients.

Objective

Evaluate the safety and the prognostic value of regadenoson stress CMR in heart transplant recipients.

Methods

This study analysed 234 regadenoson stress CMR studies: 78 of them were performed in 57 patients with heart transplant (OHT) and 156 in non-heart transplant patients. Interestingly, 34 stress CMR studies in the heart transplant group were performed within 2 years of heart transplantation.

Regadenoson stress CMRs were performed using a 1.5 Tesla scanner. Regadenoson 0.4 mg (Astellas, Northbrook, Illinois, USA) was injected over approximately 10 s into a peripheral vein followed by a 5 mL saline flush. The patient was centered back into the scanner and the perfusion sequence was started within 1–2 min of regadenoson injection. Gadolinium-based contrast (0.075 mmol/kg gadobenate dimeglumine, Bracco Imaging or 0.1 mmol/kg gadobutrol, Bayer HealthCare LLC, Milan, Italy) was infused at 4–5 ml/s followed by a saline flush (50 ml) via an antecubital vein for both stress and rest perfusion.

Prior to April 2014, aminophylline was used for significant patient symptoms. All studies performed after April 2014 routinely received aminophylline 100 mg intravenously for reversal of hyperemia after stress images were acquired.

All stress CMR exams were interpreted blinded to patient outcomes by a consensus of two CMR physicians.

Collected clinical outcomes included: myocardial infarction, percutaneous intervention, cardiac hospitalization, retransplantation and death. These events together formed the composite endpoint of major adverse cardiovascular events.

Results

There were no differences in the rates of adverse effects between heart transplant recipients and non-heart transplant patients.

Adverse effects are listed in the following table:

Adverse effect	Heart transplant recipients (n = 78)	Non-transplant patients (n = 156)	p value
Death, n (%)	0	0	N/A

Asystole, n (%)	0	0	N/A
Sinus pause or arrest, n (%)	0	0	N/A
High-grade atrioventricular block, n (%)	0	0	N/A
Ventricular tachycardia or ventricular fibrillation, n (%)	0	0	N/A
Atrial fibrillation, n (%)	0	0	N/A
Chest pain requiring sublingual nitroglycerin, n (%)	1 (1)	0	0.33
Myocardial infarction, n (%)	0	0	N/A
Symptomatic hypotension, n (%)	1 (1)	1 (0.6)	0.65
Dyspnoea, n (%)	6 (7)	9 (6)	0.58
Nausea, n (%)	6 (7)	3 (2)	0.08
Headache, n (%)	2 (3)	0	0.11
Allergic reaction (rash, hives, etc.), n (%)	0	0	N/A
Contrast extravasation, n (%)	0	2 (1)	0.55
Thrombophlebitis, n (%)	0	0	N/A
Hospitalization, n (%)	0	0	N/A

Hemodynamic changes

In the heart transplant recipient group, the mean heart rate increased from 92 ± 11 bpm to 107 ± 12 bpm, while it increased from 73 ± 15 bpm to 100 ± 13 bpm in the comparison group. There were no significant changes in pre- and post-stress blood pressures in both the heart transplant recipient and comparison groups.

Safety

2 patients in the heart transplant group had a side effect requiring intervention; one patient complained of chest pain requiring nitroglycerin, and one had symptomatic hypotension requiring perfusion. One patient in the non-heart transplant group had symptomatic hypotension requiring perfusion. Another patient in the heart transplant group complained of regadenoson-related abdominal cramps, which resolved spontaneously. The patient received a second injection and the examination was performed without incident. Minor side-effects not requiring any interventions such as dyspnoea, nausea and headache occurred at similar rates in both groups. No case of death, high degree AV block, myocardial infarction, cardiac arrest, sinus arrest, or sinus pause occurred. No patient required hospitalization or emergency room evaluation. Those results are of high interest because it is well known that adenosine induced CMR is at risk in transplanted patients due to cardiac denervation. The period of risk covers the 2 years following transplantation when there is a risk of super-sensitivity to adenosine (risk of conduction disorder). The second objective of this study regarded the prognostic value of regadenoson stress CMR. This part of the study was also positive as there was a significant difference in terms of prognosis between transplanted patients with abnormal vs normal CMR. Regadenoson stress CMR seems capable to detect transplanted patients with cardiac allograft vasculopathy.

