Aligning Coronary Anatomy and Myocardial Perfusion Territories: An Algorithm for the CORE320 Multicenter Study

Cerci et al: Aligning Coronary and Myocardial Anatomy

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Abstract
Background—Appropriate clinical decisions concerning diagnosis and treatment of coronary artery disease rely on correct integration of coronary anatomy and myocardial perfusion data. The purpose of this manuscript is to introduce a new left ventricular segmentation model for improved alignment of coronary arterial segments and myocardial perfusion territories, designed for the CORE320 study.

Methods and Results—CORE320 is a prospective, multicenter study with a primary objective to evaluate the diagnostic accuracy of 320-row detector computed tomography to detect coronary artery luminal stenosis and corresponding myocardial perfusion deficits in patients with suspected CAD compared with the gold standard of conventional coronary angiography and single photon emission computed tomography myocardial perfusion imaging. We describe a 19 coronary segment and 13 myocardial territory alignment model, its application in both standard and CT image datasets and the adjudication process of the initial cohort of patients recruited for the CORE320 study. Adjudication committees reviewed the images of the first 101 gold standard and 107 CT datasets. Based on the presented model and rules, all cases for adjudication were correctly identified. During image review, 6 (5.9%) gold standard and 9 (8.4%) CT datasets needed further realignment not triggered by the algorithm.

Conclusions—We present a vascular territory distribution model developed for the CORE320 multicenter study which accounts for variability in coronary anatomy and potential myocardial perfusion territory overlap.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00934037.

Key Words: cardiac computed tomography, myocardial CT perfusion imaging, coronary atherosclerosis, single photon emission computed tomography
Appropriate clinical decisions concerning diagnosis and treatment of coronary artery disease (CAD) rely on the correct integration of coronary anatomy and myocardial perfusion data\(^1\). Revascularization of coronary stenosis is only justified if it relieves angina complaints and improves patient outcome, which depends on the extent and severity of inducible myocardial ischemia related to the lesion\(^2\)\(^{-5} \).

In clinical practice, conventional coronary angiography (CCA) and single-photon emission tomography myocardial perfusion imaging (SPECT) are the standard imaging methods for detection and quantification of coronary artery stenosis and myocardial perfusion defects. In order to define a treatment strategy, physicians must mentally create a correlation map, merging the anatomical data from CCA, a projection imaging method, with the functional data from SPECT, a mix of projection and tomographic imaging methods, overcoming image foreshortening, differences on image acquisition times, and differences in spatial and temporal resolution between the methods.

Myocardial perfusion defects have also been assigned to vascular territories using left ventricular segmentation models \(^6\)\(^{-8} \). This approach is usually applied in research settings, where standardization between different imaging methods is attempted. However, standard assumptions about the vascular territory distribution in myocardial perfusion analysis are frequently inaccurate due to morphologic variability in the coronary tree \(^9\)\(^{-12} \). Nonetheless, cardiac computed tomography (CT), a rapidly evolving image modality, has the potential advantage of acquiring coronary angiography and myocardial perfusion data at the same time \(^13\)\(^{-16} \), displaying the coronaries and the underlying myocardium in the same image where the anatomical relationship can be easily accessed.
The purpose of this manuscript is to introduce a novel vascular territory distribution model that accounts for coronary anatomy variability, and to describe its application during the adjudication selection algorithm and process of the initial cohort of patients recruited for the CORE320 multicenter study.

Methods

CORE320 study design and patient population

CORE320 is a prospective, multicenter study designed to test the diagnostic accuracy of 320 detector row computed tomography (CT) for identifying physiologic significant CAD. The primary diagnostic parameters are the areas under the receiver operating characteristic curve, sensitivity and specificity of combined multi-detector computed tomography coronary angiography (CTA) and myocardial CT perfusion imaging (CTP) for identifying coronary artery stenosis greater than 50% with a corresponding myocardial perfusion defects in patients with suspected CAD compared with conventional coronary angiography (CCA) and single-photon emission tomography myocardial perfusion imaging (SPECT). Since the primary aim of the CORE 320 study is to detect obstructive atherosclerosis causing corresponding myocardial perfusion deficits, abnormal myocardial territories require anatomic co-registration with the culprit vessel.

The study protocol and informed consent were approved by central and local institutional review boards (IRB). Adverse events were tracked, reported, and reviewed by an independent Data Safety and Monitoring Board.
Vascular territory distribution model

Coronary arterial segments were defined using a 19-coronary segment model as previously described (Figure 1)\textsuperscript{18, 19}. Segments were grouped in six coronary vessels: left main coronary artery (LM), proximal left anterior descending artery (proximal LAD), mid-distal left anterior descending artery (mid-distal LAD), right coronary artery (RCA), left circumflex coronary artery (LCX) and ramus (Table 1). Myocardial territories were defined using a 13-territory model as previously described (Figure 2)\textsuperscript{20, 21}. The 13 myocardial territories were aligned to each coronary vessel based on anatomical variance data\textsuperscript{8-12, 22-25} and further classified as: Primary vascular territories, when blood flow is usually supplied by the coronary vessel in the most common right dominant anatomical coronary pattern; Secondary vascular territories, when blood flow may be supplied by the coronary vessel in some normal anatomic variations; and Tertiary vascular territories, when blood flow is usually not supplied by the coronary vessel. Since each coronary vessel–myocardial vascular territory association is unique, six vessel–territory maps were generated and are displayed in Figure 3. Each map was designed to define if a myocardial perfusion defect can be anatomically related to a coronary stenosis in a specific coronary vessel. As an example, the proximal LAD vessel-territory map is used when a proximal LAD has a 50% or greater stenosis by angiography. A myocardial perfusion defect in a primary vascular territory (colored red) is considered to be aligned and matched with the LAD lesion; whereas a defect in a secondary vascular territory (colored yellow) is considered to be a possible match with the lesion in some predefined anatomical variations which need further confirmation during the adjudication process. Perfusion defects in a tertiary vascular territory (colored blue) are not considered to be aligned to the proximal LAD lesion and are considered a mismatch.
Image acquisition and data analysis

A detailed description of the CORE320 image acquisition and interpretation methods have been published elsewhere. In summary, all subjects were submitted to SPECT rest/stress testing, conventional coronary angiography, and computed tomography using a combined CTA and rest/stress CTP protocol. Therefore, two sets of anatomic angiography and rest/stress myocardial perfusion imaging data were available. All imaging data were forwarded to individual core laboratories after de-identification and were analyzed by independent blinded investigators. Coronary arterial segments were defined using a 19-coronary segment model and myocardial territories were defined using a 13-territory model. All coronary arterial segments of at least 1.5 mm in diameter were analyzed by CCA and CTA for significant coronary artery stenoses defined as ≥50% obstructive lesions. Myocardial territories were analyzed by SPECT and CTP for rest and stress myocardial perfusion abnormalities with severity and reversibility scored. All data were stored directly into a database designed specifically for the CORE320 study. A detailed description of the data analysis algorithm can be found online (Appendix). The database aligned coronary arterial stenoses with myocardial vascular territories, applying the vascular territory distribution model.

