Evidence Assist: Coronary Computed Tomography Angiography Innovations in Non-invasive Diagnosis of Coronary Artery Disease Supplemental Materials

August 2019

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence Synthesis Program (ESP)
Coordinating Center
VA Portland Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:
Mark Helfand, MD, MPH, MS
Johanna Anderson, MPH
Kim Peterson, MS
Donald Bourne, MPH

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

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APPENDIX A. SEARCH STRATEGIES

1. Search for current systematic reviews (limited to 2017 forward) **Date Searched: 2/7/19**	
Sources:	**Strategy:**
AHRQ	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
CADTH	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
NICE (NHS Evidence)	Search: heartflow; FFFRct; fractional flow reserve; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
ECRI Institute	Search: heartflow; FFFRct; fractional flow reserve; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
HTA: Health Technology Assessments	Database: EBM Reviews - Health Technology Assessment <4th Quarter 2016> Search Strategy: -- 1 (HeartFlow or FFFRct or CT-FFR or CT-based FFR or FFR CT or noninvasive FFR or noninvasive fractional flow reserve or non-invasive FFR or non-invasive fractional flow reserve).mp. (0) 2 exp Fractional Flow Reserve, Myocardial/ or (Fractional Flow Reserve or FFR).mp. (7) 3 exp Computed Tomography Angiography/ (0) 4 (Computed Tomography Angiogra* or CCTA or coronary CT angiogra* or CT coronary angiogra*).mp. (14) 5 or/3-4 (14) 6 2 and 5 (0) 7 1 or 6 (0) ***************************
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ C. http://art.puget-sound.med.va.gov/default.cfm D. https://www.hsrd.research.va.gov/publications/esp/ Search: heartflow; FFFRct; fractional flow reserve; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
Cochrane Database of Systematic Reviews	Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 6, 2019> Search Strategy: -- 1 (HeartFlow or FFFRct or CT-FFR or CT-based FFR or FFR CT or noninvasive FFR or noninvasive fractional flow reserve or non-invasive FFR or non-invasive fractional flow reserve).mp. (0) 2 exp Fractional Flow Reserve, Myocardial/ or (Fractional Flow Reserve or FFR).mp. (1) 3 [exp Computed Tomography Angiography/] (0) 4 (Computed Tomography Angiogra* or CCTA or coronary CT angiogra* or CT coronary angiogra*).mp. (15) 5 or/3-4 (15) 6 2 and 5 (0)

	7 1 or 6 (0) ***************************

2. Systematic reviews currently under development (forthcoming reviews & protocols) **Date Searched: 2/7/19**	
Sources:	**Strategy:**
[PROSPERO](https://www.crd.york.ac.uk/PROSPERO/) (SR registry)	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA Relevant Results: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=96660
DoPHER (SR Protocols)	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA

3. Current Guidelines **Date Searched: 1/17/19**	
Sources:	**Strategy:**
VA/DoD Clinical Practice Guidelines	NA
Guideline Central	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA
The American College of Cardiology	Search: heartflow; FFFRct; fractional flow reserve; non-invasive CAD imaging; Coronary Computed Tomography Angiography; coronary CT angiography; CCTA

4. Current primary literature (limited to 2017 forward) **Date Searched: 2/7/19**	
Sources:	**Strategy:**
MEDLINE	Search: Relevant Results: Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 06, 2019> Search Strategy: -- 1 (HeartFlow or FFFRct or CT-FFR or CT-based FFR or FFR CT or noninvasive FFR or noninvasive fractional flow reserve or non-invasive FFR or non-invasive fractional flow reserve).mp. (140) 2 exp Fractional Flow Reserve, Myocardial/ or (Fractional Flow Reserve or FFR).mp. (3728) 3 exp Computed Tomography Angiography/ (6063) 4 (Computed Tomography Angiogra* or CCTA or coronary CT angiogra* or CT coronary angiogra*).mp. (14309) 5 or/3-4 (14309) 6 2 and 5 (397) 7 1 or 6 (431) 8 limit 7 to yr="2017 -Current" (215) 9 limit 8 to english language (210)

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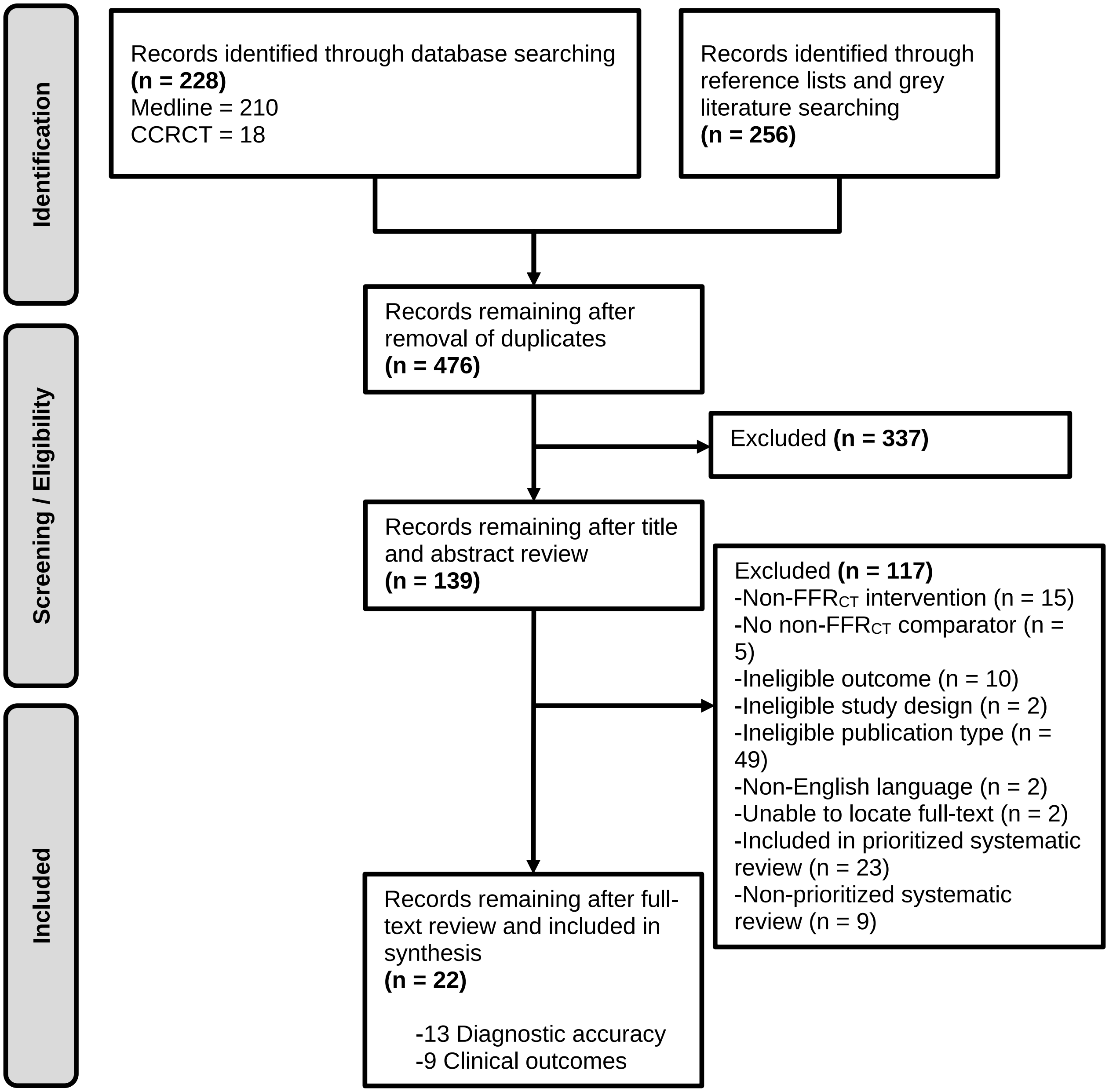
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2018> Search Strategy: -- 1 (HeartFlow or FFFRct or CT-FFR or CT-based FFR or FFR CT or noninvasive FFR or noninvasive fractional flow reserve or non-invasive FFR or non-invasive fractional flow reserve).mp. (19) 2 exp Fractional Flow Reserve, Myocardial/ or (Fractional Flow Reserve or FFR).mp. (427) 3 exp Computed Tomography Angiography/ (0) 4 (Computed Tomography Angiogra* or CCTA or coronary CT angiogra* or CT coronary angiogra*).mp. (885) 5 or/3-4 (885) 6 2 and 5 (40) 7 1 or 6 (47) 8 limit 7 to yr="2017 -Current" (19) 9 limit 8 to english language (18) ***************************
Heartflow.com	NA