Conclusions

Although the population and indication differ from the approved one, the safety data about using regadenoson according to the approved indication are taken into account.

The same adverse events were observed in clinical trials as well in postmarketing experience, where syncope and transient ischaemic attacks have been reported.

The rest of the AEs reported in this study were minor side-effects not requiring any interventions, such as dyspnoea, nausea and headache that occurred at similar rates in both groups. There were no occurrences of death, asystole, sinus pause, sinus arrest, high-degree atrioventricular block, ventricular arrhythmias, stress-induced atrial fibrillation, or myocardial infarction. No patients required hospitalization or emergency room evaluation.

The safety profile of regadenoson in CMR with heart transplant patients does not appear to differ from the safety profile when regadenoson is used for the approved indication. –

Positron Emission Tomography (PET) Myocardial Perfusion Imaging (MPI)

- Lazarus et al. 2020

Objective

The objective of this study was to determine the safety of regadenoson stress testing with ^{82}Rb PET imaging in patients who have undergone orthotopic heart transplantation (OHT). Routine screening for cardiac allograft vasculopathy is necessary after OHT. Adenosine stress is contraindicated after heart transplantation due to super-sensitivity in denervated hearts. Safety of regadenoson stress following OHT has not been well studied.

Methods

Data from OHT patients (N = 123) who were referred for regadenoson stress testing were retrospectively reviewed. Medical records were reviewed to determine hemodynamic and ECG response to regadenoson and to identify adverse reactions.

All patients were injected 0.4 mg of regadenoson while lying supine over 5 to 10 seconds. After a minimum of 10 mililiters of saline flush, radiotracer (Rb-82) was injected intravenously. After a total of 8 minutes all patients without contraindications were routinely administered 75 mg of aminophylline intravenously to reverse the effects of regadenoson, except in the presence of contraindications, such as a history of seizures or prior allergic reactions. After regadenoson infusion symptom inventory was collected by qualified exercise physiologists on a sheet where a list of side-effects including dyspnea, headache, nausea, fatigue, palpitations, dizziness, chest pressure, and ‘‘other’’ were noted. Chest pain was quantified on a 1 = 10 scale but other symptoms including dyspnea were not quantified.

Results

The hemodynamic stress response caused by Regadenoson was appropriate as it is shown in the table below:

	Pre-infusion	Post-infusión	P
HR (bpm)	83 ± 12	96 ± 13	< 0.001
Systolic BP (mmHg)	140 ± 21	116 ± 24	< 0.001
Diastolic BP (mmHg)	86 ± 14.7	69 ± 14	< 0.001

MAP (mmHg)	104 ± 14	85 ± 16	< 0.001

HR: Heart rate; BP: Blood pressure; MAP: mean arterial pressure

No SAEs occurred. No life-threatening arrhythmias or hemodynamic changes occurred. Dyspnoea was the most common symptom occurring in 82 (66.7%) patients, followed by nausea and flushing (12.2%), dizziness (4.9%), headache and chest discomfort (3.3%), and palpitations/fatigue (1.6%). 19 patients (15.4%) reported no symptoms. In comparison to pooled analysis from two randomized clinical trials (ADVANCE phase 3 and ADVANCE MPI results), dyspnoea and nausea were more frequent (28% and 6% respectively in clinical trials) in the OHT cohort. Side-effects occurring during stress testing did not require specific intervention, beyond routine aminophylline administered as part of the stress protocol.