Adjudication selection algorithm

An adjudication selection algorithm was created to detect studies with potential misalignment between coronary anatomy and myocardial territories that could be automatically identified by the database and corrected during the adjudication process (Figure 4). The same algorithm was used separately for both CCA/SPECT and CTA/CTP.
**Algorithm entry criteria:** The entry criterion for the algorithm was the presence of both: a) at least one coronary arterial lesion of $\geq 50\%$ diameter stenosis and b) at least one myocardial perfusion defect.

In addition, the presence of coronary stents in conjunction with myocardial perfusion defects was an algorithm entry criterion, as lesions within stented segments cannot be reliably excluded with current CT technology in subjects with different stent types and sizes$^{27,28}$. Finally, the presence of any special coronary conditions which include: anomalous coronary artery origin and epicardial course, coronary fistulæ, greater than 50% lesions within the first 5 mm after the left main bifurcation when a visible ramus branch is present, greater than 50% ramus lesions, and greater than 50% left main lesions; in conjunction with myocardial perfusion defects also met criteria to enter the algorithm since they may cause ischemia and be related to less predictable myocardial alignment.

**Criteria for triggering adjudication:** The adjudication process was triggered in two scenarios:

1) **Coronary vessel-myocardial vascular territory alignment in special coronary conditions:** Any special coronary conditions described above and a perfusion defect in a myocardial territory triggered the adjudication process.

Some anomalous coronary anatomies like the origin of the LAD from the right aortic sinus of valsalva can cause myocardial ischemia. These anomalous coronaries have a highly variable course, justifying realignment with the myocardium.

The coronary angiography segmentation model defines a ramus branch as any vessel within the first 5 mm after the left main bifurcation that follows a diagonal or obtuse marginal course. In subjects where a ramus branch is present, it is possible that an upstream LAD or LCX ostial lesion causes ischemia in a myocardial territory supplied by the ramus, with a consequent
misalignment during analysis since the ramus itself may not have any obstructive lesion that justifies the perfusion defect (Figure 5). These cases were also submitted to adjudication for possible realignment. In addition, since the myocardial territories supplied by the ramus branch can be highly variable, overlapping the LAD and LCX territories, adjudication was mandatory in all studies with a greater than 50% lesion in this branch.

Finally, left main lesions can be responsible for perfusion defects in almost all myocardial perfusion territories depending on anatomical coronary dominance. As left main lesions are upstream in coronary circulation, they may physiologically act as LAD, LCX, and ramus lesions which may need special alignment.

2) Possible coronary vessel-myocardial vascular territory misalignment due to common anatomic variants: Studies were submitted to adjudication if there was a greater than 50% lesion or stent in any coronary vessel and a perfusion defect in at least one related secondary myocardial vascular territory, without a perfusion defect in any primary vascular territory (Figure 4). Since secondary vascular territories were defined as myocardial territories to which blood flow may be supplied by the coronary vessel in some normal anatomy variations, the presence of such variations needed to be confirmed during the adjudication process.

**Adjudication process**

The adjudication process was created to improve alignment of coronary anatomy and myocardial territories in both the reference standard and the test diagnostic methods. Both CCA/SPECT and CTA/CTP followed identical adjudication selection algorithm and process. Only the associations between coronary arterial stenoses and vascular territories were changed during the adjudication process; no changes of the assessment of severity of coronary arterial...
stenoses or perfusion defects were made. Alignment changes during the adjudication process followed pre-specified rules (Table 2) for each coronary vessel – myocardial vascular territory map, based on the same anatomical data used to create the model. The reference standard adjudication committee was comprised of one member from the CCA and SPECT core laboratories, as well as a third independent member. The CT adjudication committee was comprised of one member from the CTA and CTP laboratories, and a third independent member. A final decision was obtained by consensus.

In summary, the adjudication committees defined if blood flow to a specific myocardial vascular territory was supplied by a corresponding coronary vessel under pre-specified anatomical variances described in Table 2. The adjudication committee first reviewed the angiogram to identify the greater than 50% lesions, stents, or special coronary conditions and checked the overall alignment of the coronary tree with the myocardium. Secondly the myocardium perfusion images were reviewed, and lastly realignment was recorded when necessary.

Results

In order to test the applicability of the model and the accuracy of the adjudication selection algorithm, the adjudication committees reviewed all the images of the first 101 gold standard and 107 CT datasets. Based on the above rules, the database correctly identified all cases for adjudication, but during image review, 6 (5.9%) gold standard and 9 (8.4%) CT datasets needed further realignment that was not triggered by the database. In all such cases the reason for realignment was that even when a coronary stenosis was already correctly aligned or
matched to an ischemic primary myocardial territory, some ischemic secondary myocardial territories related to the same stenosis were present, but assigned to another vessel and needed to be realigned to correctly reflect the ischemic burden related to the lesion.

**Case reports**

Both subjects described in this manuscript were recruited during the qualification and accreditation period of the CORE320 study. Subjects provided signed informed consent and followed the IRB approved CORE320 protocol, but will not be included in the main CORE320 cohort. Studies were acquired, analyzed, and submitted to the adjudication selection algorithm and process for testing purposes.

*Reference standard case report (Figure 5):* In this study, an obstructive ostial LAD lesion prior to the origin of a large ramus branch was detected by CCA. SPECT revealed reversible myocardial perfusion defects in the distal anterior, distal anterolateral, and distal inferolateral territories. This study was triggered for adjudication because of the presence of a special coronary condition (greater than 50% lesion within the first 5 mm after the left main bifurcation when a visible ramus branch is present) associated with myocardial perfusion defects. During the adjudication process, the reference standard committee determined that the blood flow to the distal anterolateral and distal inferolateral territories was supplied by the ramus and its branches. Since the LAD ostial lesion precedes the ramus origin, the distal anterolateral and inferolateral territories were realigned to the LAD.

