**Video Files to accompany Figure 2 from the manuscript.**

**Video 1.** Summarizes stress perfusion on the top row and rest perfusion on the bottom row for the patient in figure 2. This version of the video has motion corrected perfusion images. Filename: **Video1\_GadaCAD\_perfusion\_MOCO.mp4**

**Video 2.** Summarizes stress perfusion on the top row and rest perfusion on the bottom row for the patient in figure 2. This version of the video has the raw perfusion images prior to motion correction. Filename: Video2\_GadaCAD\_perfusion.mp4

**Video 3.** Summarizes the cine CMR includes 8 slices out of the volumetric short axis acquisition for the patient in figure 2. Filename: Video3\_GadaCAD\_cineCMR.mp4

**Video 4.** Is the 4-chamber cine CMRfor the patient in figure 2.Filename: **Video4\_GadaCAD\_cineCMR\_4ch.mp4**

**Video 5.** Is the 3-chamber cine CMR for the patient in figure 2. Filename: **Video5\_GadaCAD\_cineCMR\_3ch.mp4**

**Video 6.** Is the 2-chamber cine CMR for the patient in figure 2. Filename: **Video6\_GadaCAD\_cineCMR\_2ch.mp4**

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**Practical and Technical Considerations for CMR imaging with Single Dose Contrast**

The American College of Radiology recommends that, “…multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain.”(1)

The protocol for image acquisition and stress testing was created to increase odds of successful imaging when using a gadobutrol dosing scheme aimed at 0.1 mmol/kg body weight. For example, SSFP perfusion was used at 1.5T to benefit from higher signal to noise ratio than other perfusion methods but FLASH perfusion was used at 3T to avoid potential artifacts.(2) The timing allowed about 10 minutes between stress and rest perfusion imaging and started LGE imaging about 5 minutes after the second dose of contrast. Use of other GBCA should consider the relative relaxivity and other agent specific characteristics that might alter the dose of GBCA selected.

When using low doses of GBCAs for CMR, it is important to carefully manage time between the contrast administration and the LGE imaging for optimizing the contrast-to-noise ratio. A fixed inversion time (TI) for LGE imaging was used to reduce the need for a technologist to adjust TI as the time to make adjustments may have allowed the contrast to washout before good quality LGE images were obtained.

Gadobutrol has a relatively high relaxivity,(3) a term that describes the strength of a GBCA. A higher relaxivity leads to a shorter T1 and thus generally translates to higher signal intensity on a heavily T1-weighted perfusion sequence as used in CMR stress tests. From the perspective of different GBCAs, the relaxivity of gadoterate meglumine (Dotarem™) is approximately 40% lower than Gadobutrol (Gadavist™)(4) and thus might be expected to require a higher dose for equivalent effect on a T1 weighted sequence like perfusion or LGE imaging. Gadobutrol also has relatively high stability.(5)

The GadaCAD LGE image acquisition protocol also included both conventional magnitude (6) and phase sensitive inversion recovery (PSIR) reconstructions(7). With a correct inversion time, the magnitude and PSIR LGE images look similar. When the inversion time is too long or too short, magnitude images may be non-diagnostic but the same data can produce diagnostic quality PSIR LGE images even if the inversion time were off by 100 ms.

During review of the GadaCAD studies, the availability of 4 types of LGE images (single shot magnitude IR, single shot PSIR, high resolution magnitude IR and high resolution PSIR) meant that diagnostic quality images could be obtained in the great majority of participants. Single shot images are often better than the high resolution in patients who cannot hold their breath well, who have arrhythmias, or have poor ECG gating. PSIR images, either single shot or high resolution, are typically better than magnitude LGE images when the inversion time is incorrect. When the inversion time is correct, the segmented magnitude IR LGE images are frequently the best LGE images.

Excluding patients with an acute MI within the prior 14 days may have helped avoid possible overestimation of infarct transmurality due to edema (8). Overestimation of MI size by early gadolinium enhanced imaging is a controversial issue that may occur in non-STEMI when starting LGE imaging 5 minutes after a dose of contrast. Other carefully controlled studies have not seen overestimation of MI size when imaged 5 minutes after administration of gadolinium-based contrast agents (9,10).

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**Supplementary Table 1**

**Inclusion Criteria**

1) Male or female subjects aged 18 years.

2) Subjects with suspected or known CAD based on signs and/or (typical or atypical) chest pain who:

a) have undergone routine CA without intervention within 4 weeks prior to gadobutrol enhanced

CMRI or

b) are scheduled for routine CA within 4 weeks after gadobutrol-enhanced CMRI or

c) are at low risk for CAD and have undergone / are scheduled for routine CTA for the clinical purpose of exclusion of CAD within ± 4 weeks of gadobutrol-enhanced CMRI.

1) A subject is included if CTA excludes significant CAD.