There was no sustained ventricular tachycardia, ventricular fibrillation, or second-or third-degree atrioventricular block. Regadenoson stress testing appears to be well tolerated and safe in OHT patients.

Conclusions

Since initial approval of regadenoson, imaging modalities within nuclear medicine have evolved and PET MPI is another option other than SPECT. The American Society of Nuclear Cardiology (ASNC) and the American Heart Association (AHA) have published recommendations for reducing radiation exposure in MPI. ASNC recommends using PET MPI, if PET is available, as one of the first-line strategies for reducing patient radiation exposure in radionuclide MPI due to the short physical half-lives of the PET perfusion tracers, which lead to lower patient radiation exposure. This would be aligned with the AHA which recommend alternatives to tests involving radiation (eg cardiac MRI). It is noted however in section 4.6 of the SmPC that regadenoson should not be used during pregnancy unless clearly necessary and that fertility studies with regadenoson have not been performed. Foetal toxicity was noted following repeated daily administration of regadenoson, but at doses sufficiently in excess of the recommended human dose.

Patients differ from the clinical trials population that supported the approved indication, but safety data from heart transplanted patients have been taking into account.

This study has limitations because it is retrospective, single centre and the selected patients may not represent the general OHT population. Dosing and procedure administration of regadenoson are aligned with the use in the approved indication.

As expected, the regadenoson safety profile in PET radionuclide imaging is similar than the stablished in the current regadenoson product information for SPECT imaging, because both modalities use radionuclides as tracers.

Computed Tomography (CT) Perfusion Techniques

Sponsored Clinical Study (Phase 2 Study 3606-CL-2001)

A Phase 2, Open-Label, Randomized, Cross-Over Study of Regadenoson in Subjects Undergoing Stress Myocardial Perfusion Imaging by Multidetector Computed Tomography (MDCT) and Single Photon Emission Computed Tomography (SPECT).

Methods

SPECT imaging was performed in sequence prior to regadenoson stress SPECT imaging, regardless of randomization sequence. Imaging could be conducted with one of two radiotracers (99mTc sestamibi or tetrofosmin).

Regadenoson stress CTP was performed in sequence prior to rest CCTA/CTP imaging, regardless of randomization sequence. Contrast solution was administered intravenously for imaging.

Population

Mets the inclusion criteria according the Phase 2 Study 3606-CL-2001.

Pathology characteristics: subjects with typical angina.

Subjects met at least 1 of the following 3 criteria:

a. had a suspected (clinical impression) or known diagnosis of CAD with typical angina that had been referred from nuclear cardiology lab schedule or cardiac CT schedule.

b. had stable symptoms with possible elective catheterization procedure scheduled and where further imaging might be beneficial.

c. had known CAD from a previous ICA performed more than 12 weeks prior to screening who currently presented with new cardiac symptoms.

4. Subject had been referred for a clinically indicated myocardial perfusion imaging procedure or cardiac CT procedure for suspected moderate or high-risk CAD.

Results

No clinically important differences in vital signs were seen when regadenoson was administered for SPECT or MDCT imaging. Heart rate increased by about 16 bpm following the administration of regadenoson.

AEs were reported for 81 of the 118 patients. The most common treatment-emergent AEs (defined as an AE observed from the time of administration of regadenoson to 1 day after study drug administration within each modality) were flushing, with an overall incidence of 33.9% (15.4% and 22.4% of subjects in the SPECT and MDCT modalities, respectively) and headache, with an overall incidence of 25.4% (12.8% and 19.8% of subjects in the SPECT and MDCT modalities, respectively) (see the table below).

All remaining treatment-emergent AEs were reported by ≤11.1% of subjects in either modality group. All cases of flushing (n = 40) and 24 of 30 cases of headache were considered drug-related and all cases of both events were categorized as mild or moderate in intensity. Of the total 265 treatment-emergent AEs reported during the study, 7 events (2 for SPECT and 5 for MDCT) were categorized as severe.