*Computed tomography case report (Figure 6):* In this study, a proximal RCA occlusion and myocardial perfusion defects in the distal anterolateral and inferolateral territories were detected by CT. Since the inferolateral territory is considered a secondary myocardial territory to the
RCA, the study was triggered for adjudication because of a possible misalignment due to a common anatomical coronary variant that needed to be confirmed. During the adjudication process, the CT committee reviewed the images and determined that the blood flow to the inferolateral territory was supplied by a right posterolateral branch in place of an obtuse marginal or distal LCX, following the pre-specified rules presented in Table 2. The distal inferolateral territory was realigned to the RCA.

Discussion

The American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging recommends a 17-territory model of the left ventricle as an optimal approach for the visual interpretation of regional left ventricular abnormalities by multiple cardiac imaging techniques8. In spite of potential anatomic variability, these territories were assigned to one of the three major coronary arteries. Individual myocardial territories were assigned to a coronary artery based on available data with little correlation with delineated myocardial segmentation22. We employed a 13-myocardial territory model, which reduces granular differences between imaging modalities with different spatial resolutions by using larger myocardial territories that can be more easily aligned to coronary vessels, combined with some flexibility on anatomical variations.

The coronary vascular tree is highly variable and coronary dominance is the most common classification method. Coronary circulation is considered right dominant when the posterior descending artery (PDA) and posterolateral branches originate from the RCA and left dominant when they both originate from the LCX. A balanced coronary circulation is defined when the PDA originates from the RCA and all posterolateral branches from the LCX. The
typical right dominant circulation is found in 71% of patients\textsuperscript{23, 24}. In this pattern the RCA supplies approximately 16% and the left coronary artery approximately 84% of the flow to the left ventricle\textsuperscript{25}. A left dominant circulation pattern is present in 12% of cases where the left coronary artery supplies 100% of the flow to the left ventricle, and usually the LCX gives rise to the PDA. The remaining 17% of hearts have balanced circulation.

Numerous other normal variations exist. A long LAD that wraps around the left ventricular apex can supply a variable portion of the inferior wall. The LCX usually supplies a variable extent of the lateral wall, depending on the number and size of the obtuse marginal branches, number and size of diagonal branches from the LAD, presence of posterolateral branches from the RCA and the presence of a ramus branch. Finally, the RCA can supply the left ventricular apex in cases where a long PDA branch and a short LAD are present.

Studies from our institution and others have demonstrated the need to account for variation in coronary anatomy and perfused territories\textsuperscript{10-12, 16}. Pereztol-Valdes et al. studied the correspondence between a 17-territory model and coronary anatomy by injecting \textsuperscript{99m}Tc-labelled compound (tetrosfosmin and methoxyisobutyl isonitrile) during balloon inflation in 50 patients with single vessel disease scheduled for PCI. The subsequent comparison of myocardial perfusion defects on SPECT images with the standard segmental assignment showed that only 9 of the 17 territories corresponded to a single coronary artery (8 to LAD and 1 to LCX) in all patients\textsuperscript{11}. Inferoseptal territories could be attributed to LAD or RCA, inferior and inferolateral territories to RCA or LCX, and anterolateral territories to LAD or LCX. Correspondence was also studied by Ortiz-Perez et al., comparing delayed territorial gadolinium hyperenhancement on MRI with invasive angiography in 93 patients after acute myocardial infarction treated with primary PCI\textsuperscript{10}. They showed discordance between hyperenhancing territories and the empirically
assigned coronary distribution according to the AHA model in 23.4% of the territories. Using this methodology only 4 segments were completely specific for LAD occlusion and none was specific for RCA or LCX occlusion. In a per-patient analysis, perfect agreement was found in only 33% of the patients. Finally, Javadi et al. studied 71 patients who underwent $^{82}$Rb perfusion PET/CT, including CT angiography on a 64-slice PET/CT scanner for CAD work-up. Coronary arteries were assigned to myocardial territories using fusion images, and were compared with the standard AHA model. In a per-patient analysis, 72% demonstrated differences from the standard assignment in at least 1 myocardial territory. From all the reassigned territories, 39% were standard RCA territories reassigned to the LCX territory, 30% were standard LCX territories reassigned to the LAD territory and 23% were standard LAD territories reassigned to either LCX or RCA territories. A common finding of these studies was that the inferior wall demonstrated the largest variability of vascular supply, with alignment within the RCA, LAD, and LCX usually a result of the anatomical coronary dominance. In several patients, the distal inferior wall of the heart was supplied by a large-caliber LAD instead of the distal branches of the RCA. There was also variability in the vessel assignment of the anterior and lateral territories, mostly related to the presence and size of diagonal, obtuse marginal and ramus branches.

Based on the above mentioned data and the conclusion that standard assumptions about vascular territory distribution in myocardial perfusion analysis are frequently inaccurate because of morphologic variability of the coronary tree, our group designed and proposed a new alignment model for the CORE320 study. Some of the rules presented in this manuscript were applied during the George et al. analysis, which reported that CTP imaging, when combined with CTA, can accurately predict atherosclerosis causing perfusion abnormalities in comparison with
combined CCA/ SPECT\textsuperscript{16}. The main strength of the model is to introduce the normal variability of the coronary anatomy in a standardized fashion, using a specified algorithm.

An important limitation is that the model has not yet been tested in a large number of subjects and some anatomical variations may not be included. Since the model was based in well described anatomical and physiological data, we anticipate that these unusual variations will not be frequent. Also, although a pre-defined set of rules were followed during the adjudication process; their applicability may be subjective and may differ by the adjudicators, even if a consensus is reached.

Conclusion

We present a vascular territory distribution model that aligns myocardial perfusion territories and coronary arteries developed for the CORE320 multicentre study which accounts for variability in coronary anatomy and potential myocardial perfusion territory overlap.

Sources of Funding

This study was supported by Toshiba Medical Systems.

