Cross-Discipline Team Leader Review

Application Type	Supplemental New Drug Application
Application Number(s)	NDA 020351 s44
Priority or Standard	Priority
Submit Date(s)	October 6th, 2016
Received Date(s)	October 18th, 2016
PDUFA Goal Date	April 5th, 2017
Division/Office	Division of Medical Imaging Products/Office of Drug Evaluation IV
Reviewer Name(s)	Anthony Fotenos, MD, PhD
Review Completion Date	March 22nd, 2017
Established Name	Iodixanol
(Proposed) Trade Name	Visipaque Injection
Applicant	GE Healthcare
Formulation(s)	320mgI/mL
Dosing Regimen	70-80 mL main bolus volume (does not include optional test bolus volume of 20 mL) at a flow rate of (b) (4) mL/s, followed by 20 mL saline flush
Applicant Proposed Indication(s)/Population(s)	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.
Recommendation on Regulatory Action	Approval
Recommended Indications	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.

1. Introduction

This is a cross-discipline team leader (CDTL) review focused on GE Healthcare's efficacy supplement to NDA 20351 (associated NDA 20808 and IND 34585) in support of an expanded indication for the use of Visipaque (320 mgI/mL) "for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease" (CAD). This review is based on reading the primary reviews written by Karen Bleich (clinical), Michele Fedowitz (labeling), Satish Misra (biometrics), John Christy (Clinical Pharmacology), Zarna Patel (Drug Promotion), selective reading and data analysis of the submission, and study of published literature. My aim is briefly to summarize highlights from the primary reviews, provide some cross-disciplinary context and commentary regarding the submission, and document my opinion of benefit-risk.

2. Background

This efficacy supplement is being reviewed in FDA's Office of New Drugs (OND) under a PDUFA priority review timeline because CCTA addresses diagnostic needs for a serious condition and, if approved, would provide an improvement in effectiveness for the class of iodinated contrast drugs, none of which are currently approved for CCTA. The supplement meets the filing requirements under Section 505(b)(1) of the FD&C Act because the two pivotal investigations relied upon by the applicant were conducted by and for the sponsor. However, relative to clinical practice in 2017, there is little new about CCTA, which requires the use of intravenous iodinated contrast to create a visible difference in attenuation between the coronary arteries and surrounding myocardium during CT imaging of the heart. I provide the following larger contextual timeline to whet the interest of the reader curious about the history and contemporary patterns of general CCTA and associated procedure use (see also Figure 1); note this falls outside the scope of evidence relied upon by the review team:

- 1998: Achenbach and colleagues publish early CCTA images [Achenbach 1998].

- 2008: The Council for Certification in Cardiovascular Imaging establishes of the Certification Board of Cardiovascular Computed Tomography (CBCCT) "to develop and administer a practice-related examination in the field of CCTA and to award certification to those physicians who successfully complete the CBCCT examination process" (http://www.cccvi.org/).

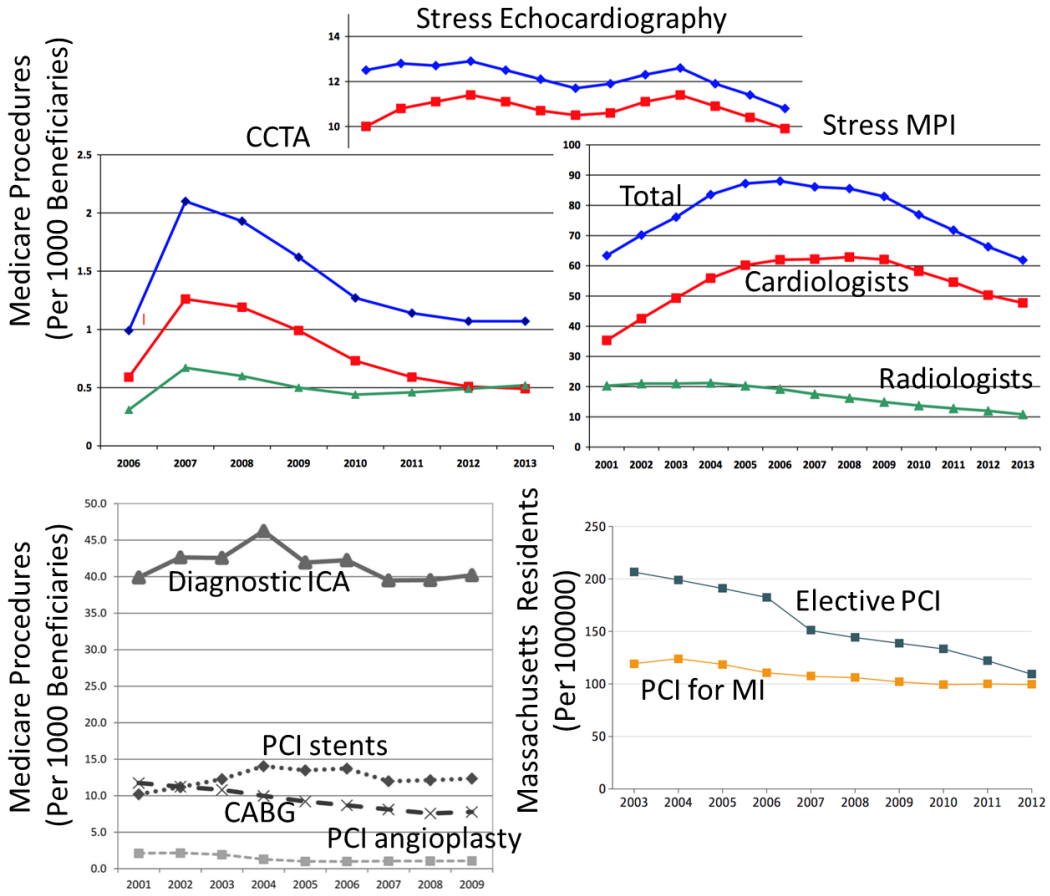
- 2008: In considering whether to alter the prevailing pattern of third-party payer reimbursement at the local level, based on the concern that providers "are using CCTA as an additional test added to exercise testing and nuclear imaging rather than thoughtfully considering the appropriate mix of these tests," the Centers for Medicare and Medicaid Services (CMS) publishes a