Two subjects experienced SAEs that led to discontinuation from the study, gastritis (within 24 hours of regadenoson administration) and uncontrolled hyperglycemia (>24 hours after regadenoson administration). Neither event was regadenoson-related. Aside from the subject with gastritis, there were no other SAEs within 24 hours after regadenoson administration. No deaths were reported.

Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Either Treatment Sequence Classified by System Organ Class and Preferred Term

MedDRA (V11.1) System Organ Class Preferred Term	Regadenoson		
	SPECT (n = 117)	MDCT (n = 116)	Total (n = 118)
	n (%)	n (%)	n (%)
Overall	53 (45.3)	59 (50.9)	81 (68.6)
Nervous System Disorders	25 (21.4)	31 (26.7)	45 (38.1)

Headache	15 (12.8)	23 (19.8)	30 (25.4)
Dizziness	11 (9.4)	6 (5.2)	16 (13.6)
Vascular Disorders	19 (16.2)	26 (22.4)	41 (34.7)
Flushing	18 (15.4)	26 (22.4)	40 (33.9)
Gastrointestinal Disorders	18 (15.4)	14 (12.1)	25 (21.2)
Nausea	9 (7.7)	6 (5.2)	11 (9.3)
General Disorders and Administration Site Conditions	11 (9.4)	11 (9.5)	19 (16.1)
Chest discomfort	11 (9.4)	9 (7.8)	17 (14.4)
Respiratory, Thoracic and Mediastinal Disorders	14 (12.0)	11 (9.5)	17 (14.4)
Dyspnoea	13 (11.1)	10 (8.6)	16 (13.6)
Cardiac Disorders	5 (4.3)	12 (10.3)	15 (12.7)
Angina pectoris	4 (3.4)	9 (7.8)	11 (9.3)

Safety Analysis Set (SAF): All randomized subjects who receive at least 1 dose of regadenoson. Regadenoson SPECT: stress Single Photon Emission Computed Tomography; Regadenoson MDCT: stress Multidetector Computed Tomography. Treatment-emergent adverse event: An adverse event observed from the time of administration of regadenoson to 24 hours after study drug administration within each modality

The overall incidence of TEAEs was 68.6% and most were considered drug related (66.9%) with a similar incidence when regadenoson was administered for either SPECT or MDCT imaging. Most of these TEAEs were categorized as mild intensity.

Conclusions

The design of this phase 2 study, open-label, randomized, cross-over was adequate. Also, population and methodology are in line with the studies performed with regadenoson to support the current approved indication.

The contrast agents used for MDCT are not specified in the study, and as well as in CMR and PET imaging modalities, no discussion about potential interferences between contrasts and regadenoson were provided by the MAH.

The safety profile when regadenoson is used in MDCT is similar than the SPECT imaging one. The most frequently reported adverse events (≥5%) included headache, dizziness, flushing, nausea, chest discomfort, dyspnoea and angina pectoris, similar to those seen in previous studies and in line with the regadenoson safety profile in the approved indication. However, the study does not compare regadenoson with adenosine in both imaging modalities (SPECT and MDCT).

Given the total radiation dose is higher using CT compared to SPECT, it was discussed if this could potentially impact the safety profile of regadenoson and if this result should be captured in the labelling. However, the pharmacological effect of regadenoson is independent from the imaging modality used for assessing myocardial blood flow changes, thus, the safety profile of regadenoson is not influenced by the radiation dose and thus this radiation exposure should not be captured in the regadenoson labelling but in tracer's labelling. It is physician's decision to select the most appropriate diagnostic modality based on patient's characteristics, local experience, and ultimate goal of the examination according to the guidelines. ALARA principle should guide the modality prescription.

The adverse events observed are consistent with the known safety and tolerability profile of regadenoson and captured in the current labelling. The safety profiles were overall similar across imaging modalities. No new safety issues have emerged with submission of the CSR.

