Supplementary Material Table 1: Diagnostic Performance of FFR_{CT}

Study	Objectives	No. patients	No. vessels	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Comments
DISCOVER-FLOW [18]	Diagnostic performance of FFR_{CT} in patients with suspected or known CAD	103	159	Per patient = 87 Per vessel = 84	Per patient = 93 Per vessel = 88	Per patient = 82 Per vessel = 82	Per patient = 85 Per vessel = 74	Per patient = 91 Per vessel = 89	Per patient = 0.90 Per vessel = 0.92	Reported significant correlation between FFR_{CT} and invasive FFR (r=0.717, p<0.001) with a trend towards FFR_{CT} underestimation (0.022 ± 0.116, p=0.016).
DeFACTO [27]	Diagnostic accuracy of FFR_{CT} compared with invasive FFR in stable patients with suspected or known CAD	252	408	Per patient = 73	Per patient = 80 Per vessel = 90	Per patient = 61 Per vessel = 54	Per patient = 67	Per patient = 84	Per patient = 0.81	Per-vessel correlation of FFR_{CT} to invasive FFR (r=0.63, 95% CI [0.56–0.68]) with underestimation of FFR_{CT} compared with invasive FFR (mean difference 0.058; 95% CI [0.05–0.07]).

NXT trial[28]	Diagnostic performance of FFR_{CT} using invasive FFR as the reference standard	254	484	Per patient = 81 Per vessel = 86 CAC ≥ 400 = 75	Per patient = 86 Per vessel = 84 CAC ≥ 400 = 88	Per patient = 79 Per vessel = 86 CAC ≥ 400 = 69	Per patient = 65 Per vessel = 61	Per patient = 93 Per vessel = 95	Per vessel = 0.93 Per patient = 0.9	A positive correlation of per-vessel FFR_{CT} and invasive FFR ($r=0.82$; $p<0.001$) was observed with a slight underestimation of FFR_{CT} compared with invasive FFR (mean ± SD 0.03 ± 0.074; $p<0.01$)
Renker et al.[60]	Diagnostic performance of a novel FFR_{CT} algorithm, developed for time-efficient in-hospital evaluation of hemodynamically indeterminate coronary lesions in a blinded fashion.	53	67	–	Per patient = 94 Per lesion = 85	Per patient = 84 Per lesion = 85	Per patient = 71 Per lesion = 71	Per patient = 97 Per lesion = 93	Per patient = 0.91 Per lesion = 0.92	FFR_{CT} had greater diagnostic yield in detecting lesion-specific ischemia than CCTA anatomic interpretation (0.92 versus 0.72, $p=0.0049$).
Kim et al.[17]	Diagnostic accuracy of	44	48 lesion	Before stenting = 77	Before stenting = 85	Before stenting = 57	Before stenting = 83	Before stenting = 62	–	Prospective, multicenter

	FFR_{CT} to predict functional status of coronary lesions prior to and after stenting		s	After stenting = 96	After stenting = 100	After stenting = 96	After stenting = 50	After stenting = 10 0		study.
NOVEL-FLOW [61]	diagnostic performance of FFR_{CT} compared to CCTA by using a new novel method based on vessel length of coronary arteries	117	218	Per patient = 86 Per vessel = 86 CAC ≥ 400 = 7 5	Per patient = 93 Per vessel = 86 CAC ≥ 400 = 8 8	Per patient = 75 Per vessel = 86 CAC ≥ 400 = 6 9	Per patient = 84 Per vessel = 80	Per patient = 88 Per vessel = 90	Per vessel = 0.93 Per patient = 0.92	Specificity of CCTA was improved with FFR_{CT} from 60% to 86% on a per-vessel basis. A higher AUC for FFR_{CT} was observed compared with CCTA (0.93 versus 0.74, $p<0.0001$) and FFR_{CT} showed a significant correlation with invasive FFR ($r=0.76$, $p<0.001$) with slight underestimation by FFR_{CT} (0.014 ± 0.077, $p=0.007$)

Kruk et al.[62]	Compared diagnostic accuracy of FFR_{CT} with invasive FFR	90	96 lesion s	Per lesion = 74	Per lesion = 76	Per lesion = 72	Per lesion = 67	Per lesion = 80	Per lesion = 0.83	AUC for FFR_{CT} for identification of stenosis was significantly higher than for CCTA (p=0.007) and ICA (p=0.004)
Coenen et al.[63]	Validated FFR_{CT} against invasive FFR and its diagnostic performance compared with CCTA	106	189	Per lesion = 75	Per lesion = 88	Per lesion = 65	Per lesion = 65	Per lesion = 88	-	Correlation between FFR_{CT} and invasive FFR was good (R=0.59), which was similar to that in the DeFACTO study but lower than that in the DISCOVER-FLOW and NXT trial On-site computational FFR_{CT} software required only 5–10 min to calculate the CFD per