Decision Memo for CCTA stating, "While public comments and specialty society opinion following the CMS proposed decision to use Coverage with Evidence Development [CED] did not dispel the uncertainty of the test's clinical utility, they did strongly favor maintaining the local coverage policies for CTA. In light of this, CMS has decided to make no change in the current National Coverage Determination" [CMS 2008].

- 2016: The United Kingdom's National Institute for Health and Care Excellence (NICE) upgrades CCTA to first-line investigation for all stable patients without known significant CAD who present with typical or atypical angina or non-anginal/ECG-abnormal chest pain. Functional imaging or invasive angiography are recommended only secondarily in patients whose CCTA is equivocal or positive [NICE 2016].

- 2017: A group of clinical trialists writes on their efforts to advance beyond diagnostic performance endpoints for trials of CCTA and, by extension, at the vanguard of the larger field of diagnostic evidence generation, "Several themes emerge from reviewing recent randomized controlled trials (RCTs) in stable ischemic heart disease imaging...The preponderance of negative trials reveals weaknesses in trial design, eligibility criteria, or other factors...Future RCTs should incorporate more innovative trials designs to focus on reducing novel clinical outcomes while achieving cost minimization. Possible RCTs may also consider randomization by varied diagnostic/therapeutic or care planning management approaches and their impact on clinical outcomes" [Shaw 2017].

Figure 1 Published data on the utilization of CCTA and related procedures
CAD-related procedures, including CCTA, are common in the United States. Upper: *The number of non-invasive diagnostic imaging procedures between 2001 and 2013 for stress echocardiography, CCTA (2001-2013), and stress MPI billed to Medicare in total (blue) and broken down by physician specialization (cardiologist=red, radiologist=green) appeared to peak around 2007.* Bottom left: *Though practice guidelines recommend non-invasive imaging as a gatekeeper for ICA, there does not appear to be an obvious correlation between the number of non-invasive diagnostic procedures and the gap between diagnostic and invasive procedures ("ICA diagnostic yield") between 2001 and 2009.* Bottom right: *In a Massachusetts population, PCIs done in the absence of MI were considered elective and trended down between 2003 and 2012 to the point where the breakdown is most recently approximately balanced. Assuming total volume ~ 2*Medicare, the following are reasonable ballpark volume estimates for 2009: total non-invasive diagnostic imaging procedures ~5 million (≈4 million MPIs, 600 thousand stress echocardiograms, 90 thousand CCTAs); total invasive diagnostic catheterizations ~2 million; total revascularizations ~1 million (700 thousand stents [60% elective], 400 hundred thousand CABGs [70% elective], 50 thousand angioplasties). For comparison, the annual population incidence of acute MI was estimated to be 600 thousand in 2008 (25% STEMI; Benjamin 2017). Adapted from [Levin 2016, Riley 2011, and Yeh 2015]. CAD = coronary artery disease; CCTA = coronary CT angiography; CABG = coronary artery bypass graft; ICA = interventional coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; PCI= percutaneous coronary intervention.*



Dr. Bleich's tabulation of regulatory milestones leading up to the current submission describes an evolution in thinking by the review team between 2009 and 2015 regarding the filability of the sponsor's pivotal diagnostic performance study (Table 1).

Table 1: Dr. Bleich's tabulation of regulatory milestones

Date	Application	Description
8/27/2009	IND 034585	Meeting minutes (3/22/2009) from face-to-face meeting regarding sponsor's submitted clinical trial results. FDA concluded "given the inadequacy of the reviewed study data to form the basis for an approvable NDA submission, FDA recommends that additional pivotal studies are needed to support the use of Visipaque as an imaging agent in CCTA for diagnosis and exclusion of CAD."
6/16/2015	IND 034585	Sponsor submitted correspondence requesting a meeting to discuss Phase 3 study design and clinical program to support a coronary CTA indication for Visipaque
11/10/2015	IND 034585	Face-to-face meeting for re-positioning of sponsor's request based on newly available information and guidelines. The sponsor-proposed Phase 3 study was deemed unnecessary by FDA. FDA suggested a future pre sNDA meeting for presentation of the relevant studies and publications.
5/13/2016	IND 034585	Pre-sNDA meeting requested by sponsor to discuss the studies
		and publications for an sNDA filing for CCTA.
6/13/2016	IND 034585	Meeting package was submitted by the sponsor.
7/11/2016	IND 034585	Written responses were provided by DMIP
7/13/2016	IND 034585	Face-to-face meeting in which FDA agreed that the currently proposed indication "to assist in the diagnostic evaluation of patients with suspected CAD" appeared sufficiently supported for sNDA filing review.
10/6/2016	NDA 020351	Receipt of sNDA 44

Why did the review team's thinking evolve?

- Reason #1: the primary gatekeeper role of CCTA in a two-gatekeeper testing sequence has crystalized over time (primary-non-invasive testing: prior to invasive coronary angiography [ICA]; secondary ICA testing: prior to invasive revascularization). As a primary gatekeeper, CCTA is more similar in purpose to stress-rest myocardial perfusion imaging (MPI) than to ICA, despite the "coronary angiography" in two of the three procedure terms. This reframing of the role of CCTA from ICA-replacement to ICA-gatekeeper is reflected in revision of the proposed Visipaque CCTA indication from the one proposed in 2009 ("(b) (4)") compared

to now ("assist in the diagnostic evaluation of patients with suspected coronary artery disease").