Serious adverse event / deaths / other significant events

Only 2 serious adverse events have been identified in the literature provided by the MAH (Kazmirczak et al. 2019) to support the safety when regadenoson is used in the approved indication with other imaging modalities (CMR): chest pain requiring nitroglycerin, and one had symptomatic hypotension requiring perfusion. These adverse events were observed in clinical trials as well in postmarketing experience, where syncope and transient ischaemic attacks have been reported.

In the Sponsored Clinical Study (Phase 2 Study 3606-CL-2001) two subjects experienced SAEs that led to discontinuation from the study, gastritis (within 24 hours of regadenoson administration) and uncontrolled hyperglycemia (>24 hours after regadenoson administration). Neither event was considered to be regadenoson-related. Aside from the subject with gastritis, there were no other SAEs within 24 hours after regadenoson administration. No deaths were reported.

Safety related to drug-drug interactions and other interactions

Two articles about interactions with caffeine were submitted: one study in Positron Emission Tomography (Kitkungvan et al. 2019) and other study in Cardiac Magnetic Resonance (van Dijk et al. 217).

However, these studies have limited value since there is already a warning in SmPC (section 4.5) about methylxanthines intake before regadenoson administration.

Moreover, these interactions are independent from the modality used for stress myocardial perfusion imaging.

2.5.1. Discussion on clinical safety

Regadenoson is a pharmacologic stress agent indicated for radionuclide MPI in patients unable to undergo adequate exercise stress. Regadenoson has been shown to be non-inferior to adenosine in the detection of myocardial ischemia in patients undergoing SPECT MPI.

Regadenoson is widely available and its use improves protocol simplicity (a single bolus instead of a continuous infusion) and safety (better safety profile because of selectivity to the A2A receptors).

Since initial approval of regadenoson, imaging modalities within nuclear medicine have evolved and PET isotope MPI is another option other than SPECT. The American Society of Nuclear Cardiology (ASNC) and the American Heart Association (AHA) have published recommendations for reducing radiation exposure in MPI. ASNC recommends using PET MPI, if PET is available, as one of the first-line strategies for reducing patient radiation exposure in rMPI due to the short physical half-lives of the PET perfusion tracers, which lead to lower patient radiation exposure. This would be aligned with the AHA which recommends alternatives to tests involving radiation (eg cardiac MRI). It is noted however in section 4.6 of the SmPC that regadenoson should not be used during pregnancy unless clearly necessary and that fertility studies with regadenoson have not been performed. Foetal toxicity was noted following repeated daily administration of regadenoson, but at doses sufficiently in excess of the recommended human dose.

For this variation, it is argued that the safety profile remains unchanged, hence the Risk Management Plan and the information about safety in the regadenoson product information are not changed. This is agreed by the CHMP.

According to the scarce bibliographic evidence submitted by the MAH, there are no new safety concerns regarding the use of regadenoson in the proposed indication with other imaging modalities such as Cardiac Magnetic Resonance, PET imaging and Multi-detector Computed Tomography. Dose and administration method of regadenoson with those mentioned imaging modalities are aligned with the current product information for SPECT myocardial perfusion imaging, then, similar safety profile as in the current approved indication is expected.

The literature provided is scarce and with limitations because some studies are retrospective, single study centre and without an appropriate design to obtain comparative data with adenosine (or dipiridamol). However, it can be envisaged that the regedenoson safety profile for the other imaging modalities is aligned with the current data and post marketing experience when regadenoson is used for SPECT myocardial perfusion imaging.

The population in the studies provided is not very well characterised, and in two of them (Kazmirczak et al. 2019 and Lazarus et al. 2020) with heart transplant patients, population differs from the clinical trials population that supported the approved indication for MPI. However, safety data from heart transplant patients have been taking into account when regadenoson is used in CMR and PET. In this regard, 2 serious adverse events have been identified in the heart transplant group from the study provided by the MAH (Kazmirczak et al. 2019) to support safety when regadenoson is used in the approved indication with CMR: chest pain requiring nitroglycerin, and symptomatic hypotension requiring perfusion. These SAE could be related to the special conditions in the group with heart transplant, but the MAH has not provided discussion about these events. However, these adverse events were observed in clinical trials as well in postmarketing experience, where syncope and transient ischaemic attacks have been reported.