Disclosures

Drs. Lima, George, Di Carli and Miller report receiving grant support from Toshiba Medical Systems.
References


8. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ,


Table 1. Nineteen coronary segments grouped in six vessels

<table>
<thead>
<tr>
<th>Coronary Vessel</th>
<th>Coronary Segments (Figure 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Main Artery</td>
<td>L1 - left main</td>
</tr>
<tr>
<td></td>
<td>L2 - proximal LAD</td>
</tr>
<tr>
<td></td>
<td>L5 - first diagonal branch</td>
</tr>
<tr>
<td></td>
<td>L3 - mid-LAD</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td>L4 - distal LAD</td>
</tr>
<tr>
<td></td>
<td>L6 - second diagonal branch</td>
</tr>
<tr>
<td>Mid-distal LAD</td>
<td>C1 - proximal LCX</td>
</tr>
<tr>
<td></td>
<td>C2 - mid-LCX</td>
</tr>
<tr>
<td></td>
<td>C3 - first obtuse marginal</td>
</tr>
<tr>
<td>Left Circumflex</td>
<td>C4 - second obtuse marginal</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>C5 - third obtuse marginal</td>
</tr>
<tr>
<td></td>
<td>C6 - grouped distal LCX and left posterolateral</td>
</tr>
<tr>
<td></td>
<td>C7 - left posterior descending</td>
</tr>
<tr>
<td>Ramus</td>
<td>C8 - ramus branch</td>
</tr>
</tbody>
</table>
R1 - proximal RCA
R2 - mid-RCA
R3 - distal RCA
R4 - right posterior descending
R5 - grouped right posterolateral

Right Coronary Artery

Abbreviation: LAD, Left Anterior Descending Artery; LCX, Left Circumflex Coronary Artery; RCA, Right Coronary Artery
Table 2. Adjudication realignment pre-specified rules by coronary anatomy variant

<table>
<thead>
<tr>
<th>Coronary Vessel</th>
<th>Anatomical Variant</th>
<th>Secondary Myocardial Vascular Territories where Realignment is Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Main</td>
<td>Left coronary dominance</td>
<td>basal inferior&lt;br&gt;basal inferoseptal&lt;br&gt;distal inferior&lt;br&gt;distal inferoseptal</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td>Presence of a large first diagonal branch that supplies the anterolateral and distal inferolateral wall in place of an obtuse marginal or ramus branch</td>
<td>basal anterolateral&lt;br&gt;distal anterolateral&lt;br&gt;distal inferolateral</td>
</tr>
<tr>
<td></td>
<td>LAD continues beyond the apex, through the inferior wall, towards the crux cordis</td>
<td>basal inferior&lt;br&gt;basal inferoseptal&lt;br&gt;distal inferior&lt;br&gt;distal inferoseptal</td>
</tr>
<tr>
<td><strong>LAD</strong></td>
<td><strong>Basal Anterior</strong></td>
<td></td>
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<tr>
<td>--------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Gives rise to a very proximal septal or diagonal branch</td>
<td>Basal Anteroseptal</td>
<td></td>
</tr>
<tr>
<td>Presence of a large second diagonal branch that supplies the anterolateral and distal inferolateral wall in place of an obtuse marginal or ramus branch</td>
<td>Basal Anterolateral Distal Inferolateral</td>
<td></td>
</tr>
<tr>
<td>Mid-distal LAD</td>
<td>Basal Inferior Distal Inferoseptal</td>
<td></td>
</tr>
<tr>
<td>Continues beyond the apex, through the inferior wall, towards the crux cordis</td>
<td>Distal Inferolateral</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Left Circumflex Coronary Artery</strong></th>
<th><strong>Basal Inferoseptal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Circumflex Coronal Artery</td>
<td>Left coronary dominance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ramus</strong></th>
<th><strong>Basal Inferolateral</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Extends to the inferolateral wall in place of a posterolateral branch</td>
<td>Distal Inferolateral</td>
</tr>
</tbody>
</table>
Large group of right posterolateral branches supplies the inferolateral wall in place of an obtuse marginal or distal left circumflex circumflex Right coronary artery reaches the apex. 

Abbreviation: LAD, Left Anterior Descending Artery.
Figure Legends

Figure 1. Coronary artery segmentation model with 19 segments: R1=proximal right coronary artery (RCA), R2=mid-RCA, R3=distal RCA, R4=right posterior descending, R5=grouped right posterolateral (RPL): first RPL, second RPL, and third RPL (segments 5, 6, 7, 8 of the CASS model), L1 = left main, L2 = proximal left anterior descending (LAD), L3=mid-LAD, L4=distal LAD, L5=first diagonal branch, L6= second diagonal branch, C1=proximal left circumflex coronary artery (LCX), C2=mid-LCX, C3=first obtuse marginal, C4=second obtuse marginal, C5=third obtuse marginal, C6=grouped: distal LCX (segments 19.1, 23, 24, 25, 26 of the CASS model), first left posterolateral (LPL), second LPL, and third LPL, C7=left posterior descending, C8= Ramus branch. Adapted from Miller JM, et al. Euro.Radiol 2009;19:816-821.

Figure 2. Myocardial territory segmentation model with 13 segments used for the computed tomography and SPECT perfusion analysis. The model consists of six basal segments: 1 = anterior, 2 = anteroseptal, 3= inferoseptal, 4 = inferior, 5 = inferolateral, 6 = anterolateral; six distal segments: 7 = anterior, 8 = anteroseptal, 9= inferoseptal, 10 = inferior, 11 = inferolateral, 12 = anterolateral; and one apical segment (13).

Figure 3. Coronary vessel – myocardial vascular territory maps. In red, primary territories = myocardial territories in which blood flow is supplied by the coronary vessel in the most common right dominant anatomical coronary pattern. In yellow, secondary territories = myocardial territories for which blood flow may be supplied by the coronary vessel under some normal anatomical variations that need confirmation. In blue, tertiary territories = myocardial territories where blood flow is usually not supplied by the coronary vessel.
**Figure 4.** Adjudication selection algorithm of the CORE320 Multi-centre study.

**Figure 5.** Example of an obstructive ostial left anterior descendent (LAD) lesion (white arrow) prior to the origin of a large ramus branch (white arrow heads) associated with reversible myocardial perfusion defects in the distal anterior (yellow arrows) and distal inferolateral (yellow arrow heads) territories. A: conventional coronary angiography (right anterior oblique caudal projection). B: Rest and stress short axis SPECT images.