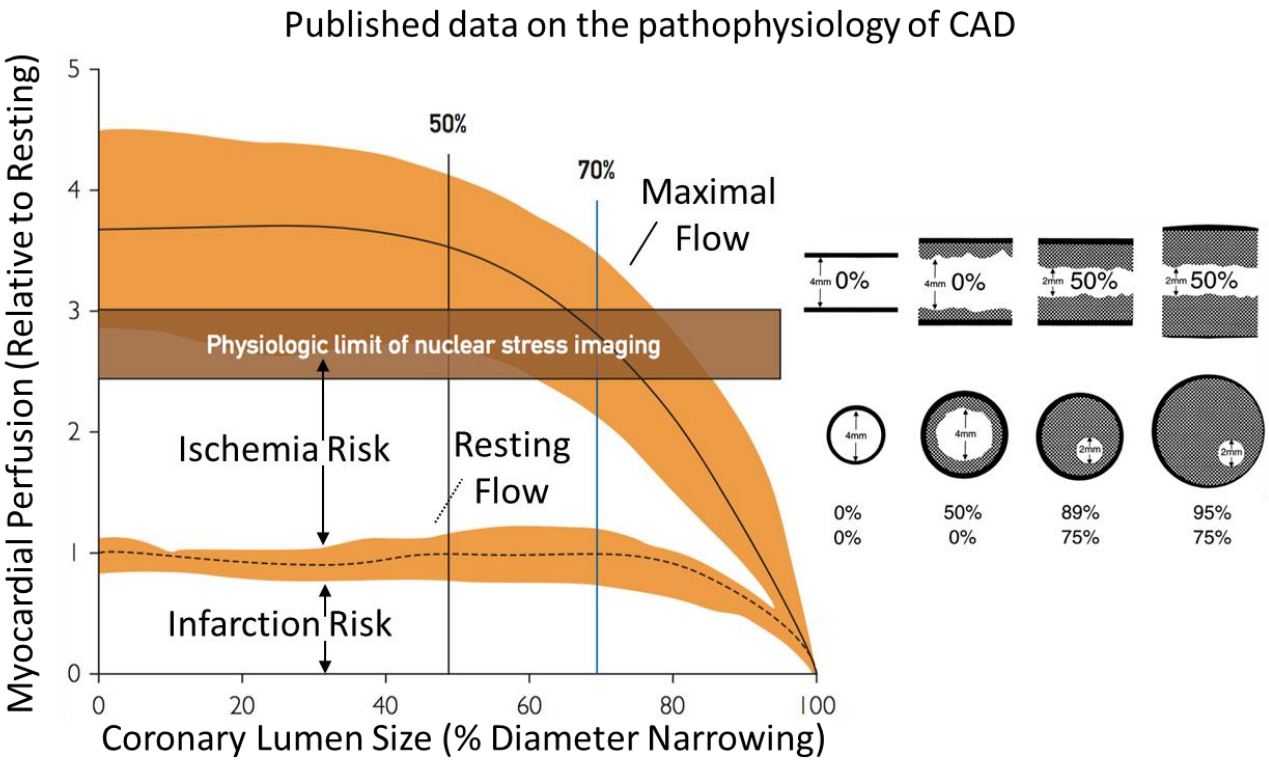
- Reason #2: Given the shared gatekeeping roles of CCTA and MPI, it is pertinent that the Division of Medical Imaging Products (DMIP) has not required superiority against pre-specified better-than-chance sensitivity and specificity thresholds for approval of the following imaging drugs (ICA consistently used as the standard of reference): Cardiolite (NDA 19785, 1995), Myoview (NDA 20372, 2001), Thallium-201 (NDA 18150, 2004), Ammonia-13 (NDA 22119, 2006), and CardioGen (NDA 19414, 2009).

- Reason #3: Multiple controlled trials have randomized patients with stable ischemic heart disease to CCTA vs. stress MPI or ECG testing. A recent published review of these found CCTA to be consistently non-inferior or better for CAD-related events over a period between 1 to 2.1 years of follow-up [Shaw 2017]. In addition, under particularly well controlled therapeutic trial conditions, baseline CAD severity quantified by ICA has been found more prognostic for death and MI compared to CAD severity quantified by MPI over 2.5 to 7 years of follow-up [Mancini 2014].

- Reason #4: Previous reviewers have argued for minimum sensitivity performance thresholds as high as 95% based on the rationale that "false negatives based on CCTA images could have dire clinical consequences" (IND 34585, 8/25/2009). Current evidence on the magnitude of benefit from invasive revascularization suggests that the probability of dire consequences from delayed intervention may be smaller than previously appreciated, particularly in patients excluded by ECG/troponins for ST-elevation myocardial infarction (STEMI; see Figures 2 and 3).