There should not be a change in the patient population or identification of a new patient population when using regadenoson with other imaging modalities however this has not been discussed adequately by the applicant. The pivotal studies in the initial approval in 2010 utilised the radionuclide SPECT technique only and as highlighted by the applicant; other radionuclide imagine techniques have been used since then (PET). It is noted that the type of radionuclide imaging is not specified in the current therapeutic indication. Obviously, the type of imaging modality used will also depend on a patient's medical history for example patients with renal impairment may not be a candidate for contrast enhanced CT or MRI if a pacemaker is in situ. This should not affect the safety profile of regadenoson specifically as clinical restrictions also apply to radionuclide imaging modalities that are not required to be specified in the labelling for regadenoson.

The potential interferences between regadenoson and the contrast agents used, mainly in Cardio Magnetic Resonance and Computed Tomography imaging, were evaluated.

It could be assumed that interference with radiopharmaceuticals when regadenoson is used with PET, is null or minimal, because of the trace quantity used in this imaging modality (radionuclide imaging) and similar when SPECT agents are used according the product information.

For gadolinum based agents and iodinated contrast agents, a potential interference with regadenoson cannot be excluded, taking into consideration the higher doses used compared to when radionuclides agents are used. In addition, the safety profile of these agents shares some similarities with the regadenoson's safety profile. Therefore, this issue maybe an important confounding factor that could jeopardize the regadenoson safety profile characterisation when these contrast agents are used in

conjunction with regadenoson. Using these contrast agents (GBCA and iodinated contrasts) is a worse scenario than when regadenoson is used with radionuclide.

In the Uhlig et al. 2019 study, the possibility of interference between cardiac stress agents and gadolinium-based contrasts is addressed. But due to the retrospective design and the limitations of the study, no firm conclusions can be drawn regarding potential interferences. It appears that there may be a potentiation between the vasodilator agent and the contrast medium used.

In conclusion, it is considered sufficient that the type of contrast received) is reviewed in the PSURs.

An advantage when CMR is used versus the rest of imaging modalities is that patients are not exposed to ionizing radiation. On the other hand, an important inconvenience for using regadenoson in Cardiac Magnetic Resonance imaging is the interference and distortion in ECG by the strong magnetic field limiting the diagnosis of heart block. Moreover, with regadenoson, the fixed rapid bolus administration does not allow for dose-modification based on ECG findings.

For MDCT, the MAH only provides the comparative cross-over phase 2 study (3606-CL-2001) between MDCT and SPECT when regadenoson is used with both imaging modalities, but there is not comparative data with adenosine. As expected, regadenoson safety profile is similar with both imaging modalities.

The CSR for this non-inferiority supportive study has been submitted and assessed in the efficacy section. No new safety issues have emerged with submission of the CSR and the safety profile of regadenoson is not influenced by the radiation dose and thus this radiation exposure should not capture in the regadenoson labelling but in tracer's labelling. It is physician's decision to select the most appropriate diagnostic modality based on patient's characteristics, local experience, and ultimate goal of the examination according to the guidelines. ALARA principle should guide the modality prescription.

Considering the studies submitted by the MAH with this variation, the reported adverse events and its frequency are aligned with the regadenoson safety profile in the approved indication. Therefore, even taking into account the above-mentioned limitations, it can be assumed that the safety profile continues unchanged when regadenoson is used with the other imaging modalities (PET, CMR and MDCT).