5. Primary literature currently under development (forthcoming studies & protocols) Date Searched: 2/7/19	
Sources:	**Strategy:**
Clinicaltrials.gov	Search: heartflow; FFFRct

APPENDIX B. PRISMA DIAGRAM



APPENDIX C. LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible setting, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review, 9=Non-English language, 10=Unable to retrieve full text, 11=Trial included in prioritized systematic review

#	Citation	Exclude reason
1	Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain. 2017.	E7
2	Noninvasive computed fractional flow reserve from computed tomography (FFRCT) for coronary artery disease. *Centre for Reviews and Dissemination.* 2017.	E10
3	ACR–NASCI–SPR Practice Parameter for the Performance and Interpretation of Cardiac Computed Tomography (CT). 2017.	E2
4	ACR–NASCI–SPR Practice Parameter for the Performance of Quantification of Cardiovascular Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). 2017.	E2
5	Al-Mallah MH, Ahmed AM. Controversies in the Use of Fractional Flow Reserve Form Computed Tomography (FFRCT) vs. Coronary Angiography. *Current Cardiovascular Imaging Reports.* 2016;9(12).	E7
6	Andreini D, Mushtaq S, Pontone G, Rogers C, Pepi M, Bartorelli AL. Severe in-stent restenosis missed by coronary CT angiography and accurately detected with FFR_{CT}. *The International Journal of Cardiovascular Imaging.* 2017;33(1):119-120.	E6
7	Artzner C, Daubert M, Ehieli W, et al. Impact of computed tomography (CT)-derived fractional flow reserve on reader confidence for interpretation of coronary CT angiography. *European Journal of Radiology.* 2018;108:242-248.	E4
8	Ball C, Pontone G, Rabbat M. Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography Datasets: The Next Frontier in Noninvasive Assessment of Coronary Artery Disease. *Biomedical Research International.* 2018;2018:2680430.	E7
9	Baumann S, Becher T, Schoepf UJ, et al. Fractional flow reserve derived by coronary computed tomography angiography : A sophisticated analysis method for detecting hemodynamically significant coronary stenosis. *Herz.* 2017;42(6):604-606.	E7
10	Baumann S, Lossnitzer D, Renker M, Borggrefe M, Akin I. Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve Assessment: Many Roads to Reach the Same Goal. *Circulation Journal.* 2018;82(9):2448.	E7
11	Baumann S, Renker M, Akin I, Borggrefe M, Schoepf UJ. FFR-Derived From Coronary CT Angiography Using Workstation-Based Approaches. *Jacc: Cardiovascular Imaging.* 2017;10(4):497-498.	E7
12	Benton SM, Tesche C, De Cecco CN, Duguay TM, Schoepf UJ, Bayer RR, II. Noninvasive Derivation of Fractional Flow Reserve From Coronary Computed Tomographic Angiography: A Review. *Journal of Thoracic Imaging.* 2018;33(2):88-96.	E7
13	Bernhardt P, Walcher T, Rottbauer W, Wohrle J. Quantification of myocardial perfusion reserve at 1.5 and 3.0 Tesla: a comparison to fractional flow reserve. *International Journal of Cardiovascular Imaging.* 2012;28(8):2049-2056.	E2
14	Bilbey N, Blanke P, Naoum C, Arepalli CD, Norgaard BL, Leipsic J. Potential	E6

	impact of clinical use of noninvasive FFRCT on radiation dose exposure and downstream clinical event rate. *Clinical Imaging.* 2016;40(5):1055-1060.	
15	Cademartiri F, Seitun S, Clemente A, et al. Myocardial blood flow quantification for evaluation of coronary artery disease by computed tomography. *Cardiovascular Diagnosis & Therapy.* 2017;7(2):129-150.	E7
16	Cheruvu C, Naoum C, Blanke P, Norgaard B, Leipsic J. Beyond Stenosis With Fractional Flow Reserve Via Computed Tomography and Advanced Plaque Analyses for the Diagnosis of Lesion-Specific Ischemia. *Canadian Journal of Cardiology.* 2016;32(11):e1-1315.	E7
17	Chinnaiyan KM, Akasaka T, Amano T, et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFRCT in Coronary Care (ADVANCE) registry. *Journal of Cardiovascular Computed Tomography.* 2017;11(1):62-67.	E7
18	Chung JH, Lee KE, Nam CW, et al. Diagnostic Performance of a Novel Method for Fractional Flow Reserve Computed from Noninvasive Computed Tomography Angiography (NOVEL-FLOW Study). *American Journal of Cardiology.* 2017;120(3):362-368.	E11
19	Coenen A, Lubbers MM, Kurata A, et al. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology.* 2015;274(3):674-683.	E11
20	Coenen A, Rossi A, Lubbers MM, et al. Integrating CT Myocardial Perfusion and CT-FFR in the Work-Up of Coronary Artery Disease. *JACC Cardiovasc Imaging.* 2017;10(7):760-770.	E11
21	Curzen NP, Nolan J, Zaman AG, Norgaard BL, Rajani R. Does the routine availability of CT-Derived FFR influence management of patients with stable chest pain compared to CT angiography alone?: The FFRCT RIPCORD Study. *JACC Cardiovascular Imaging.* 2016;9(10):1188-1194.	E11
22	De Geer J, Sandstedt M, Björkholm A, et al. Software-based on-site estimation of fractional flow reserve using standard coronary CT angiography data. *Acta Radiologica.* 2016;57(10):1186-1192.	E11
23	Donnelly PM, Kolossváry M, Karády J, et al. Experience With an On-Site Coronary Computed Tomography-Derived Fractional Flow Reserve Algorithm for the Assessment of Intermediate Coronary Stenoses. *American Journal of Cardiology.* 2018;121(1):9-13.	E11
24	Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *New England Journal of Medicine.* 2015;372(14):1291-1300.	E2
25	Duguay TM, Tesche C, Vliegenthart R, et al. Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve Based on Machine Learning for Risk Stratification of Non-Culprit Coronary Narrowings in Patients with Acute Coronary Syndrome. *American Journal of Cardiology.* 2017;120(8):1260-1266.	E4
26	Eckert J. Coronary CTA with FFRCT: a safe strategy for diagnosis of CAD? *Kardiologe.* 2016;10(6):336-338.	E9
27	Eftekhari A, Min J, Achenbach S, et al. Fractional flow reserve derived from coronary computed tomography angiography: diagnostic performance in hypertensive and diabetic patients. *European Heart Journal Cardiovascular Imaging.* 2017;18(12):1351-1360.	E11
28	Fearon WF, Lee JH. Pulling the RIPCORD: FFRCT to Improve Interpretation of Coronary CT Angiography∗. *JACC: Cardiovascular Imaging.* 2016;9(10):1195-1197.	E7
29	Feldmann K, Cami E, Safian RD. Planning percutaneous coronary interventions	E7