Figure 2: Published data on the pathophysiology of CAD

Inadequate delivery of oxygen secondary to poor or absent blood flow to the myocardium is the common pathophysiological mechanism of CAD. Upper left: *The relation between myocardial perfusion and coronary lumen size is non-linear (solid and dashed lines) and variable (orange areas). Functional testing, including qualitative stress-rest myocardial perfusion imaging, aims to characterize relative regional decreases in the white space between the orange areas marked "Ischemia Risk" and depends on the finding that the decline in maximal flow occurs to the left of the onset of decline in resting flow. Upper right: Anatomical testing, including coronary angiography, typically aims to evaluate vessel lumen size quantified as percent diameter narrowing. Note the potential differences between percent luminal diameter narrowing (upper numbers), cross-sectional atheroma involvement (middle numbers), and luminal area narrowing (bottom numbers) in the illustrated example of coronary atherosclerosis, reflecting both geometrical principles and pathological processes of "negative" (lumen-independent) and "positive" (lumen dependent) remodeling.* Lower left: *CAD manifests clinically in the form of angina, a more deterministic causal link. In populations with high-calorie, low-exercise lifestyles, atherogenesis is detectable on gross pathology in childhood. Angina reflects atherosclerotic progression to the point where a patient seeks medical care, typically for activity-related chest pain in middle age or older adulthood. The micrographs show cross sections through a normal coronary artery (left) and an obstructive plaque (right; the medial lesion between 3 and 6 o'clock represents calcification).* Lower right: *CAD also manifests clinically in the form of acute coronary syndromes (ACS), a more stochastic causal link, associated with increased risk of death from arrhythmia and/or pump failure. The illustrated waveform comes from an unplanned live observation of plaque disruption during an ultrasound experiment in a mouse model of atherosclerosis [Daeichin 2016]. Note the change in the normal pattern of arterial pulsatility (upper row) over a period of a few seconds (bottom row), leading to downstream cessation of blood flow (not shown). Long-running debate continues regarding the use of percent diameter narrowing to predict rupture [Niccoli 2013] and supports the need for further research to identify and time culprit lesions in ACS prospectively. Note that both stable and acute heart disease may also occur in the absence of CAD, which is why the more general term ischemic heart disease is sometimes preferred. Adapted from [Daeichin 2016, Daniels 2012, Fishbein 2006, Rumberger 2017, and http://library.med.utah.edu/WebPath]. CAD = coronary artery disease.*


Published data on the pathophysiology of CAD
Myocardial Perfusion (Relative to Resting)
Coronary Lumen Size (% Diameter Narrowing)
50%
70%
Maximal Flow
Physiologic limit of nuclear stress imaging
Ischemia Risk
Resting Flow
Infarction Risk
0%
0%
50%
0%
50%
75%
95%
75%

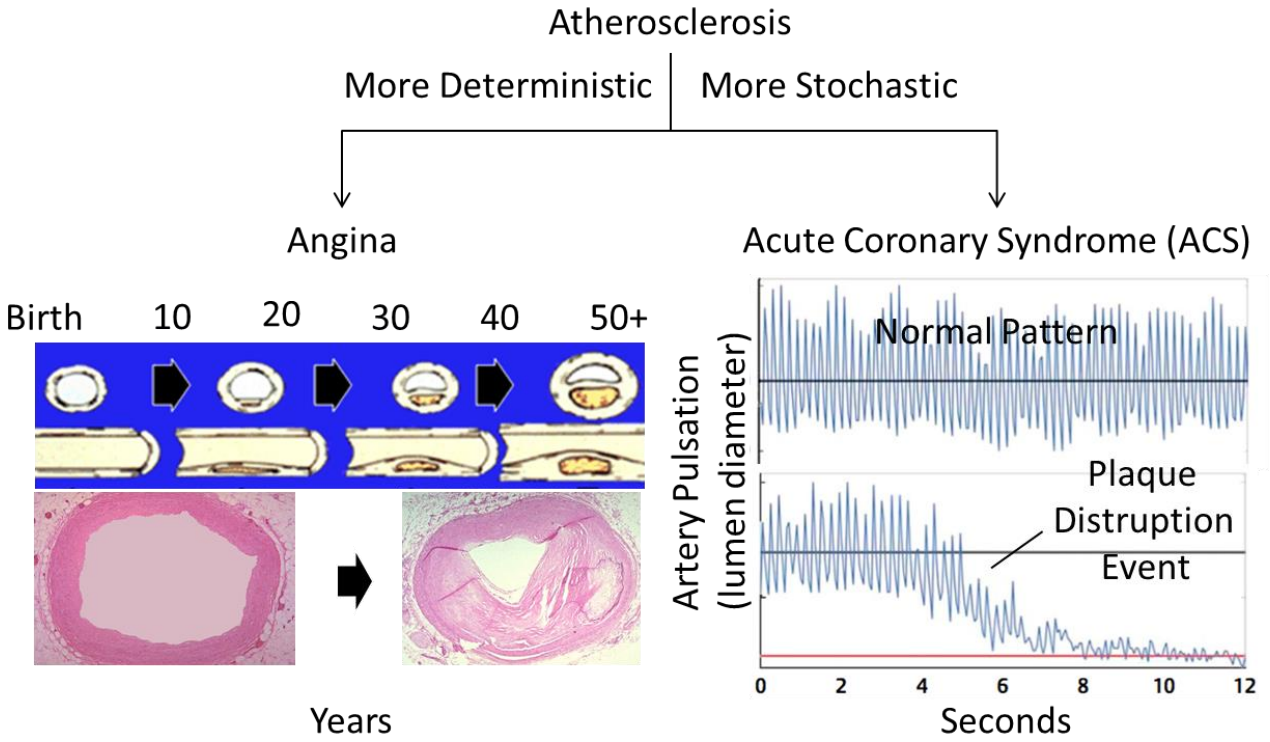
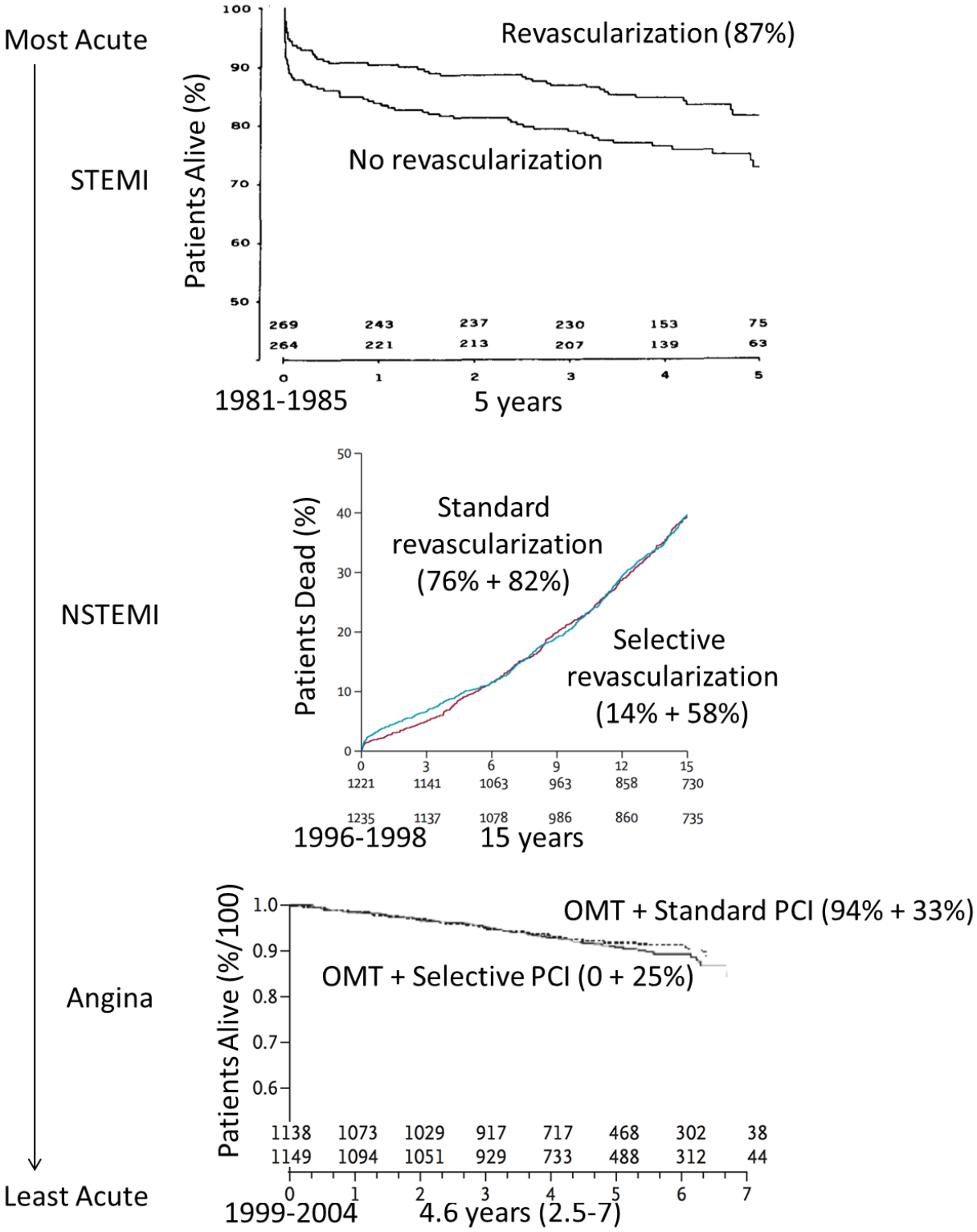