2.5.2. Conclusions on clinical safety

While the limitations of literature review are acknowledged, the data presented demonstrates an acceptable safety profile when using regadenoson with other imaging modalities such as MR & CT which would be aligned with current clinical practice. Regadenoson is widely available and its use improves protocol simplicity (a single bolus instead of a continuous infusion) and safety (better safety profile because of selectivity to the A2A receptors). There does not seem to be a worse safety profile for regadenoson when using other modalities however again, this interpretation of the literature is associated with uncertainty.

No new safety concerns have been raised in the submitted studies and it is assumed that the safety profile does not change when regadenoson is used with the other imaging modalities.

In addition, the MAH should submit the following safety data as part of the next PSUR: a review of the safety profile of regadenoson based on the type of imaging modality including the potential interferences between regadenoson and contrast agents used in other imaging modalities (CMR, CT).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH has not submitted an updated RMP, which is agreed by the CHMP.

2.7. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 5.1 of the SmPC have been updated The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The objective of all forms of stress testing in coronary artery disease (CAD) is to assess the extent and adequacy of the hyperaemic response, testing the ability of the coronary circulation to augment flow (the coronary flow reserve [CFR]). In the presence of CAD, perfusion image abnormalities result from heterogeneity of coronary blood flow reserve. Pharmacological stress testing has high clinical use for risk stratifying patients with known or suspected CAD, in patients after myocardial infarction, and in patients needing noncardiac surgery.

Stress is commonly induced in two ways: by exercise (on a stationary bicycle or treadmill) or by pharmacological agents. The available pharmacological agents differ in terms of the mechanism by which they simulate changes induced by exercise: vasodilators such as adenosine, dipyridamole and regadenoson induce vasodilation, while dobutamine induces an increase in heart rate and contractility.

Regadenoson was approved for use for radionuclide MPI in 2010 based on data with SPECT. Perfusion assessment should be independent from the stress applied either physical or drug-induced in the sense that the stress has the objective to increase the local blood flow demand while the imaging modality has the objective to measure the relative changes in the blood flow response to this stress itself. That would mean that any imaging modality able to measure perfusion at the cardiac level would therefore be suitable to assess stress-induced perfusion changes related to the effect of regadenoson. Nevertheless, the MAH has provided data from a bibliographic search to support the use of regadenoson with different imaging techniques.

Regadenoson produces hyperemia with rapid onset (30 seconds) for a longer period (approximately two to four minutes) than adenosine, which permits more convenient administration (injection of 400 mcg over 10 seconds for regadenoson instead of 6-min infusion of a weighted-adjusted dose for adenosine). Straightforward dosing (no weight adjustment) facilitates use and reduce errors due to dose calculations in comparison to adenosine.

3.1.2. Available therapies and unmet medical need

Pharmacological stress testing is included in the European and North-American guidelines for SPECT MPI. Dipyridamole was the first vasodilator used for myocardial perfusion stress testing (Paganelli et al. 2017). It is an indirect coronary artery vasodilator, whose mechanism of action is the building up of adenosine in tissues by blocking the cellular reuptake of endogenous adenosine. Dipyridamole has the longest history of use and has the most data available in the literature in relation to MPI; however, it is not approved for this indication in many European countries (Sciagrà et al. 2021). Adenosine is a direct coronary artery vasodilator and acts on the 4 known types of receptors. Adenosine is currently licenced nationally in many European countries as a coronary dilator for use with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate. Adenosine was considered as an appropriate reference standard against which to compare a pharmaceutical stress agent when regadenoson was registered in Europe in 2010. Regadenoson is another direct coronary artery vasodilator and it is a selective A2A receptor agonist.

This application for an extension of indication for regadenoson aims to expand the indication to any imaging modality.

3.1.3. Main clinical studies

The application is mainly based on bibliography that has been retrieved through a systematic literature review performed by the MAH. The main clinical data to assess efficacy of regadenoson as a stress pharmacological agent in cardiac CT are from a company-sponsored phase 2 clinical study (Study 3606-CL-2001), in addition to bibliography.