	using computed tomography angiography and fractional flow reserve-derived from computed tomography: A state-of-the-art review. *Catheterization and Cardiovascular Interventions.* 2018.	
30	Fordyce CB, Douglas PS. Optimal non-invasive imaging test selection for the diagnosis of ischaemic heart disease. *Heart.* 2016;102(7):555-564.	E7
31	Fordyce CB, Newby DE, Douglas PS. Diagnostic strategies for the evaluation of chest pain clinical implications from SCOT-HEART and PROMISE. *Journal of the American College of Cardiology.* 2016;67(7):843-852.	E7
32	Gaur S, Achenbach S, Leipsic J, et al. Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) study. *Journal of Cardiovascular Computed Tomography.* 2013;7(5):279-288.	E7
33	Gaur S, Bezerra HG, Lassen JF, et al. Fractional flow reserve derived from coronary CT angiography: variation of repeated analyses. *Journal of Cardiovascular Computed Tomography.* 2014;8(4):307-314.	E4
34	Gaur S, Øvrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *European Heart Journal.* 2016;37(15):1220-1227.	E4
35	Giannopoulos AA, Tang A, Ge Y, et al. Diagnostic performance of a Lattice Boltzmann-based method for CT-based fractional flow reserve. *Eurointervention.* 2018;13(14):1696-1704.	E11
36	Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). *Journal of the American College of Cardiology.* 2012;59(5):462-474.	E2
37	Hecht HS, Narula J, Fearon WF. Fractional Flow Reserve and Coronary Computed Tomographic Angiography: A Review and Critical Analysis. *Circulation Research.* 2016;119(2):300-316.	E7
38	Hulten E, Blankstein R, Di Carli MF. The value of noninvasive computed tomography derived fractional flow reserve in our current approach to the evaluation of coronary artery stenosis. *Current Opinion in Cardiology.* 2016;31(6):670-676.	E7
39	Hulten E, Di Carli MF. FFRCT: Solid PLATFORM or Thin Ice? *Journal of the American College of Cardiology.* 2015;66(21):2324-2328.	E7
40	Hulten EA. Does FFRCT have proven utility as a gatekeeper prior to invasive angiography? *Journal of Nuclear Cardiology.* 2017;24(5):1619-1625.	E7
41	Hwang D, Lee JM, Koo BK. Physiologic assessment of coronary artery disease: Focus on fractional flow reserve. *Korean Journal of Radiology.* 2016;17(3):307-320.	E7
42	Kawaji T, Shiomi H, Morishita H, et al. Feasibility and diagnostic performance of fractional flow reserve measurement derived from coronary computed tomography angiography in real clinical practice. *International Journal of Cardiovascular Imaging.* 2017;33(2):271-281.	E11
43	Kerut EK, Turner M. Fractional flow reserve-CT assessment of coronary stenosis. *Echocardiography.* 2018;35(5):730-732.	E7
44	Kim HJ, Vignon-Clementel IE, Coogan JS, Figueroa CA, Jansen KE, Taylor CA. Patient-specific modeling of blood flow and pressure in human coronary arteries. *Annals of Biomedical Engineering.* 2010;38(10):3195-3209.	E2
45	Kim KH, Doh JH, Koo BK, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovascular Interventions.* 2014;7(1):72-78.	E11

46	Kitabata H, Leipsic J, Patel MR, et al. Incidence and predictors of lesion-specific ischemia by FFRCT: Learnings from the international ADVANCE registry. *Journal of Cardiovascular Computed Tomography.* 2018;12(2):95-100.	E4
47	Knaapen P. FFR_{CT} Versus SPECT to Diagnose Coronary Artery Disease: Toward a Tailored Approach. *Jacc: Cardiovascular Imaging.* 2018;11(11):1651-1653.	E7
48	Ko BS, Cameron JD, Munnur RK, et al. Noninvasive CT-Derived FFR Based on Structural and Fluid Analysis: A Comparison With Invasive FFR for Detection of Functionally Significant Stenosis. *JACC: Cardiovascular Imaging.* 2017;10(6):663-673.	E11
49	Ko BS, Wong DT, Norgaard BL, et al. Diagnostic Performance of Transluminal Attenuation Gradient and Noninvasive Fractional Flow Reserve Derived from 320-Detector Row CT Angiography to Diagnose Hemodynamically Significant Coronary Stenosis: An NXT Substudy. *Radiology.* 2016;279(1):75-83.	E11
50	Kolossváry M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT-A comprehensive review on coronary CT angiography based risk assessment. *Cardiovascular Diagnosis and Therapy.* 2017;7(5):489-506.	E7
51	Koo B-K, Erglis A, Doh J-H, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) Study. *Journal of the American College of Cardiology.* 2011;58(19):1989-1997.	E11
52	Kueh SH, Boroditsky M, Leipsic J. Fractional flow reserve computed tomography in the evaluation of coronary artery disease. *Cardiovascular Diagnosis and Therapy.* 2017;7(5):463-474.	E7
53	Leber WA. Is FFR-CT a “game changer” in the diagnostic management of stable coronary artery disease? *Herz.* 2016;41(5):398-404.	E7
54	Lee JH, Hartaigh BÓ, Han D, Rizvi A, Lin FY, Min JK. Fractional flow reserve measurement by computed tomography: An alternative to the stress test. *Interventional Cardiology Review.* 2016;11(2):105-109.	E7
55	Leipsic J, Weir-McCall J, Blanke P. FFR_{CT} for Complex Coronary Artery Disease Treatment Planning: New Opportunities. *Interventional Cardiology.* 2018;13(3):126-128.	E7
56	Leipsic JA, Koweek LH. CT fractional flow reserve for stable coronary artery disease: The ongoing journey. *Radiology.* 2018;287(1):85-86.	E7
57	Liu X, Peng C, Xia Y, et al. Hemodynamics analysis of the serial stenotic coronary arteries. *BioMedical Engineering Online.* 2017;16(1).	E2
58	Lobanova I, Qureshi AI. Editorial to 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease. *Cardiovascular Diagnosis and Therapy.* 2017;7:S115-S118.	E7
59	Lu MT, Ferencik M, Roberts RS, et al. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. *JACC: Cardiovascular Imaging.* 2017;10(11):1350-1358.	E4
60	Mangla A, Oliveros E, Williams KA, Sr., Kalra DK. Cardiac Imaging in the Diagnosis of Coronary Artery Disease. *Current Problems in Cardiology.* 2017;42(10):316-366.	E7
61	Mastrodicasa D, Albrecht MH, Schoepf UJ, et al. Artificial intelligence machine learning-based coronary CT fractional flow reserve (CT-FFR_{ML}): Impact of iterative and filtered back projection reconstruction techniques. *Journal of Cardiovascular Computed Tomography.* 2018.	E3
62	Mathew RC, Gottbrecht M, Salerno M. Computed Tomography Fractional Flow	E7