Atherosclerosis
More Deterministic
More Stochastic
Angina
Acute Coronary Syndrome (ACS)
Birth
10
20
30
40
50+
Years
Artery Pulsation (lumen diameter)
Normal Pattern
Plaque Disruption Event
Seconds

Figure 3 Published data on the benefit of invasive revasculaization

The value of non-invasive diagnostic testing used as a gatekeeper for ICA and invasive revascularization depends in part on the benefit of the intervention. Current guidelines recommend invasive revascularization ideally within 2 hours of symptom onset in patients with STEMI, within 24 to 48 hours for most patients with NSTEMI, and as second-line therapy after optimal medical treatment for symptomatic relief in most patients with stable ischemic coronary artery disease. Efficacy evidence from representative trials underlying these guidelines strengthens in proportion to patient acuity and is briefly summarized. Upper: *In the Netherlands Interuniversity Trial [Simoons 1989], more patients with STEMI survived for 5 years after randomization to intracoronary thrombolysis within 4 hours of symptom onset compared to after no revascularization (assuming extremely non-uniform distribution of benefit, "number needed to treat" [NNT] to save one death over five years = 10; assuming uniform distribution of benefit, estimated gain in life expectancy for a 55-year-old patient = 1.5-5 years [Wright 1999]). Unspecified rates of post-randomization revascularization procedures in the control group may have attenuated reported efficacy.* Middle: *In the FRISC-II trial [Wallentin 2016], no survival advantage was demonstrated over 15 years for patients with NSTEMI (i.e., patients with significant ECG changes or positive cardiac enzymes) randomized to invasive angiography and revascularization (within 7 days and for ≥70% epicardial stenosis) compared to patients selectively revascularized for refractory symptoms or severe ischemia on exercise testing. Nevertheless, the 15-year rate of recurrent MI favored the standard revascularization group (38% vs 45%, NNT 14, mostly limited to the first 3 years post-randomization). The small numerical difference in mortality observed during the first 3 years (point benefit estimate ~24 days) was not statistically significant, a null finding also replicated in a recent meta-analysis [Elgendy 2016].* Bottom: *In the PROMISE trial [Boden 2007], no survival advantage was demonstrated over 2.5 to 7 years for patients with angina, objective evidence of myocardial ischemia, and ≥70% epicardial stenosis on invasive angiography randomized to OMT plus standard PCI compared to OMT plus selective PCI (recommended for patients with severe ischemia on MPI and progressive or intolerable angina after 6 to 8 weeks of maximum medical therapy). The same null result was found for myocardial infarction, stroke, and ACS hospitalization event rates, including pre-specified combinations. However, randomization to the more invasive treatment arm did lead to favorable patient-reported outcomes, particularly freedom from angina (for example, 53% vs. 42% at 3 months [compared to 21% vs. 23% at baseline]; NNT 9), an effect which persisted for up to 3 years. It is uncertain the extent to which unblinded patient bias may have contributed to this positive finding or the extent to which the 25% of patients who underwent delayed, selective PCI may have contributed to the general similarity between trial arms. Note that patients with left main stenosis ≥ 50% were excluded from the PROMISE trial and may represent a target population of particular potential CCTA benefit. No benefit in terms of overall or cardiac death or MI was similarly found in the FAME 2 trial (not shown; [De Bruyne 2012]). ICA = invasive coronary angiography; STEMI = ST elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.*