**Figure 6.** Example of a study where an occlusive mid right coronary artery (RCA) atherosclerotic lesion (arrow head) and myocardial perfusion defects in the inferolateral territory (arrows) are present. Since the inferolateral territory is considered a secondary myocardial territory to the RCA, the study would trigger adjudication. A: Computed tomography (CT) maximum intensity projection in an oblique plane visualizing the RCA lesion. B: CT multi-planar reconstruction in a short axis view visualizing the inferolateral wall perfusion defect.
Core 320 Adjudication Selection Algorithm

Entry criteria

Presence of Both:
- At least one ≥ 50% stenosis or stent in any coronary segment; or special coronary condition*
- At least one myocardial perfusion defect

*Special coronary condition
- Left Main ≥ 50% stenosis
- Rannus ≥ 50% stenosis
- ≥ 50% stenosis within the first 5mm after the Left Main bifurcation when a visible Rannus branch is present.
- Anomalous coronary artery origin and epicardial course
- Coronary fistulae
- Presence of stent

No Adjudication

≥ 50% coronary stenosis

AND

Perfusion defect in any PRIMARY myocardial vascular territory

No Adjudication

≥ 50% coronary stenosis

AND

Perfusion defect in a SECONDARY myocardial vascular territory

Adjudication

≥ 50% coronary stenosis

AND

Perfusion defect in only a TERTIARY myocardial vascular territory

No Adjudication

†Based on the coronary vessel-myocardial vascular territory maps (Figure 3).
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SUPPLEMENTAL MATERIAL

CORE320 Algorithm for primary analysis

Tested method – Computed Tomography

Primary End Points

1: CT ability to identify a $\geq 50\%$ coronary artery stenosis and a corresponding myocardial perfusion deficit when compared to the gold standard ($\geq 50\%$ coronary artery stenosis by Cath (QCA) and a corresponding myocardial perfusion deficit by SPECT-MPI) at a patient level.

2: CT ability to identify a $\geq50\%$ coronary artery stenosis and a corresponding myocardial perfusion deficit when compared to the presence of $\geq50\%$ coronary artery stenosis by Cath (QCA) alone as the gold standard, at a patient level

The primary diagnostic parameter will be the area under the ROC curve of combined CTA and CTP for identifying the combination of a coronary artery stenosis $\geq 50\%$ and a corresponding myocardial perfusion defect or a coronary artery stenosis $\geq 50\%$ alone by the gold standard.

In order to build the ROC curve we will need a dichotomized gold standard definition of patient disease (positive or negative, already discussed and defined) and a continuous measurement of disease by the tested method (CT). Differently from the gold standard, CT analysis will be the same for both primary end points. The CT continuous patient level measurement of disease will be derived from a combination of CTA and CTP related values as described below.

In addition to the ROC analysis, sensitivity and specificity analysis will be performed. The same gold standard dichotomized definition of patient disease (positive or negative) will be used by CT for this analysis. Two threshold definitions of a positive myocardial territory by CT: a) SSS $\geq 1$ and b) SSS $\geq 2$ will be used. This is what defines a myocardial territory as being positive as outlined in the definitions below.
1 - Dichotomized vessel-territory level definitions of disease by CT:

- ≥50% coronary stenosis by CTA AND aligned/matched myocardial perfusion defect on CTP = **Positive** (1).
- All remaining combination of results possibilities = **Negative** (0).

**Step 1: Remove ineligible segments by CTA**

1. Drop all segments with a reference diameter of <1.0 mm
2. Drop all segments in which phase 1 (visual score of 7) was read as “too small to evaluate”

**Step 2: Compress coronary segments into vessels (exclude ineligible QCA segments from CT compression)**

1. RCA – coronary segments 1, 2, 3, 4, and 5.
2. LM – coronary segment 11.
3. Proximal LAD – coronary segments 12 and 15.
4. Mid-distal LAD – coronary segments 13, 14, and 16.
5. LCX – coronary segments 18, 19, 20, 21, 22, 23, and 27.

*Note: Only segments with corresponding values defined by QCA will be compressed (segments with cath phase 1 score of 0 or 7 or which have a segment reference diameter < 1.5 mm are not compressed).

**Step 2 B: Compress coronary segments into vessels**

1. RCA – coronary segments 1, 2, 3, 4, and 5
2. LM – coronary segment 11
3. Proximal LAD – coronary segments 12 and 15
4. Mid-distal LAD – coronary segments 13, 14, and 16
5. LCX – coronary segments 18, 19, 20, 21, 22, 23, and 27
6. Ramus – coronary segment 28

*Note: Compress all CTA defined segments into vessels. No cross reference of QCA defined segments is needed.

**Step 3: Compress myocardial territories into vessel-territory myocardial regions**

1. RCA – myocardial segments 3, 4, 9 and 10
2. LM – myocardial segments 1, 2, 5, 6, 7, 8, 11, 12 and 13
3. Proximal LAD – myocardial segments 1, 2, 7, 8 and 13
4. Mid-distal LAD – myocardial segments 7, 8 and 13
5. LCX – myocardial segments 5, 6, 11 and 12
6. Ramus – myocardial segments 1, 6, 7 and 12
Step 4: Align conventional coronary artery vessels with CTP perfusion myocardial segments to create a final vessel-territory result

1. Adjudication process
2. After the adjudication process, there will be 2 possible vessel-territory results:
   a. Positive: ≥50% stenosis (CTA) + downstream myocardial perfusion defect (CTP).
   b. Negative
      i. ≥50% stenosis (CTA) + unrelated myocardial perfusion defect (CTP).
      ii. ≥50% stenosis (CTA) + no myocardial perfusion defect (CTP).
      iii. <50% stenosis (CTA) + downstream myocardial perfusion defect (CTP).
      iv. <50% stenosis (CTA) + unrelated myocardial perfusion defect (CTP).
      v. <50% stenosis (CTA) + no myocardial perfusion defect (CTP).

In addition, issues of coronary segment and myocardial segment uninterpretability and treatment of stents are outlined below.

2 - Continuous vessel-territory level measurement of disease by CT

Step 5: Convert all per-myocardial segment stress scores coded 4 to a 3. Both scores represent severe perfusion deficits.

Step 6: Generate matching vessels and territories according to adjudication rules and results.
   1. For each vessel, select the highest stenosis ≥50% to represent the vessel combined with the vessel-territory SS.

Step 7: Compress the 6 vessels-territories into 3 vessels-territories: LAD, LCX, and RCA:
   i. Group Proximal LAD and Mid-distal LAD as LAD.
   ii. Maintain RCA as RCA.
   iii. Group Ramus with LCX.
   iv. Account a >50% LM lesion as a LAD and LCX lesion (as already incorporated on the adjudication process). The left main percent stenosis value should be imputed to the proximal LAD and proximal LCX.

Step 8: Datasets for Sensitivity and Specificity Analysis- Per-patient analysis
   1. Diagnostic accuracy will be determined using two thresholds that define whether CTA/CTP is positive or negative.
      a. CTA/CTP will be considered to be positive in the per-patient analysis when there is a matched ≥50% stenosis and corresponding perfusion with a SSS ≥1.
b. CTA/CTP will be considered to be positive in the per-patient analysis when there is a matched ≥50% stenosis and corresponding perfusion with a SSS ≥2.

c. CTA/CTP will be considered to be negative for all other scenarios- Please refer to Step 5.2.b.