	Reserve to Guide Coronary Angiography and Intervention. *Interventional Cardiology Clinics.* 2018;7(3):345-354.	
63	Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA.* 2012;308(12):1237-1245.	E11
64	Min JK, Taylor CA, Achenbach S, et al. Noninvasive fractional flow reserve derived from coronary CT angiography clinical data and scientific principles. *JACC: Cardiovascular Imaging.* 2015;8(10):1209-1222.	E7
65	Miyoshi T, Osawa K, Ito H, et al. Non-invasive computed fractional flow reserve from computed tomography (CT) for diagnosing coronary artery disease - Japanese results from NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *Circ J.* 2015;79(2):406-412.	E11
66	Mordi IR, Badar AA, John Irving R, Weir-McCall JR, Houston JG, Lang CC. Efficacy of noninvasive cardiac imaging tests in diagnosis and management of stable coronary artery disease. *Vascular Health and Risk Management.* 2017;13:427-437.	E7
67	Nakanishi R, Budoff MJ. Noninvasive FFR derived from coronary CT angiography in the management of coronary artery disease: Technology and clinical update. *Vascular Health and Risk Management.* 2016;12:269-278.	E7
68	Nakazato R, Park HB, Gransar H, et al. Additive diagnostic value of atherosclerotic plaque characteristics to non-invasive FFR for identification of lesions causing ischaemia: results from a prospective international multicentre trial. *EuroIntervention.* 2016;12(4):473-481.	E2
69	Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circulation Cardiovascular Imaging.* 2015;8(3).	E2
70	NICE. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography : Tools and resources. 2017.	E7
71	NICE. QAngio XA 3D/QFR imaging software for assessing coronary obstructions - medtech innovation briefing (MIB146). 2018.	E2
72	Norgaard BL, Botker HE, Jensen JM. Recent controversy regarding the accuracy of CT-FFR. The truth is out there. *Journal of Cardiovascular Computed Tomography.* 2018;12(1):e1.	E7
73	Norgaard BL, Gaur S, Leipsic J, et al. Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. *JACC Cardiovasc Imaging.* 2015;8(9):1045-1055.	E11
74	Nørgaard BL, Jensen JM, Blanke P, Sand NP, Rabbat M, Leipsic J. Coronary CT Angiography Derived Fractional Flow Reserve: The Game Changer in Noninvasive Testing. *Current Cardiology Reports.* 2017;19(11).	E7
75	Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *Journal of the American College of Cardiology.* 2014;63(12):1145-1155.	E11
76	Norgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT Angiographic and Flow Reserve-Guided Management of Patients With Stable Ischemic Heart Disease. *Journal of the American College of Cardiology.* 2018;72(18):2123-2134.	E3
77	Osawa K, Miyoshi T, Miki T, et al. Coronary lesion characteristics with mismatch between fractional flow reserve derived from CT and invasive catheterization in clinical practice. *Heart & Vessels.* 2017;32(4):390-398.	E11
78	Otake H, Taylor CA, Matsuo H, Tanaka N, Akasaka T. Noninvasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography - Is	E7

	This Just Another New Diagnostic Test or the Long-Awaited Game Changer? *Circulation Journal.* 2017;81(8):1085-1093.	
79	Packard RR, Li D, Budoff MJ, Karlsberg RP. Fractional flow reserve by computerized tomography and subsequent coronary revascularization. *European Heart Journal Cardiovascular Imaging.* 2017;18(2):145-152.	E4
80	Pontone G, Andreini D, Guaricci AI, et al. Rationale and design of the PERFECTION (comparison between stress cardiac computed tomography PERfusion versus Fractional flow rEserve measured by Computed Tomography angiography In the evaluation of suspected cOroNary artery disease) prospective study. *Journal of Cardiovascular Computed Tomography.* 2016;10(4):330-334.	E7
81	Pontone G, Carita P, Verdecchia M, et al. Fractional flow reserve: Lessons from PLATFORM and future perspectives. *Minerva Cardioangiologica.* 2017;65(3):235-251.	E7
82	Pontone G, Muscogiuri G, Andreini D, et al. The New Frontier of Cardiac Computed Tomography Angiography: Fractional Flow Reserve and Stress Myocardial Perfusion. *Current Treatment Options in Cardiovascular Medicine.* 2016;18(12).	E7
83	Rabbat M, Kauh B, Pontone G, Norgaard B, Lopez J, Mathew V. Fractional flow reserve derived from coronary computed tomography safely reduces invasive coronary angiography rates and cost in patients with stable coronary artery disease. *Journal of the American College of Cardiology.* 2017;69(11 Supplement):72.	E7
84	Rajani R, Modi B, Ntalas I, Curzen N. Non-invasive fractional flow reserve using computed tomographic angiography: Where are we now and where are we going? *Heart.* 2017;103(15):1216-1222.	E7
85	Rajani R, Webb J, Marciniak A, Preston R. Comparative efficacy testing - fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain. *Int J Cardiol.* 2015;183:173-177.	E4
86	Renker M, Schoepf UJ, Becher T, et al. Computed tomography in patients with chronic stable angina: Fractional flow reserve measurement. *Herz.* 2017;42(1):51-57.	E9
87	Renker M, Schoepf UJ, Wang R, et al. Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve. *American Journal of Cardiology.* 2014;114(9):1303-1308.	E11
88	Roobottom C. Radical changes to the investigation of stable chest pain following the 2016 NICE update. *British Journal of Radiology.* 2018;91(1087).	E10
89	Ropp A, White C. Current and Future Applications of Coronary CT Angiography with and Without FFR in the Emergency Room. *Current Cardiovascular Imaging Reports.* 2016;9(11).	E7
90	Schuijf JD, Ko BS, Di Carli MF, et al. Fractional flow reserve and myocardial perfusion by computed tomography: A guide to clinical application. *European Heart Journal Cardiovascular Imaging.* 2018;19(2):127-135.	E7
91	Sevag Packard RR, Karlsberg RP. Integrating FFRCT Into Routine Clinical Practice: A Solid PLATFORM or Slippery Slope?∗. *Journal of the American College of Cardiology.* 2016;68(5):446-449.	E7
92	Shah AB, Kirsch J, Bolen MA, et al. ACR Appropriateness Criteria((R)) Chronic Chest Pain-Noncardiac Etiology Unlikely-Low to Intermediate Probability of Coronary Artery Disease. *Journal of the American College of Radiology.* 2018;15(11S):S283-S290.	E7
93	Shi C, Zhang D, Cao K, et al. A study of noninvasive fractional flow reserve derived from a simplified method based on coronary computed tomography	E11

	angiography in suspected coronary artery disease. *Biomedical Engineering Online.* 2017;16(1):43.	
94	Sigurdsson G. Improved Precision of Initial Chest Pain Evaluation With Fractional Flow Reserve Computed Tomography. *Journal of the American Heart Association.* 2017;6(8):22.	E7
95	Siontis GC, Mavridis D, Greenwood JP, et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ.* 2018;360:k504.	E2
96	Skelly AC, Hashimoto R, Buckley DI, et al. Noninvasive Testing for Coronary Artery Disease. In: *AHRQ Comparative Effectiveness Reviews.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.	E2
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APPENDIX D. EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Data Abstraction of Primary Studies Evaluating Diagnostic Accuracy