Published data on the benefit of invasive revascularization



Reason #5: The quality of supportive evidence in addition to the originally reviewed diagnostic performance study grew between 2009 and 2015 (see Table 2).

Table 2: Dr. Bleich's tabulation of sponsor's first pivotal study (GE-189-001) second pivotal study (GE-189-002) and selected supportive publications

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Main Evaluation	No. of patients enrolled	Study Population	No. of Centers
GE-Sponsored Studies							
GE-189-002 (VCT002)	Open-label, prospective, multi-center, non-randomized	Test bolus: 20 mL at 4-5 mL/s Main injection: 70-80 mL Visipaque at 3.5-5 mL/s	Diagnostic performance of CCTA using LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in subjects with chest pain when compared against ICA as SOR	Blinded CCTA image evaluation using AHA 15 coronary segmental model	245	Outpatients with chest pain, scheduled for ICA	16
GE-189-002 reread (GE-012-101)	Open-label, prospective, multi-center, non-randomized, re-read	Re-read (n/a)	Same as above, with re-interpretation ICA and CCTA images from GE-189-002 according to new standards	Blinded CCTA image evaluation using SCCT 18 coronary segment model	232	Data from subjects previously dosed with Visipaque and imaged in GE-189-002	16
GE-012-096	Prospective, multi-center, registry	Not pre-specified, mean dose of 91.5 mL Visipaque, range of 30-180 mL	Prognostic value in terms of sensitivity, specificity, PPV, and NPV of CCTA compared to subsequent ICA findings or binary subject outcomes	CCTA compared to clinical outcomes or ICA up to 12 months	885	Outpatients with chest pain scheduled to undergo CCTA	17
Published Visipaque-only Studies							
ROMICAT	Prospective, single-center	80-100 mL Visipaque	Prognostic value of CCTA compared to occurrence of ACS during index	Blinded CCTA evaluation compared to	368	ED patients with chest pain, normal initial	1
			hospitalization, MACE during 6-month follow-up	ACS and MACE outcomes		troponin, and ECG.	
VCT001	Prospective, multi-center, non-randomized	50-150 mL Visipaque at 4-5 mL/s	Diagnostic performance of CCTA in terms of per patient and per vessel level analysis of stenosis ≥ 50% and ≥ 70% using QCA as SOR	Blinded image evaluation using AHA 15-segment coronary artery model	77	Outpatients with chest pain referred for ICA	3
PICTURE	Prospective, multi-center, non-randomized	Timing bolus: 10-20 mL at 4-5 mL/s. Main injection:80 mL Visipaque at 3.5-5 mL/s.	Diagnostic performance of CCTA and MPI SPECT in terms of sensitivity, specificity, NPV, and PPV of stenosis ≥50% and ≥70% using QCA as SOR	Blinded evaluation of CCTA and ICA images using the AHA 15-segment coronary artery model; and MPI	230	Outpatients with chest pain referred for nuclear MPI	12
Published Studies with Multiple Agents							
PROMISE	Prospective, randomized, multi-center	Multiple contrast agents/protocols	Comparison of CCTA to functional imaging for chest pain assessment	Clinical outcomes over 25 months	10,003	Symptomatic outpatients	68
SCOT-HEART	Prospective, randomized, multicenter	Multiple contrast agents/protocols	Comparison of CCTA with standard work-up, to standard work-up alone	Clinical outcomes over 1.7 years	4,142	Symptomatic outpatients	12

3. Clinical Pharmacology

Highlights of Dr. John's review include discussion of published data that suggest weight-based dosing of Visipaque may reduce beam-hardening artifacts compared to standard volume-based dosing and without a significant loss of coronary attenuation, typically targeted in the range around 350 HU [Nakura 2008]. Dr. John recommends addition of alternative 1 mL/kg instructions to the table entitled "Recommended Dosing for CCTA" in labeling. This table also includes optional with-dilution (also known as "split-bolus") instructions; an option aimed at improving right ventricular visualization via enlargement of the contrast bolus captured during the period of coronary imaging. These instructions closely reflect the dosing protocol used for the pivotal controlled GE-189-002 study. Pending supplement approval, Visipaque will be the first ICA to contain with-dilution instructions (a point of potential interest for conformant injector device labeling). The CCTA dosing table originally proposed by the sponsor compared to the table currently recommended by the review team is shown below (Table 3; note the two numbers in the right lower cells differ compared to the label in Dr. John's 3/15/2017 review due to correction of a typographic error identified, discussed, and corrected in the interim).