3.2. Favourable effects

Overall, the data submitted by the MAH support the efficacy of regadenoson when it is used as a pharmacological stress agent for myocardial perfusion imaging. Comparative data (with adenosine or dipyridamole) have been provided and this is reassuring in terms of assessment.

3.3. Uncertainties and limitations about favourable effects

The limitations of bibliographic applications are well known. The non-comparative and/or retrospective nature of a number of provided papers represent a drawback in terms of assessment. In addition, only summaries of the bibliographic search without an overall discussion of the efficacy data of interest in this variation has been provided.

3.4. Unfavourable effects

It is acknowledged that limited data have been provided but no new safety concerns have been identified in the studies submitted. As expected, data suggest similar safety profile of regadenoson when used with the claimed diagnostic techniques.

New safety data or AEs from clinical studies was not presented. As per the efficacy sections, the active substance is well characterised and being regularly assessed by PRAC with no ongoing safety signal. The submitted data, though limited supports the proposed indication and do not indicate a significant difference in terms of safety when regadenoson is used with alternative imaging modalities.

3.5. Uncertainties and limitations about unfavourable effects

For gadolinum based agents and iodinated contrast agents, a potential interference with regadenoson cannot be excluded, taking into consideration the higher doses used compared to when radionuclides agents are used. In addition, the safety profile of these agents shares some similarities with the regadenoson's safety profile. Therefore, this issue maybe an important confounding factor that could jeopardize the regadenoson safety profile characterisation when these contrast agents are used in conjunction with regadenoson.

The potential interferences between regadenoson and the contrast agents used, mainly in Cardio Magnetic Resonance and Computed Tomography imaging were discussed, and this aspect (type of contrast received) will be reviewed in the PSURs.

Safety data was limited in the submission, still, it is accepted that the pharmacological effect of regadenoson is independent from the imaging modality used for assessing myocardial blood flow changes and the safety profile of regadenoson is not influenced by the radiation dose. Therefore, radiation exposure should not capture in the regadenoson labelling but in tracer's labelling.

3.6. Effects Table

Not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the limitations inherent to the bibliographic applications, it can be concluded that the data available support the use of regadenoson with the claimed diagnostic techniques. The use of PET was already formally covered by the current indication that refers to radionuclide (although its approval was only based on data with SPECT) and data provided with PET just confirm such practice. Similarly, the studies with CMR and CT can be considered sufficiently supportive of the claim. This is fully aligned with what is done in clinical practice.

These results support the notion that perfusion assessment by imaging techniques should be independent from the stress (physical or drug-induced) in the sense that stress increases the local blood flow demand and imaging modality measures the relative change in the blood low response to this stress itself.

From the safety point of view, the main shortcoming was the lack of discussion regarding the potential interferences between regadenoson and the contrast agents used, mainly in Cardio Magnetic Resonance and Computed Tomography imaging. The type of contrast received and potential interferences with regadenoson will be reviewed in the PSURs.

The proposed changes reflect current clinical practice, as the medicinal product is currently being used

in a broader setting, with a multitude of other imaging modalities (PET, MRI, and cardiac CT) and not only radionuclide-related. The active substance is well characterised and being regularly assessed by PRAC with no ongoing safety signal. The submitted data, though limited supports the proposed indication and do not indicate a significant difference in terms of safety when regadenoson is used with alternative imaging modalities.

3.7.2. Balance of benefits and risks

Overall, data provided support the extension of the indication to the claimed imaging modalities.

3.8. Conclusions

The overall B/R of Rapiscan is positive.

In addition, the MAH should submit the following safety data as part of the next PSUR: a review of the safety profile of regadenoson based on the type of imaging modality including the potential interferences between regadenoson and contrast agents used in other imaging modalities (CMR, CT).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to modify the existing indication to allow use in line with new imaging technologies that have evolved since initial approval of Rapiscan; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Rapiscan-H-C-001176-II-38’