Author Year N	Population (high, intermediate, or low risk CAD, other diagnoses)	FFR_{CT} Details (HeartFlow or other software)	Index Test	FFR_{CT} Outcomes (per vessel, if reported) Sensitivity (95% CI) Specificity (95% CI)	Trial Name
Driessen, 2019[1] 157	Patients with suspected stable CAD and who underwent CCTA, SPECT, PET, and FFR	HeartFlow	Invasive FFR	Per Vessel: Sensitivity: 90 (84-95) Specificity: 86 (82-89)	PACIFIC Study
Pontone, 2018[2] 147	Symptomatic patients scheduled for clinically indicated ICA+invasive FFR	HeartFlow	Invasive FFR	Per Vessel: Sensitivity: 88 (82-94) Specificity: 94 (91-96) Per Patient: Sensitivity: 90 (83-98) Specificity: 85 (77-93)	PERFECTION Study
Sand, 2018[3] 143	Patients with stable angina pectoris and suspected CAD	HeartFlow	Invasive FFR	Per Patient: Sensitivity: 91 (81-97) Specificity: 55 (44-66)	ReASSESS Study
Rother, 2018[4] 71	Patients with suspected CAD and who subsequently underwent invasive coronary angiography with FFR measurement	Other: cFFR version 3.0, Siemens Healthineers, Forchheim, Germany	Invasive FFR	Per Vessel: Sensitivity: 91 (70-99) Specificity: 96 (88-99)	None
Wardziak, 2019[5] 90	Patients with intermediate pre-test probability of CAD	Other: cFFRv2.1, Siemens	Invasive FFR	Per Vessel: Sensitivity: 70 (95% CI NR) Specificity: 67 (95% CI NR)	None
Hu, 2018[6] 105	Patients with intermediate coronary lesions	Other: Machine Learning-based FFR_{CT}	Invasive FFR	Per Vessel: Sensitivity: 61 (44-78) Specificity: 91 (85-98)	None
Nous, 2019[7] 351	Patients with and without diabetes mellitus with suspected CAD	Other: Machine Learning-based FFR_{CT} (cFFR version 2.1, Siemens Healthineers, Forchheim, Germany)	Invasive FFR	Per Vessel: Non-diabetes: Sensitivity: 79 (73-86) Specificity: 72 (66-78) Diabetes:	MACHINE Consortium

Author Year N	Population (high, intermediate, or low risk CAD, other diagnoses)	FFR_{CT} Details (HeartFlow or other software)	Index Test	FFR_{CT} Outcomes (per vessel, if reported) Sensitivity (95% CI) Specificity (95% CI)	Trial Name
				Sensitivity: 88 (77-98) Specificity: 80 (70-90)	
Fujimoto, 2018[8] 75	Patients without known CAD in whom CAD was suspected	Other: Novel algorithm employing fluid structure interaction	Invasive FFR	Per Vessel: Sensitivity: 90.9 (78.3-97.5) Specificity: 78.3 (65.8-87.9)	None
Ihdayhid, 2018[9] 46	Patients with suspected CAD	Other: Reduced-order FFR_{CT}	Invasive FFR	Per Vessel: Sensitivity: 81 (62-94) Specificity: 84 (71-92)	None
Kishi, 2018[10] 61	Patients with a lesion of intermediate-diameter stenosis (25%–69%) at CCTA who underwent FFR measurement within 90 days.	Other: Three different computational fluid dynamics-based FFR_{CT} algorithms. Toshiba Cardiac Analysis Package, Toshiba Medical Systems	Invasive FFR	Murray Law: Per Vessel: Sensitivity: 90.9 (73.9-98.3) Specificity: 82.1 (72.4-86.2) Huo-Kassab Rule: Per Vessel: Sensitivity: 86.4 (69.0-96.0) Specificity: 84.6 (74.8-90.0) TAG: Per Vessel: Sensitivity: 94.9 (85.9-99.0) Specificity: 86.4 (70.5-93.6)	None
Coenen, 2018[11] 351	Patients receiving CCTA and invasive FFR at 5 study sites without complicated invasive FFR pressure wire position, non-diagnostic CCTA image quality and incomplete CTA coverage	Other: Machine Learning- or computational fluid dynamics-based FFR_{CT}. cFFR version 1.4, Siemens Healthcare GmbH	Invasive FFR	ML-based: Per Vessel: Sensitivity: 81 (75-86) Specificity: 76 (71-81) CFD-based: Per Vessel: Sensitivity: 82 (77-87) Specificity: 76 (71-81)	MACHINE Consortium

Abbreviations: CAD – coronary artery disease; CCTA – coronary computed tomography angiography; CFD – computational fluid dynamics; FFR – fractional flow reserve; FFR_{CT} – fractional flow reserve using computed tomography; ICA – invasive coronary angiography; ML – machine-learning; PET – positron emission tomography; SPECT – single-photon emission computed tomography; TAG – transluminal attenuation gradient

Data Abstraction of Primary Studies Evaluating Other Outcomes

Author, Year Trial Name Study Design N	Population (high, intermediate, or low risk CAD, other diagnoses)	FFR_{CT} Details (HeartFlow or other software); Comparator	Clinical Outcomes (planned ICA with no significant obstructive CAD)	MACE outcomes: death, myocardial infarction, etc.	Other adverse events	Cost outcomes	QoL Outcomes
Colleran, 2017[12] PLATFORM (German sub-analysis) Prospective cohort 116	Patients with intermediate likelihood of obstructive CAD, without known CAD	HeartFlow; Usual care	ICA with no obstructive CAD: 7.7% FFR_{CT} vs 85.9% usual care	None	No adverse clinical events at 1 year in patients with cancelled ICA based on FFR_{CT} results Radiation exposure significantly lower in FFR_{CT} cohort compared to usual care cohort	Mean 1 year of patient cost significantly lower in FFR_{CT} vs usual care group	Greater improvement in QoL scores in FFR_{CT} group vs usual care (EQ-5D score)
Douglas, 2016[13] PLATFORM Prospective cohort 584	Symptomatic patients with intermediate likelihood of obstructive CAD, without known CAD	HeartFlow; Usual care	Same as Douglas 2015	2 in each arm of the planned invasive group; 1 in the planned non-invasive group	No adverse clinical events at 1 year in patients with cancelled ICA based on FFR_{CT} results	In the planned invasive stratum, mean 1 year of patient cost was 33% lower in FFR_{CT} vs usual care group In the planned noninvasive stratum, mean 1 year of patient cost did not differ when using an FFR_{CT} cost weight of zero, but were higher when using an FFR_{CT} cost weight equal to CCTA	QoL scores similar at 1 year for both groups; in the noninvasive stratum, QoL had higher mean change in FFR_{CT} group vs usual care group