Table 3 sponsor's originally proposed and currently recommended labeling for CCTA dosing

Originally Proposed

(b) (4)

Recommended

- **Coronary Computed Tomography Angiography (CCTA)** (320 mg Iodine/mL)

Recommended dosage of VISIPAQUE is dependent on: the administration procedure, patient weight, and CT device factors, as detailed in Table 3.Calibrate the intravenous injection rate so that image acquisition coincides with peak arteria concentration. The time between VISIPAQUE injection and peak arterial concentration varies between patients.

ADULTS and PEDIATRIC PATIENTS[1] 12 YEARS OF AGE AND OLDER VISIPAQUE (320 mg Iodine/mL) DOSING RECOMMENDATIONS FOR CCTA						
Procedure	**Main VISIPAQUE Volume[2]**	**VISIPAQUE /saline Dilution Volume**	**Saline Flush**	**Injection Rate**	**Minimum VISIPAQUE Volume**	**Maximum VISIPAQUE Volume**
Without Dilution	70-80 mL[3,4]		40-50 mL	4-7 mL/sec	50 mL	150 mL
With Dilution	50-60 mL[4]	50 mL diluted VISIPAQUE (20 mL VISIPAQUE plus 30 mL saline)	20 mL	4-7 mL/sec	50 mL	150 mL

[1]For pediatric patients aged 12-17, recommended dose is 1-2 mL/kg.
[2]The main VISIPAQUE volume may be preceded by a test bolus consisting of 20 mL VISIPAQUE, immediately followed by a 20 mL saline flush, both injected at rate of 4-7 mL/sec.
[3]Alternatively, a dose of 1 mL/kg may be used to calculate total VISIPAQUE dose (excluding any test bolus).
[4]For CCTA acquired at < 120 kVp, the dose of VISIPAQUE may be reduced by up to 15% in patients < 85 kg and BMI < 30 kg/m^2. For CCTA acquired on a scanner with more than 64 detector rows, the dose of VISIPAQUE may be reduced in proportion to the scan duration.

4. Clinical/Statistical - Efficacy

Highlights of Dr. Bleich's and Misra's efficacy review include the following:

- Outcome-independent consensus around the use of vessel-level[1], original-read[2], per-reader[3], non-visualized-imputed-wrong[4], true-positive-ICA-stenosis≥50%[5], ICA-unevaluable-or-≤2mm-excluded[6] sensitivity/specificity[7] (Sn/Sp) as the co-primary endpoints for quantifying diagnostic performance in the first-pivotal GE-198-002 study. See Dr. Misra's summation (Table 3). Note the lower bound of all 95% confidence intervals (CI) comfortably exceed chance. This experimental design, albeit with ample precedent for imaging drug efficacy evaluation, does not permit inference regarding whether or the degree to which the Sn/Sp of Visipaque CCTA improves the Sn/Sp of referring clinicians in the absence of imaging or compared to competing non-invasive diagnostic procedures.

Table 3: Dr. Misra's summation of all vessels (stenosis ≥ 50%) by reader for original data

	Readers – Original Read Data (Stenosis ≥ 50%)								
	Reader 1			Reader 2			Reader 3		
	CATH +	CATH -	Total	CATH +	CATH -	Total	CATH +	CATH -	Total
CCTA +	57	68	125	67	126	193	58	74	132
CCTA -	14	708	722	8	699	707	14	740	754
Unevaluable	4	55	59	0	6	6	3	17	20
All Total	75	831	906	75	831	906	75	831	906
Sensitivity (%)	57/75 = 76.0			67/75 = 89.3			58/75 =77.3		
95% CI*	(64.8, 85.1)			(80.1, 95.3)			(66.2, 86.2)		
95% CI**	(63.1, 85.5)			(78.8, 95.0)			(64.8, 86.3)		
Specificity (%)	708/831 = 85.2			699/831 = 84.1			740/831 = 89.1		
95% CI*	(82.6, 87.5)			(81.5, 86.5)			(86.7, 91.1)		
95% CI**	(81.1, 88.5)			(80.6, 87.1)			(86.1, 91.4)		

*based on exact binomial confidence interval assuming independent vessels
** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

[1] because patient-level analysis negates the localizing value of imaging whereas segment delineation is less anatomically defined/standardized in the coronaries than in arterial regions where we have relied upon segment-level analysis for approval of other MR angiography (MRA) indications;
[2] because of the theoretical potential for bias to improve specificity after failing to meet FDA's 2009-recommended Sp threshold;
[3] DMIP's minimum standard for feasibly assessing generalizability to typical per-reader practice;
[4] because this is most conservative; we have also accepted 50%-wrong-imputation for prior MRA approvals;
[5] historical standard (see Figure 2) and increases feasibility against challenge to power for Sn, though ICA ≥ 70% or FFR is increasingly used to dichotomize PCI decision-making;
[6] too small for PCI;
[7] least dependent of 2x2-table-derivations on population sample variance.

- In second sponsored study GE-012-096, documentation that the 95% (87-99)/87% (84-89) Sn/Sp of Visipaque CCTA "to predict 12-month" major adverse cardiac events (MACE, defined as death, MI, hospitalization for unstable angina, or revascularization) was almost entirely driven by differential rates of revascularization procedures (see pdf page 50 of Dr. Bleich's review). GE-012-096 was a study with control essentially limited to pre-specification of eligibility criteria and a plan for follow-up after CCTA at 1, 6, and 12 months (i.e., a registry study). I appreciate the potential of real-world evidence such as this to improve generalizability compared to controlled trials, especially in the present context of a second/supplement study. However, I would not recommend the use of this design to generate first-pivotal or stand-alone efficacy evidence for diagnostic imaging drugs. To what extent did revascularization depend on CCTA findings? Independence would promote interpretability but is highly unlikely here. Even if assumed as a hypothetical, near-chance diagnostic performance of referring clinicians for prognosis in the absence of imaging is less plausible compared to for the diagnosis of stenosis ≥ 50% at the vessel level (as in GE-198-002), meaning the desirability of comparative design/analysis is even greater. Finally, beyond the challenging-to-quantify point of impacting management, even statistically significant gains in prognostic performance attributable to a diagnostic procedure lose their clinical relevance.