2) In case of an equivocal or positive CTA, the subject is included only if CA is available for that particular subject either within 4 weeks prior to gadobutrol enhanced CMRI or up to 6 weeks after gadobutrol-enhanced CMRI.

3) Subjects who are scheduled for / have undergone routine GSPECT or undergo GSPECT as a study procedure at stress and at rest within ± 4 weeks of gadobutrol-enhanced CMRI. This only applied to GadaCAD2

4) Willingness to undergo unenhanced wall motion and gadobutrol-enhanced CMRI at stress/rest and GSPECT (if GSPECT will be a study procedure). This only applied to GadaCAD2

5) Willingness and ability to follow directions and complete all study procedures as specified in the protocol.

6) Women of childbearing potential only: use of any medically accepted means of contraception and a negative pregnancy test on the day of gadobutrol-enhanced CMRI prior to administration of study drug.

Women without childbearing potential only: one or more of the following has to apply:

age ≥ 60 / history of surgical sterilization or hysterectomy / last spontaneous bleeding at least 2 years prior to study.

7) Written informed consent (IC), including information about the provisions of the Health Insurance Portability and Accountability Act (HIPAA) as applicable.

**Exclusion Criteria**

1) Pregnant or nursing (including pumping for storage and feeding).

2) Received any other investigational product or participation in any other interventional clinical study within 15 days prior to enrollment in this study.

3) Suspected clinical instability or unpredictability of the clinical course during the study period (e.g. due to previous surgery or acute stroke).

4) Any scheduled procedure such as interventional (PCI, stenting) or surgical treatment that may alter / may have altered the cardiac condition regarding myocardial perfusion status and / or stenosis degree between CMRI, GSPECT, and CA or CTA. GSPECT criterion only applied to GadaCAD2

5) Any contrast agent ± 24 h prior to or after gadobutrol-enhanced CMRI (i.e. ensure minimum interval of 24 h between the SoR and the CMRI). This does not apply to the nuclear tracer needed for GSPECT and for emergency CA. GSPECT criterion only applied to GadaCAD2

6) Contraindication to the cardiac MRI examination (e.g. inability to hold breath; severe arrhythmias preventing gated acquisition; very low cardiac output, severe claustrophobia, defibrillators, or other metallic devices not approved for MRI, e.g. pace makers).

7) History of severe allergic or anaphylactoid reaction to any allergen including drugs and contrast agents according to the investigator’s assessment / judgment.

8) Estimated glomerular filtration rate (eGFR) value <30 mL/min/1.73 m2 derived from a serum / blood creatinine result within 2 weeks prior to gadobutrol injection. Any subject on hemodialysis or peritoneal dialysis is excluded from enrollment. Note: if there are multiple eGFR values, the value obtained prior to and closest to the time of the gadobutrol-enhanced CMRI should be used.

9) Acute renal insufficiency of any intensity.

10) Previous enrollment into this study or any other Bayer-sponsored study using gadobutrol.

11) Coronary artery bypass grafting (CABG).

12) Acute myocardial infarction (< 14 days prior to inclusion), unstable angina / acute coronary syndrome, severe congestive heart failure (New York Heart Association Class IV), decompensated heart failure with ejection fraction <35%.

13) Irregular heart rhythm preventing gating for gadobutrol-enhanced CMRI (e.g. absolute arrhythmia) and/or CTA.

14) Sinus node disease (e.g. SA block) or symptomatic bradycardia, second or third degree atrioventricular (AV) block.

15) Pre-existing obstructive lung disease (e.g. asthma) that precludes the safe administration of the pharmacological stressor according to the approved label.

16) Uncontrolled and severe hypertension (e.g. systolic blood pressure >200 mmHg, diastolic blood pressure >110 mmHg) (warnings in regadenoson and adenosine product information).

17) Baseline hypotension (e.g. systolic blood pressure < 90 mmHg, diastolic blood pressure <50 mmHg) (warnings in regadenoson and adenosine product information).

18) Subject has a close affiliation with the investigational site; e.g. a relative of the investigator, or a dependent person (e.g. employee or student of the investigational site).

**Additional Statistical references for the main paper:**

We calculated the confidence limits with methods described by Blyth and Still. (Blyth CR, Still HA. Binomial confidence intervals. Journal of the American Statistical Association. 1983 Mar 1;78(381):108-16.).

AUC comparisons were performed using the method developed by DeLong; within each trial, AUCs for each reader were compared to each other using pairwise comparisons. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988 Sep 1:837-45.