Author, Year Trial Name Study Design N	**Population (high, intermediate, or low risk CAD, other diagnoses)**	**FFR_{CT} Details (HeartFlow or other software); Comparator**	**Clinical Outcomes (planned ICA with no significant obstructive CAD)**	**MACE outcomes: death, myocardial infarction, etc.**	**Other adverse events**	**Cost outcomes**	**QoL Outcomes**
Douglas, 2015[14] PLATFORM Prospective cohort 584	Symptomatic patients with intermediate likelihood of obstructive CAD, without known CAD	HeartFlow; Usual care	Planned ICA group: ICA with no obstructive CAD at 90 days: 12% CCTA/ FFR_{CT} vs 73% usual care 61% (95% CI 53.0 – 68.7; *P*<.0001)	2 MACE events in the planned ICA group; none in the planned non-invasive group	Cumulative radiation exposure to 90 days was similar in FFR_{CT} cohort as usual care cohort No difference in rates of revascularization between cohorts and arms	Not reported	Not reported
Fairbairn, 2018[15] ADVANCE Registry cohort 5,083	Clinically stable patients with symptoms for CAD and atherosclerosis	HeartFlow; CCTA	Reclassification between core lab CCTA alone and CCTA plus FFR_{CT}-based management plans occurred in 66.9% (95% CI 64.8 – 67.6) of patients	No death/myocardial infarction occurred within 90 days in FFR_{CT} >0.80 19 (0.6%) MACE and 14 (0.3%) death/MI occurred in subjects with FFR_{CT} $\leq$0.80	None	Not examined	Not examined
Hlatky, 2015[16] PLATFORM Prospective cohort 584	Symptomatic patients with intermediate likelihood of obstructive CAD, without known CAD 74% had atypical angina; pre-test probability of coronary disease was 49%	HeartFlow; Usual care	Not reported	Not reported	Not reported	In the planned ICA stratum, mean costs 32% lower among FFR_{CT} cohort vs usual care cohort In the noninvasive stratum, mean costs were not significantly different between FFR_{CT} cohort vs usual care cohort	In the planned ICA stratum, QoL scores were similar between FFR_{CT} and usual care cohorts In the noninvasive stratum, QoL scores improved more in FFR_{CT} cohort vs usual care cohort

Author, Year Trial Name Study Design N	Population (high, intermediate, or low risk CAD, other diagnoses)	FFR_{CT} Details (HeartFlow or other software); Comparator	Clinical Outcomes (planned ICA with no significant obstructive CAD)	MACE outcomes: death, myocardial infarction, etc.	Other adverse events	Cost outcomes	QoL Outcomes
Jang, 2016[17] None Retrospective cohort 75	Patients with CCTA	HeartFlow; CCTA alone	FFR_{CT} changed clinical management in 55% of patients and potentially reduced the need for ICA by 48%	No significant difference in 1-year cardiovascular events between patients with changed vs unchanged management after FFR_{CT}	None	Not examined	Not examined
Jensen, 2018[18] None Retrospective cohort 774	Symptomatic patients of varying risk with suspected stable CAD	HeartFlow; CCTA	Overall, in high-risk patients having CCTA+FFR_{CT} performed, ICA was cancelled in 75% (115/153).	4 serious clinical events occurred, but not in any patients with cancelled ICA by CCTA with selective FFR_{CT} testing	Not reported	Not examined	Not examined

Author, Year Trial Name Study Design N	Population (high, intermediate, or low risk CAD, other diagnoses)	FFR_{CT} Details (HeartFlow or other software); Comparator	Clinical Outcomes (planned ICA with no significant obstructive CAD)	MACE outcomes: death, myocardial infarction, etc.	Other adverse events	Cost outcomes	QoL Outcomes
Norgaard, 2017[19] None Retrospective cohort 3,523	Symptomatic patients with suspected CAD	HeartFlow; MPI	Downstream ICA utilization: fewer for FFR_{CT} vs comparator (absolute risk difference: -4.2; 95% CI -6.9 – -1.6; *P*=.002) Planned ICA with no obstructive CAD: decreased for FFR_{CT} vs comparator (-12.8%; 95% CI -22.2 – -3.4; *P*=.008) Rate of revascularization: increased for FFR_{CT} vs comparator (14.1%; 95% CI 3.3 – 24.9; *P*=.01)	Not reported	None	Not examined	Not examined
Norgaard, 2017c[20] None Retrospective cohort 1,248	Symptomatic patients with suspected CAD and intermediate-range coronary lesions	HeartFlow; CCTA	Not reported	No patients having FFR_{CT}, ICA, or MPI performed experienced a MACE during follow-up, including the 123 (66%) patients with FFR_{CT} >0.80 in whom ICA was deferred.	Radiation exposure	Not examined	Not examined

Abbreviations: CAD – coronary artery disease; CCTA – coronary computed tomography angiography; CI – confidence interval; EQ-5D – EuroQOL scale; FFRCT – fractional flow reserve using computed tomography; HR – hazards ratio; ICA – invasive coronary angiography; MACE – major adverse cardiovascular event; MI – myocardial infarction; MPI – myocardial perfusion imaging; QoL – quality of life

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of Diagnostic Accuracy Studies Using QUADAS-2

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Overall risk of bias
Driessen, 2019[1]	Low Consecutively selected patients with stable new-onset chest pain and suspected CAD	Low Researcher extracting FFR_{CT} values knew placement of pressure wire, but blinded to values	Low FFR gold standard functional assessment. Cardiologists blinded to CCTA, FFR_{CT} results	Low 83% of vessels evaluated by index test and reference standard	Low
Pontone, 2018[2]	Low Consecutive patients with suspected CAD referred for non-emergent, clinically indicated ICA	Low CCTA datasets sent to HeartFlow. The index test was conducted by a 3rd party, off-site, and blinded to the reference standard.	Low FFR gold standard functional assessment. Cardiologists blinded to CCTA, FFR_{CT} results	Unclear All patients underwent ICA, but invasive FFR measured in only 67%. 98% of patients had FFR_{CT}.	Unclear
Sand, 2018[3]	Unclear Patients with stable chest pain without known CAD and presence of at least 1 coronary stenosis of 40%-90% by CCTA	Low Researchers had information about lesions of interest on CCTA, but blinded to other clinical data.	Low FFR gold standard functional assessment. Cardiologists blinded to CCTA, FFR_{CT} results	Low 97% of patients had both tests	Unclear

Abbreviations: CAD – coronary artery disease; CCTA – coronary computed tomography angiography; FFR – fractional flow reserve; FFR_{CT} – fractional flow reserve using computed tomography; ICA – invasive coronary angiography