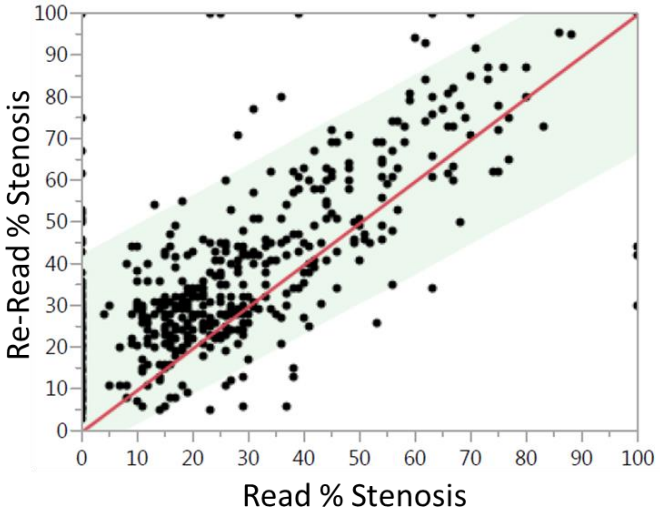
- Dr. Bleich's discussion of leading published ROMICAT and VCT001 (using Visipaque) and PICTURE, PROMISE, and SCOT-HEART (using multiple contrast agents, see pages 51-58) strongly support the generalizability of diagnostic efficacy for Visipaque CCTA found in GE-198-002 and GE-012-096.

A couple of additional observations of personal interest:

- In powering its studies, the sponsor anticipated per-patient ICA ≥ 50% stenosis rates of 50% for GE-198-002 and 12-month event rates of 25% for GE-198-096. The observed rates were 21% and 9%, respectively, suggesting CCTA was primarily studied in patients with low-to-intermediate (mostly low) global risk for 10-year MI or cardiac death.

- Reviewer's analysis of standard-of-reference (quantitative ICA or QCA) maximum per-vessel stenosis as measured in the GE-198-002 read and re-read studies supports the review team's decision to rely on the original read data (see Figure 4).

Figure 4: Reviewer's analysis of read vs. re-read reference standard
Note systematic deviation from the unity line and the wide shaded area containing 95% of individual vessel measurements, both serving as a reminder that term "truth standard" may mislead if interpreted uncritically.



5. Safety

Highlights of Dr. Bleich's review of Visipaque CCTA safety include the following:

- Documentation of one patient who experienced a coronary artery dissection during ICA in Study GE-189-002 (245 enrolled). I mention this event not as an adverse reaction to Visipaque, but as an example of the risk of ICA and an illustration of a difficult-to-quantify potential safety benefit from non-invasive ICA gatekeeping.

- Review strategy accounting for limitation of sponsor's safety data collection protocol. In its two pivotal studies, the sponsor reported only serious and unexpected adverse events, none of which appear to represent reactions to Visipaque.

- Reassuring finding of zero and symmetrically distributed 48-hour-change-in-creatinine post Visipaque in the n=232 GE-189-002 safety population, given plausibly increased risk of contrast-induced nephropathy. Note that patients with serum creatinine ≥ 1.7 mg/dL were excluded from Visipaque CCTA, reasonably representative of typical practice.

- Rationale for addition of new CCTA-pertinent language to labeling section 7.1 (Drug-Drug Interactions): "The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of hypersensitivity reactions with

epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering iodinated contrast agents to patients taking beta-blockers."

- Sensitive identification of thrombocytopenia safety signal from sponsor's large post-marketing database, as well as insightful explanation plausibly implicating heparin and without new labeling implications.

- No identification of additional CCTA-specific new safety signals.

6. Pediatrics

Dr. Bleich reviewed published evidence on the use of CCTA in patients with Kawasaki disease. Her review suggests a reasonable basis to extrapolate the efficacy and dosing of Visipaque CCTA as established in GE-189-002 and GE-012-096 down to age 12 (see Table 3).

7. Labeling

Dr. Bleich summarizes recommended new labeling downstream of the Visiapque CCTA supplement in the following review excerpt (page 80):

- 2.3 Intravenous Dosage and Administration:
  - Pediatric dosing: CCTA dosing recommendation for pediatric patients over 12 years of age (1-2 mL/kg).
  - Contrast dilution: Inclusion of guidance for variations in the dosing scheme related to the use of dilute contrast administration.
  - Main bolus Visipaque dose: adjusted to reflect the prescribed protocol dose in study GE-189-002, 70-80 mL.
- 7.1 Drug-Drug Interactions: Inclusion of beta-adrenergic blocking agents.
- 14.2 Intravenous Administration Studies: CCTA portion rewritten to reflect most robust analysis of results from the CCTA clinical trials.

The reader is referred to separate labeling reviews by Drs. Fedowitz and Patel for additional information about the concurrent PLR conversion overseen by Dr. Fedowitz.

8. Recommendations

The involved Clinical, Biometrics, and Clinical Pharmacology review teams unanimously find favorable benefit-risk for Visipaque 320 mgI/mL for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease. I concur.

9. References

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/s/

ANTHONY F FOTENOS
03/22/2017