3. Selection of the continuous patient level measurement of disease by CT

Step 9: For the ROC analysis, we will select the vessel and territory that represents the patient. For the ROC analysis, there will be two datasets. This is due to the need to impute values based on the two thresholds in Step 8.

1. Select the vessel-territory with the highest stenosis ≥50% and its corresponding SSS. This vessel-territory will represent the patient. Imputed values will depend on CTP being abnormal using a threshold SSS ≥1 and SSS ≥2.

2. Select the percent stenosis that will represent the patient from the vessel-territory selected in 1.
   a. In the setting of a single lesion ≥50% in a vessel, that lesion and its SSS will represent the patient.
   b. In the setting of multiple lesions in a vessel, the ≥50% lesion with the highest SSS will be used to represent the patient.
   c. In the setting of multiple lesions in a vessel with the same % stenosis ≥50%, select the one with the larger SSS.
   d. If there are only negative vessel-territories, select the one with the larger SSS.
   e. If there are only negative vessel-territories, all with a SSS of 0 (zero), select the one with the highest % stenosis

Step 10: Select the Leaman Location Score for each arterial segment.

1. If a patient has a co-dominant system:
   a. Assign left dominance if there is a LPDA (coronary segment 27)
   b. Assign right dominance if there is a RPDA (coronary segment 4)

2. Assign each arterial segment a base value according to the chart below. This base value is different for a right or left dominant circulation.

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<tr>
<th>Segment</th>
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Step 11: Generate a continuous CT measurement of disease, from a logistic regression model based on the vessel-territory pair of values/variables.

Model: Outcome (Presence of disease by the gold standard (Positive or negative)) = B0 + CTA value/variable + CTP value/variable + Leaman Location Score.

The CT continuous measurement derived from the model will reflect the probability of the combination of CTA and CTP variables to detect a greater than 50% stenosis by the gold standard.

Special scenarios and considerations:

Absence of a lesion with a QCA value in a Vessel

Impute a % stenosis value for non-quantified phase 2 segments based on the phase 1 (visual score) value

1. For a segment with a phase 1 score of 1, a stenosis value of 0% (zero) will be imputed.
2. For a segment with a phase 1 score of 2, a stenosis value of 15% will be imputed.

Presence of non-interpretable CT studies

1. If either the whole CTA or CTP are considered non-interpretable studies, the patient will be dropped from the primary analysis

Presence of STENT by CTA

Stents will be considered as possible lesions for analysis purposes as follows:

1. CTA segment reading process:
a. CTA reader defines if there is a STENT present in each segment.

b. A qualitative assessment is made: no intrastent reestenosis (ISR), < 50% focal ISR, > 50% focal ISR, 100% ISR, diffuse < 50% and unable to interpret.

c. If there is a visual read of more than 30% ISR, a quantitative measurement (CTA) is made and recorded as for all other segments.

d. In cases where there is two lesions in the same segment, one inside and another outside the STENT (already accounting for the 5mm from the STENT border lesions that are also considered ISR), the most occlusive one will have a phase 2 measurement for that segment and a comment will be added that confirms if that lesion measured was inside or outside the STENT.

2. Compress coronary segments into vessels

   a. If there is any segment with ≥ 50% stenosis by CTA within the same vessel where the stented segment was identified, the vessel will be considered as having a ≥ 50% stenosis by CTA.

   b. If there is no segment with ≥ 50% stenosis by CTA within the same vessel where the stented segment was identified, the vessel will be considered as having a possible ≥ 50% stenosis and the final vessel result will be defined by the CTP result.

3. Adjudication process

4. Defining dichotomized (positive and negative) vessel results for primary analysis

   a. CTA intrastent quantitative measurements will NOT be used for primary analysis as follows.

If a STENT is present, there are 2 different scenarios with 2 possible vessel final results, based primarily on the CTP result:

   a. Stented segment with a perfusion defect in a myocardial territory related to that vessel - Positive vessel-territory.

   b. Stented segment without a perfusion defect in a myocardial territory related to that vessel or no perfusion defect at all – Negative vessel-territory.

2. Impute a % stenosis into a stented segment based on the CTP result

   a. For a stented segment with a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 60% will be imputed for that segment.

   b. For a stented segment without a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 30% will be imputed for that segment.

Presence of non- interpretable segment by CTA
Non-interpretable segments will be considered as **possible lesions** for analysis purposes in a similar way as stented segments:

1. **CTA segment reading process:**
   a. CTA reader defines if a segment is not-interpretable.

2. **Compress coronary segments into vessels**
   a. If there is any segment with \( \geq 50\% \) stenosis by CTA within the same vessel where the non-interpretable segment was identified, the vessel will be considered as having a \( \geq 50\% \) stenosis by CTA.
   b. If there is no segment with \( \geq 50\% \) stenosis by CTA within the same vessel where the non-interpretable segment was identified, the vessel will be considered as having a possible \( \geq 50\% \) stenosis and the final vessel result will be defined by the CTP result.

3. **Adjudication process**

4. **Defining dichotomized (positive and negative) vessel-territory results for primary analysis**

   If a non-interpretable segment is present there are **2 possible vessel-territory final results**, based primarily on the CTP result:
   a. Non-interpretable segment with a perfusion defect in a myocardial segment related to that vessel - **Positive vessel-territory**.
   b. Non-interpretable segment without a perfusion defect in a myocardial segment related to that vessel or no perfusion defect at all – **Negative vessel-territory**.

5. **Impute a % stenosis value into a non-interpretable segment based on the CTP result.**
   a. For a non-interpretable coronary segment with a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 60% will be imputed for that segment.
   b. For a non-interpretable coronary segment without a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 30% will be imputed for that segment.

**Presence of non-interpretable myocardial segment by CTP**

Non-interpretable myocardial segments will be considered as **possible perfusion defects** for analysis purposes:

1. **CTP segment reading process:**
   a. CTP readers define if a segment is non-interpretable.

2. **Compress myocardial segments into vessel-level myocardial regions:**
a. If there is any myocardial segment with a perfusion defect by CTP within the same vessel-
level myocardial region where the non-interpretable segment was identified, the vessel-level
myocardial region will be considered as having a perfusion defect by CTP.

b. If there is no myocardial segment with a perfusion defect by CTP within the same vessel-
level myocardial region where the non-interpretable segment(s) was identified, the vessel-
level myocardial region will be considered as having a possible perfusion defect if there is \( \geq \) 50\% by CTA in the vessel supplying that segment.