Quality Assessment of Observational Studies Using ROBINS-I

Author, Year	Selection bias (High, Low, Unclear)	Bias in classification of interventions (High, Low, Unclear)	Bias due to departures from intended interventions (High, Low, Unclear)	Bias due to measurement of outcomes? (High, Low, Unclear)	Bias due to confounding? (High, Low, Unclear)	Bias due to missing data? (High, Low, Unclear)	Bias in the selection of reported results (High, Low, Unclear)	Overall bias (High, Low, Unclear)
Douglas, 2015[14]/2016[13]; Hlatky, 2015[16]; Colleran, 2017[12]	Low Consecutive selection of participants into 2 cohorts. Follow-up from study entry	Low Intervention groups clearly defined prior to measurement of outcomes.	Low All patients received planned usual care or CCTA. 10%-12% of requested FFR_{CT} could not be completed	Low ICA determined by independent core laboratory. MACE data adjudicated by independent committee	Low Groups well-balanced; propensity score-matched groups yielded similar results	Low 95%-100% follow-up. All participants included in analyses.	Low Prespecified outcomes reported	Low
Fairbairn, 2018[15]	Unclear Consecutive selection of participants meeting inclusion criteria. Excluded patients with unclear CCTA results.	Low All patients had CCTA and those with stenosis 30-90% had FFR_{CT}	Low 96% of patients with CCTA had FFR_{CT}	Unclear Core laboratory knew management plan for CCTA when making management plan for CCTA+ FFR_{CT}	Low Same patients getting CCTA and CCTA+ FFR_{CT}	Low All of those with CCTA+ FFR_{CT} had management plans re-evaluated	Low Prespecified outcomes reported	Unclear
Jensen, 2018[18]	Low All patients referred for non-emergent ICA or CCTA	Unclear Unclear who got FFR_{CT} and how that was determined	Unclear Unclear who got FFR_{CT} and how that was determined	Unclear Unclear how outcomes were obtained	Unclear Data on who patients who got FFR_{CT} and those who didn't not reported	Low Included all patients in analysis	Low Prespecified outcomes reported	Unclear
Norgaard, 2017[19]	Low Consecutive cohorts of patients with suspected CAD	Low Intervention groups defined by time period for the cohorts and standard of practice during the time period	Low FFR_{CT} performed in all but 4.3% of those requested	Unclear Unclear how outcomes were obtained	Unclear Differences in patient groups in the different time periods, but adjusted using propensity score matching	Low Included all patients in analysis	Low Prespecified outcomes reported	Unclear

Abbreviations: CAD – coronary artery disease; CCTA – coronary computed tomography angiography; FFR – fractional flow reserve; FFR_{CT} – fractional flow reserve using computed tomography; ICA – invasive coronary angiography; MACE – major adverse cardiovascular event

APPENDIX E. ONGOING HEARTFLOW STUDIES

PI or Researcher Institution	Study Title Identifier	Summary	Status Estimated completion
David Brown, MD Baylor Research Institute	HeartFlow (AFFECTS) NCT02973126	The overall objective of the AFFECTS Study is to assess agreement between SPECT and FFR_{CT} in identifying vessel-specific, hemodynamically significant CAD in patients scheduled for invasive coronary angiography (ICA) based on abnormal SPECT myocardial perfusion scans. In particular, the study will evaluate the ability of FFR_{CT} to correctly rule out hemodynamically significant CAD in patients with non-significant CAD or normal coronary arteries who had positive SPECT scans.	Recruiting October 2020
Manesh Patel, MD HeartFlow, Inc.	Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care (ADVANCE) NCT02499679	The objective of the HeartFlow ADVANCE Registry is to evaluate utility, clinical outcomes and resource utilization of FFR_{CT}-guided evaluation in clinically stable, symptomatic patients with coronary artery disease (CAD) in order to further inform patients, health care providers, and other stakeholders about which technologies are most effective and efficient in the diagnosis and management of CAD.	Enrolling by invitation February 2021
Pamela S Douglas HeartFlow, Inc.	The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) NCT03702244	PRECISE will evaluate whether a precision evaluation strategy that combines contemporary risk stratification using the PROMISE Risk Tool with functional and anatomic noninvasive evaluation with CCTA with selective FFR_{CT} can improve outcomes over usual care in stable chest pain patients while safely deferring further testing in low-risk patients and reducing cost overall	Not yet recruiting December 2019
Michael Poon, MD HeartFlow, Inc.	The Value of CT Fractional Flow Reserve (VFFRCTA) NCT03026283	This study will assess the capability of FFR_{CT} to enhance performance on both negative and positive predictive value for less experienced readers by providing feedback based on FFR_{CT} evaluation. CCTA readers will be grouped in two categories: those with more than 10 years reading experience and those with less than 10 years reading experience. Each CCTA will be read by a less experienced and a more experienced reader. Results from each reader will be correlated with each other and with the FFR_{CT} and invasive FFR results.	Enrolling by invitation September 2018

Patrick W Serruys, Prof. dr. ECRI bv	A Multicentre, Pilot Study to Evaluate the Safety and the Feasibility of Planning and Execution of Surgical Revascularization in Patients With Complex Coronary Artery Disease, Based Solely on MSCT Imaging Utilizing GE Healthcare Revolution CT and HeartFlow FFR_{CT} (CABGRevolution) NCT03851276	The CABG-REVOLUTION study is an investigator-initiated single-arm, multicenter, prospective study for patients with 3-vessel disease (with or without left-main involvement) referred to CABG treatment. Surgical revascularization strategy and treatment planning will be solely based on MSCT (with FFR_{CT}) without knowledge of the anatomy defined by conventional cine-angiography.	Not yet recruiting January 30, 2020
Bernard De Bruyne, MD, PhD Onze Lieve Vrouw Hospital	Precise Percutaneous Coronary Intervention Plan (P3) Study NCT03782688	The Precise Percutaneous Coronary Intervention (PCI) Plan Study is an investigator-initiated, international and multicenter study of patients with an indication for PCI aiming at assessing the agreement and accuracy of the HeartFlow Planner with invasive FFR as a reference.	Recruiting January 15, 2021
Hiromasa Otake, MD Kobe University	Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR (FORTUNA) NCT03665389	The objective of this study is to evaluate the relationship between FFR derived from FFR_{CT} before transcatheter aortic valve replacement (TAVR) and FFR after TAVR to investigate whether FFR_{CT} is useful for evaluating myocardial ischemia of severe AS. Furthermore, by measuring the instantaneous wave-free ratio (iFR) which is a physiological diagnostic method of coronary artery stenosis before and after TAVR and comparing iFR (iFR before and after TAVR) and FFR (FFR after TAVR) with FFR_{CT} (FFR_{CT} before and after TAVR). It also aims to deepen understanding of resting coronary artery physiology in aortic valve stenosis.	Not yet recruiting March 31, 2022
Bon-Kwon Koo, MD, PhD Seoul National University Hospital	Exploring the Mechanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary CT Angiography and Computational Fluid Dynamics II (EMERALD II) Study (EMERALD II) NCT03591328	The EMERALD II study is a multinational, multicenter, and retrospective study. ACS patients who underwent CCTA from 2 months to 3 years prior to the event will be retrospectively identified. Plaques in the non-culprit vessels will be regarded as a primary control group.	Enrolling by invitation December 31, 2020
Patrick W Serruys, Prof. dr. ECRI bv	Multislice Computed Tomography Assessment of PCSK9 Inhibition on Coronary Perfusion (MARKOV) NCT03851263	The MARKOV study is an investigator-sponsored single arm, prospective study to assess the effect of evolocumab on the improvement in coronary flow (FFR_{CT}) after 18 and 36 months of treatment in patients with coronary atherosclerosis.	Not yet recruiting February 24, 2023