**Supplementary Table 2.** Study Enrollment Summary for GadaCAD1 and GadaCAD2

|  |  |  |
| --- | --- | --- |
| **GadaCAD1 Enrollment** | **Subjects** | **Reasons Subjects were excluded from study** |
| Initial Enrollment | 456 |  |  |
|  |  | Did not receive Gadobutrol |
|  |  | 6 | Screening failures |
|  |  | 13 | Dropped out of study |
| Safety Analysis Set | 426 |  |  |
|  |  | Excluded for Imaging-related reasons |
|  |  | 5 | CMR – Mandatory images missing/not available |
|  |  | 17 | CMR – Unacceptable image quality |
|  |  | 28 | Coronary angiography/CTA not suitable for standard of reference or not performed |
| Efficacy sample size | 376 |  |  |
|  |  |  |  |
|  |  |  |  |
| **GadaCAD2 Enrollment** | **Subjects** |  | **Reasons Subjects were excluded from study** |
| Initial Enrollment | 504 |  |  |
|  |  | Did not receive Gadobutrol |
|  |  | 17 | Screening failures |
|  |  | 19 | Dropped out of study |
| Safety Analysis Set | 478 |  |  |
|  |  | Excluded for Imaging-related reasons |
|  |  | 10 | Used as training cases for blinded reading |
|  |  | 8 | CMR – Mandatory images missing/not available |
|  |  | 26 | CMR – Unacceptable image quality |
|  |  | 1 | Images not read by blinded readers (clerical error) |
|  |  | 45 | Coronary angiography/CTA not suitable for standard of reference or not performed |
| Efficacy sample size | 388 |  |  |

**Supplementary Table 3.** Determination of the optimal severity coronary artery stenosis (QCA) by ROC analysis at the Clinical Trial Level, and at the level of Combined Results for both studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Data Level** | **Optimal Threshold** | **Sample Size** | **CAD(+)** | **CAD(-)** | **Sensitivity** | **Specificity** | **AUC** | **PPV** | **NPV** | **TP** | **TN** | **FP** | **FN** |
| GadaCAD1&2 | Meta-Analysis 6 readers | ≥67% QCA | 764 | 258 | 506 | 78.9% | 86.8% | 0.855 | 77.5% | 88.5% | 204 | 439 | 58 | 67 |
| GadaCAD1 | Clinical Trial | ≥62% QCA | 376 | 108 | 108 | 79.3% | 91.2% | 0.880 | 78.2% | 91.7% | 86 | 244 | 24 | 22 |
| GadaCAD2 | Clinical Trial | ≥67% QCA | 388 | 150 | 150 | 74.8% | 88.5% | 0.861 | 80.6% | 84.7& | 112 | 211 | 27 | 38 |

|  |  |  |
| --- | --- | --- |
|  | GadaCAD 1(n = 141) | GadaCAD2(n = 150) |
| QCA Stenosis ≥70% | Gadobutrol-enhanced CMRSensitivity | Unenhanced CMRSensitivity | Difference(Lower bound of 95% CI)ap-value | Gadobutrol-enhanced CMRSensitivity | Unenhanced CMRSensitivity | Difference(Lower bound of 95% CI)ap-value |
| Reader 1 | 89.8% | 82.4% | 7.4%(0.5%)p=0.0455 | 77.1% | 56.2 | 21.0%(12.1%)p<0.00005 |
| Reader 2 | 79.6% | 45.4% | 34.3%(25.2%)p<0.0001 | 71.4% | 35.2% | 36.2%(26.3%)p<0.0001 |
| Reader 3 | 78.7% | 48.1% | 30.6%(25.2%)p<0.0001 | 76.2% | 35.2% | 41.0%(31.8%)p<0.0001 |
| QCA Stenosis ≥50% | Gadobutrol-enhanced CMRSensitivity | Unenhanced CMRSensitivity | Difference(Lower bound of 95% CI)ap-value | Gadobutrol-enhanced CMRSensitivity | Unenhanced CMRSensitivity | Difference(Lower bound of 95% CI)ap-value |
| Reader 1 | 77.6% | 77.3% | -0.7%(-0.85%)p=0.8694 | 64.7% | 48.0% | 16.7%(9.3%)p=0.00009 |
| Reader 2 | 65.2% | 36.2% | 29.1%21.7%p<0.0001 | 56.0% | 30.0% | 26.0%(18.2%)p<0.0001 |
| Reader 3 | 64.5% | 40.4% | 24.1%(16.6%)p<0.0001 | 61.3% | 29.3% | 32.0%(24.5%)P<0.0001 |

**Supplementary Table 4.** Comparison of sensitivity of gadobutrol-enhanced first-pass perfusion/LGE CMR versus unenhanced wall motion CMR versus a standard of reference of a stenosis ≥70% and ≥50% by QCA using a per subject analysis.

P-value based on McNemar test at 1-sided alpha-level of 2.5% for blinded readers 1, 2, and 3. a One-sided 95% CI for blinded readers 1, 2, and 3.

**Supplementary Table 4. Adverse Events Reported in GadaCAD1 and GadaCAD2**