3. Adjudication process

4. Defining dichotomized (positive and negative) vessel-territory results for primary analysis

If a non-interpretable segment is present there are 2 possible vessel-territory final results:

a. \( \geq \) 50\% stenosis by CTA with greater than one non-interpretable myocardial segment related
to that vessel - Positive vessel-territory.

b. \( \geq \) 50\% stenosis by CTA with one non-interpretable myocardial segment related to that vessel
- Negative vessel-territory.

c. \(< \) 50\% stenosis by CTA with a non-interpretable myocardial territory related to that vessel –
Negative vessel-territory.

5. Impute a SSS value into a non-interpretable segment based on the CTP result

a. For a non-interpretable myocardial segment with a \( \geq \) 50\% stenosis in the vessel supplying
that segment, a SSS of 0.5 will be imputed for that segment.

b. For a non-interpretable myocardial segment with a \(< \) 50\% stenosis in the vessel supplying
that segment, a SSS of 0 will be imputed for that segment.

6. Impute a SSS value into a non-interpretable segment with stent in corresponding vessel

a. For a stented coronary segment with a related non-interpretable myocardial segment, a SSS of
0.5 will be imputed for that segment.

It is important to point out, analyses of sensitivity and specificity will use two threshold definitions of a
positive myocardial territory a) SSS \( \geq \) 1 and b) SSS \( \geq \) 2.

Distribution of SSS when multiple positive vessel-territories are assigned to a single myocardial
territory.

1. In the case that multiple positive vessels are assigned to a single myocardial segment when it is
anatomically possible that both vessels supply the area and could result in the corresponding
perfusion defect, the SSS for that segment will be paired with both positive vessels.
Gold Standard – Cath (QCA) and SPECT-MPI

Primary End Point 1:

CT ability to identify a ≥50% coronary artery stenosis and a corresponding myocardial perfusion deficit when compared to the gold standard (≥50% coronary artery stenosis by Cath (QCA) and a corresponding myocardial perfusion deficit by SPECT-MPI) at a patient level.

The primary diagnostic parameter will be the area under the ROC curve of combined CTA and CTP for identifying the combination of a coronary artery stenosis ≥ 50% and a corresponding myocardial perfusion defect by the gold standard.

In order to build the ROC curve we will need a dichotomized gold standard definition of patient disease (positive or negative) and a continuous measurement of disease by the tested method (CT).

Dichotomized definition of disease by the gold standard:

- ≥50% coronary stenosis by QCA AND aligned/matched myocardial perfusion defect on SPECT = Positive (1).
- All remaining combination of results possibilities = Negative (0).

In order to achieve that we propose:

Step 1: Compress conventional coronary artery segments

1. Compress 30 coronary artery segments to the 19 segment model

Step 2: Remove ineligible segments by conventional coronary angiography

3. Drop all segments with a reference diameter of <1.5 mm
4. Drop all segments in which phase 1 (visual score of 0) was read as “not seen”
5. Drop all segments in which phase 1 (visual score of 7) was read as “too small to evaluate”

Step 3: Compress coronary segments into vessels

7. RCA – coronary segments 1, 2, 3, 4, and 5.
8. LM – coronary segment 11.
10. Mid-distal LAD – coronary segments 13, 14, and 16.
11. LCX – coronary segments 18, 19, 20, 21, 22, 23, and 27.
Step 4: Compress myocardial territories into vessel-level myocardial regions

7. RCA – myocardial segments 3,4,9 and10
8. LM – myocardial segments 1,2,5,6,7,8,11,12 and 13
9. Proximal LAD - myocardial segments 1,2,7,8 and13
10. Mid-distal LAD – myocardial segments 7,8 and 13
11. LCX – myocardial segments 5,6,11 and 12
12. Ramus – myocardial segments 1,6,7 and 12

Step 5: Align conventional coronary artery vessels with SPECT perfusion myocardial territories to create a final vessel result

3. Adjudication process

2. After the adjudication process, there will be 2 possible vessel-territory results:

   c. Positive
      i. ≥ 50% stenosis (QCA) + downstream myocardial perfusion defect (SPECT).
   d. Negative
      i. ≥ 50% stenosis (QCA) + unrelated myocardial perfusion defect (SPECT).
      ii. ≥ 50% stenosis (QCA) + no myocardial perfusion defect (SPECT).
      iii. < 50% stenosis (QCA) + downstream myocardial perfusion defect (SPECT).
      iv. < 50% stenosis (QCA) + unrelated myocardial perfusion defect (SPECT).
      v. < 50% stenosis (QCA) + no myocardial perfusion defect (SPECT).

Step 6: Generate final patient results from vessel results

3. There will be 2 possible patient results, following the dichotomized definition of disease by the gold standard:
   a. Positive
      i. If there is any positive vessel-territory for the patient
   b. Negative
      i. If there is no positive vessel-territory for the patient

Step 7: Select the Leaman Location Score for each arterial segment.

3. If a patient has a co-dominant system:
   c. Assign left dominance if there is a LPDA (coronary segment 27)
   d. Assign right dominance if there is a RPDA (coronary segment 4)

4. Assign each arterial segment a base value according to the chart below. This base value is different for a right or left dominant circulation.

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* Special scenarios and considerations:

**Absence of a lesion with a QCA value in a Vessel**

*Impute a % stenosis value for non-quantified phase 2 segments based on the phase 1 (visual score) value*

3. For a segment with a phase 1 score of 1, a stenosis value of 0% (zero) will be imputed.
4. For a segment with a phase 1 score of 2, a stenosis value of 15% will be imputed.

**Presence of non-interpretable gold standard studies**

1. If either the whole Cath and/or SPECT are considered non-interpretable, the patient will be dropped from the primary analysis.

**Presence of STENT by Cath**

Stents will be considered as possible lesions for analysis purposes as follows:

1. Cath segment reading process:

   e. Cath reader defines if there is a STENT present in each segment.

   f. A qualitative assessment is made: no intrastent reestenosis (ISR), < 50% focal ISR, > 50% focal ISR, 100% ISR, diffuse < 50% and unable to interpret.

   g. If there is a visual read of more than 30% ISR, a quantitative measurement (QCA) is made and recorded as for all other segments.
h. In cases where there is two lesions in the same segment, one inside and another outside the STENT (already accounting for the 5mm from the STENT border lesions that are also considered ISR), the most occlusive one will have a phase 2 measurement for that segment and a comment will be added that confirms if that lesion measured was inside or outside the STENT.