PEER REVIEW DISPOSITION

#	Comment	Response
Reviewer #1		
1	Page 7 table 1 – if the patients who have intermediate lesions on CCTA were to undergo standard myocardial perfusion imaging (MPI) to assess for ischemia, as opposed to the HeartFlow technique, the improvement in sensitivity and specificity would be at least as good as noted with HeartFlow. MPI is widely available already across the VA system and can be performed at much lower cost and without any need for additional infrastructure investments.	We agree that CCTA is just one of many available noninvasive diagnostic tests, including standard MPI. We added to the evidence gaps section: "we found no evidence that would justify substituting CCTA with FFR_{CT} for another noninvasive test such as nuclear MPI, especially in settings where nuclear MPI is used in accordance with current practice guidelines and is part of a well-established workflow. Additionally, we found no studies that compared FFR_{CT} to any other specific noninvasive diagnostic technologies. Direct evidence about how FFR_{CT} compares to other widely used noninvasive diagnostic tests used in the VA is a necessary precondition for considering substituting CCTA with FFR_{CT} for another noninvasive test."
2	Page 8 – adequacy of images. In a carefully selected research setting, including sites with significant experience and expertise in CCTA testing, there was a 10-13% failure rate for CCTA imaging due to poor image quality. In a real world setting, where imaging equipment is very likely to be inferior and where physician and technician expertise is very likely to be inferior, the failure rate would be expected to be much higher. This could significantly limit the applicability of this technique to the VA.	A sentence has been added to the "adequacy of images" section explaining that the failure rate may be even higher in real world settings.
3	Page 11, the scenarios do not mention by far the largest proportion of patients who might undergo cardiac imaging evaluation in the VA, namely patients with established CAD. We are not familiar with any evidence in this population, therefore the lack of data in this critical group limits applicability of the HeartFlow technique in the VA.	Yes, the scenarios do not mention patients with established CAD because we did not identify any evidence of HeartFlow FFR_{CT} use in that population. Because patients with established CAD are the highest utilizers of cardiac imaging evaluation in the VA, we agree that this limits the relevance of the HeartFlow FFR_{CT} technology itself. We added clarification about this point to the Impact section on page 13: "Although the majority of ICAs in the VA are done for patients who have known CAD, the below described scenarios do not mention this type of FFRct utilization because it has not been studied in this population."

4	Page 11, scenario 1 – the 25% of patients who are undergoing invasive assessment without noninvasive testing could be improved using other standard, less costly, and readily available imaging techniques like MPI.	We agree that HeartFlow FFR_{CT} is not the only available alternative. Thus, we a statement that other non-invasive tests as well as FFR_{CT} could also be used in this population. We also noted that the rate of patients referred to ICA without a noninvasive workup may actually be lower than the 25% cited because it did not identify stress tests outside of VA that were not captured by Medicare.
5	Page 11, scenario 1 – national VA data suggests that wait times for coronary angiography are not prolonged and the length of wait times in this particular area is not a current policy concern. Also, centers should not simply be pursuing CCTA without adequate programmatic assessment which includes extremely costly imaging equipment, cardiology physicians with expertise in this area, and radiology physicians with expertise in this area coupled with an expected annual volume of procedures which would justify the investment. In other words an entire program needs to be built to do this correctly, and it's likely that few VA sites will ever meet all of these criteria.	Yes, we found no evidence to support wider use of CCTA in place of other noninvasive tests in VA. We have added this to the first key finding.
6	Page 11, scenario 2 – whether or not radiation exposure would be increased depends widely on the CT and nuclear imaging protocols used.	We agree that radiation exposure can range widely depending on the CT protocol chosen. In fact, data from actual practice indicate that radiation doses are often higher than the minimum needed. We have added the word "likely" to scenario 2 to indicate that this may not always be the case.
7	Page 13 – we agree that if most of the patients who undergo CCTA have normal scans, or non-obstructive CAD, then there is not only no need to pursue invasive coronary angiography, but there is also no need to pursue HeartFlow/FFR assessment. In these cases, the patients can be reassured and/or treated medically without further imaging necessary.	A sentence has been added to clarify that in these cases FFR_{CT} analysis would not be necessary.
Reviewer #2		
8	In the 'CCTA Technologies' section, the authors erroneously suggest that lesion stenosis of >70% on CCTA equates to 'high risk.' Rather, stenosis severity is just one consideration when determining if a study is 'high risk' or not. Other components include high overall plaque burden (even in the absence of any highly stenotic lesions) and the presence of high-risk plaque features (i.e., napkin-ring sign, low attenuation plaque, positive remodeling, and/or spotty calcification). All of these other considerations are missing from the current report.	These other considerations have been added to the section discussing classification of risk.
9	The authors fail to mention anywhere in the report that PET myocardial perfusion imaging (MPI) is another non-invasive modality available to measure coronary flow reserve (CFR) both globally and per coronary artery territory. Furthermore, calculation of PET-derived CFR requires minimal additional cost and time over standard PET MPI alone. My understanding is that PET MPI is utilized very frequently at the West Haven	We have added PET MPI to the list of other non-invasive tests on page 3.

	VA and there may be other VAs that use this testing frequently. If so, the marginal benefit associated with addition of HeartFlow-measured FFR-CT may be reduced.	
10	As the authors mention, HeartFlow, Inc. requires that CT scan images be transmitted to their facility in Redwood City, CA for analysis and report generation. Historically, the VA has heavily restricted any external digital transmission of Veterans' health data (i.e., to third-party data registries, to other electronic health records). It is unclear from the authors' report what, if any, Veteran protected health information (PHI) would need to accompany the image transmission, how reports would be received and incorporated into CPRS, and exactly how Veteran PHI will be secured throughout the process. This should've been included in the 'Considerations for the Anticipated Impact of HeartFlow FFR-CT' and 'Key Findings' sections of the report.	We agree that these practical barriers are important to consider, but they were outside the scope of this report. We have added a sentence to the limitations section stating this.
11	The authors have presented important data suggesting that CCTA use is very low across the VA and that <3% of VA facilities can be considered 'high-volume' CCTA centers. As such, it is unclear that the VA currently has the infrastructure and expertise to routinely conduct high-quality 'plain' CCTA. Nationwide VA data on the types of CT scanners being used for CCTA (which the authors acknowledge influences test sensitivity and specificity) and the proportion of unreadable CCTAs performed are unknown but needed prior to any consideration of VA adoption of more 'advanced' CCTA technologies like FFR-CT.	We agree that assessment of nationwide VA data on CT scanner type and unreadable CCTAs rate should be considered prior to any consideration of VA adoption of more 'advanced' CCTA technologies like FFR_{CT}. We added that study of this technology in the VA is needed prior to consideration of adoption.
12	Finally, I believe the authors need to be more definitive in their Key Findings. In my opinion, they should state that the available evidence thus far is either insufficient or inconclusive to recommend routine use/coverage of HeartFlow FFR-CT for any indication at this time. However, if individual VA medical centers performing high-volume CCTA would like to experiment with using HeartFlow (or other FFR-CT technologies), that is reasonable as proof-of-concept.	We agree that the evidence does not yet support routine use/coverage of HeartFlow FFR_{CT}. To better emphasize this point we repositioned our related finding statement to the first in our list of Key Findings.

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