2. Compress coronary segments into vessels
   
   c. If there is any segment with $\geq 50\%$ stenosis by QCA within the same vessel where the stented segment was identified, the vessel will be considered as having a $\geq 50\%$ stenosis by QCA.

   d. If there is no segment with $\geq 50\%$ stenosis by QCA within the same vessel where the stented segment was identified, the vessel will be considered as having a possible $\geq 50\%$ stenosis and the final vessel result will be defined by the SPECT result.

3. Adjudication process

4. Defining dichotomized (positive and negative) vessel results for primary analysis
   
   b. Cath intrastent quantitative measurements will NOT be used for primary analysis.

If a STENT is present there are 2 different scenarios with 2 possible vessel-territory final results, based primarily on the SPECT result:

   c. Stented segment with a perfusion defect in a myocardial territory related to that vessel- Positive vessel-territory.

   d. Stented segment without a perfusion defect in a myocardial territory related to that vessel or no perfusion defect at all- Negative vessel-territory.

**Impute a % stenosis into a stented segment based on the SPECT result.**

   a. For a stented segment with a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 60% will be imputed for that segment.

   b. For a stented segment without a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 30% will be imputed for that segment.

**Presence of non-interpretable segment by Cath**

Non-interpretable segments will be considered as possible lesions for analysis purposes in a similar way as stented segments are:

1. Cath segment reading process:
   
   b. Cath reader defines if a segment is not-interpretable.

2. Compress coronary segments into vessels
c. If there is any segment with ≥ 50% stenosis by QCA within the same vessel where the non-interpretable segment was identified, the vessel will be considered as having a ≥ 50% stenosis by QCA.

d. If there is no segment with ≥ 50% stenosis by QCA within the same vessel where the non-interpretable segment was identified, the vessel will be considered as having a possible ≥ 50% stenosis and the final vessel result will be defined by the SPECT result.

3. Adjudication process

4. Defining dichotomized (positive and negative) vessel results for primary analysis

If a non-interpretable segment is present there are 2 possible vessel final results, based primarily on the SPECT result:

c. Non-interpretable segment with a perfusion defect in a myocardial segment related to that vessel - Positive vessel-territory.

d. Non-interpretable segment without a perfusion defect in a myocardial segment related to that vessel or no perfusion defect at all – Negative vessel-territory.

5. Impute a % Stenosis value into a non-interpretable segment based on the SPECT result.

   a. For a non-interpretable coronary segment with a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 60% will be imputed for that segment.

   b. For a non-interpretable coronary segment without a perfusion defect in a myocardial segment related to that vessel, a stenosis value of 30% will be imputed for that segment.

Presence of TID (transient ischemic dilatation) on SPECT

1. In cases where and only where there is at least one matched stenosis ≥50% and myocardial perfusion defect and TID present on SPECT, the following action will be taken:

   a. All myocardial territories initially considered normal by the SPECT analysis will be reassigned as abnormal. In this scenario, the vessel-territory result will also become positive if the vessel has a ≥ 50% stenosis by QCA and remain negative when there is a < 50% stenosis by QCA.

   b. For the primary analysis, any vessel-territories that become positive as a result of TID will be assigned the same SSS as the initial vessel-territory with a positive match.

Presence of inadequate exercise stress test on SPECT (less than 85% of maximum HR achieved)

1. For the primary analysis all cases, regardless of the percentage of age predicted maximum heart rate achieved, will be included.
Primary End Point 2:

CT ability to identify a $\geq 50\%$ coronary artery stenosis and a corresponding myocardial perfusion deficit when compared to the presence of $\geq 50\%$ coronary artery stenosis by Cath (QCA) alone as the gold standard, at a patient level.

The primary diagnostic parameter will be the area under the ROC curve of combined CTA and CTP for identifying a coronary artery stenosis $\geq 50\%$ and a corresponding myocardial perfusion defect by the gold standard.

In order to build the ROC curve we will need a **dichotomized** gold standard definition of patient disease (positive or negative) and a continuous measurement of disease by the tested method (CT).

**Dichotomized definition of disease by the gold standard:**

- $\geq 50\%$ coronary stenosis by QCA = **Positive** (1).
- No $\geq 50\%$ coronary stenosis by QCA = **Negative** (0).

In order to achieve that we will:

**Step 1: Compress conventional coronary artery segments**

2. Compress 30 coronary artery segments to the 19 segment model

**Step 2: Remove ineligible segments by conventional coronary angiography**

6. Drop all segments with a reference diameter of $< 1.5$ mm
7. Drop all segments in which phase 1 (visual score of 0) was read as “not seen”
8. Drop all segments in which phase 1 (visual score of 7) was read as “too small to evaluate

**Step 3: Compress coronary segments into vessels**

13. RCA – segments 1, 2, 3, 4, and 5.
17. LCX – segments 18, 19, 20, 21, 22, 23, and 27.

**Step 4: Create a final vessel result**
4. There is no need for adjudication to align conventional coronary artery vessels with perfusion myocardial territories on the gold standard side for this analysis.

5. There will be 2 possible vessel results:
   e. **Positive**
      i. $\geq 50\%$ stenosis (QCA)
   f. **Negative**
      i. $< 50\%$ stenosis (QCA)

**Step 5: Generate final patient results from vessel results**

4. There will be 2 possible patient results, following the dichotomized definition of disease by the gold standard:
   a. **Positive**
      i. If there is any positive vessel for the patient
   b. **Negative**
      i. If there is no positive vessel for the patient

**Step 6: Select the Leaman Location Score for each arterial segment.**

5. If a patient has a co-dominant system:
   e. Assign left dominance if there is a LPDA (coronary segment 27)
   f. Assign right dominance if there is a RPDA (coronary segment 4)

6. Assign each arterial segment a base value according to the chart below. This base value is different for a right or left dominant circulation.

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* Special scenarios and considerations:

**Impute a % stenosis value for non-quantified phase 2 segments based on the phase 1 (visual score) value**

5. For a segment with a phase 1 score of 1, a stenosis value of 0% (zero) will be imputed.
6. For a segment with a phase 1 score of 2, a stenosis value of 15% will be imputed.

**Presence of non-interprettable gold standard study**

1. If the whole Cath is considered non-interprettable, the patient will be dropped from the primary analysis.

**Presence of STENT by Cath**

Stents will be considered as possible lesions for analysis purposes and the imputed QCA value from the gold standard endpoint 1 algorithm will be used.

**Presence of non-interprettable segment by Cath**

Non-interprettable segments will be considered as lesions for analysis purposed and the imputed QCA value from the gold standard endpoint 1 algorithm will be used.