										patient
Ko et al.[64]	Feasibility and accuracy of the FFR_{CT} technique based on alternative boundary conditions	52	56	Per vessel = 84	Per vessel = 78	Per vessel =87	Per vessel =74	Per vessel =89	Per vessel = 0.88	Mean time per patient for FFR_{CT} analysis was 27.07 ± 7.54 m in. FFR_{CT} versus CCTA (AUC 0.88 versus 0.77; p=0.22)
Yang et al.[65]	Compared the diagnostic accuracies of on-site FFR_{CT} and CTP in patients with CAD	72	138	Per patient = 81 Per vessel = 84	Per patient = 87 Per vessel = 90	Per patient = 77 Per vessel = 79	Per patient = 71 Per vessel = 74	Per patient = 90 Per vessel = 93	Per patient = 0.89 Per vessel = 0.91	Prospective, single-center study
Tang et al.[66]	Feasibility and diagnostic performance of on-site FFR_{CT} in detecting lesion-specific ischemia using invasive FFR as the reference standard in a large Chinese multicenter	338	422	Per patient = 90 Per vessel = 91 CAC ≥ 400 = 9 6	Per patient = 89 Per vessel = 89 CAC ≥ 400 = 9 1	Per patient = 91 Per vessel = 91 CAC ≥ 400 = 1 00	Per patient = 88 Per vessel = 86 CAC ≥ 400 = 100	Per patient = 92 Per vessel = 94 CAC ≥ 400 = 94	Per patient = 0.92 Per vessel = 0.92 CAC ≥ 400 = 0 .97	No difference in the diagnostic accuracy of FFR_{CT} was found for different levels of coronary calcium.

	cohort study									
Zhou et al.[67]	Diagnostic performance of FFR_{CT} in detecting ischemia in myocardial bridging	104	48	Per vessel = 89	Per vessel = 96	Per vessel = 84	Per vessel = 84	Per vessel = 96	Per vessel = 0.95	PPV (0.97 versus 0.59, p=0.001) in the ≥70% stenosis group was significantly higher than that in the 50–69% stenosis group. Good correlation between FFR_{CT} and FFR (p<0.001)
De Geer et al.[68]	Evaluated the accuracy of FFR_{CT}	21	23	Per lesion = 78	Per lesion = 83	Per lesion = 76	Per lesion = 56	Per lesion = 93	–	Retrospective, single-center study
Zhang et al.[69]	Diagnostic performance of FFR_{SS} and FFR_{AM} was validated against the invasive FFR as a reference method	21	32	Per patient: Steady state = 91 Analytical model = 86 Per vessel: Steady state = 91	Per patient: Steady state = 89 Analytical model = 78 Per vessel: Steady state = 80	Per patient: Steady state = 92 Analytical model = 92 Per vessel: Steady state = 96	Per patient: Steady state = 89 Analytical model = 88 Per vessel: Steady state = 89	Per patient: Steady state = 92 Analytical model = 85 Per vessel: Steady state = 91	Per patient: Steady state = 0.96 Analytical model = 0.95 Per vessel: Steady state = 0.95	Pilot study to compute FFR^{SS} and FFR_{AM} from CCTA using steady state (SS) flow simulation and analytical model (AM), respectively SS flow

				Analytical model = 88	Analytical model = 80	Analytical model = 91	Analytical model = 80	Analytical model = 91	Analytical model = 0.96	simulation to obtain FFR_{SS} reduced the computational time to 0.5–2 h, together with a good correlation between FFRSS and invasive FFR (r=0.843)
Gaur et al. [70]	Diagnostic performance of FFR_{CT} for the diagnosis of lesion-specific ischemia in STEMI patients	60	124	Per vessel = 72	Per vessel = 83	Per vessel = 66	Per vessel = 56	Per vessel = 89	-	Clinical utility of FFR_{CT} in patients with ACS needs further investigation
Kawaji et al.[71]	Feasibility of FFR_{CT} in patients with planned ICA due to suspected CAD	48	–	Per vessel = 69	Per vessel = 93	Per vessel = 52	Per vessel = 57	Per vessel = 92	Per vessel = 0.87	FFR_{CT} showed significant correlation with invasive FFR (Spearman's rank correlation = 0. 69, p<0.001)
Shi et al.[72]	Diagnostic performance of FFR_{CT} in the clinic, and	29	36	Per patient = 79	Per patient = 94	Per patient = 62	Per patient = 75 Per	Per patient = 89 Per	Per patient = 0.90 Per	The computation time for the steady state

	to discuss the feasibility of using the simplified pulsatile simulation method in identifying ischemia-related stenosis of CAD			Per vessel = 81	Per vessel = 94	Per vessel = 68	vessel = 73	vessel = 93	vessel = 0.93	method and simplified pulsatile simulation were 1.2 ± 0.6 h and 2.3 ± 1.2 h, respectively.
Studies based on CCTA image quality, coronary calcification and motion artifacts										
Leipsic et al.[32]	Impact of patient preparation, CT scan protocol, and factors related to image quality on the diagnostic accuracy of FFR_{CT}	252	407	Misalignment = 56 Motion artifacts = 65 CAC ≥ 400 = 70	Misalignment = 43 Motion artifacts = 71 CAC ≥ 400 = 64	Misalignment = 63 Motion artifacts = 63 CAC ≥ 400 = 64	–	–	–	Substudy of the prospective multicenter international DeFACTO study
Di Jiang et al. [73]	Effect of coronary calcification morphology and severity on diagnostic performance of machine learning	442	544	Per lesion = 90	Per lesion = 84	Per lesion = 94	–	–	Per lesion = 0.89	FFR_{CT} showed improved discrimination of ischemia compared with CCTA in lesions with mild–moderate calcification (AUC 0.89

	based-FFR_{CT}									versus 0.69, p<0.001) and calcification remodeling index ≥ 1 (AUC 0.89 versus 0.71, p<0.001)
Tesche et al.[22]	Influence of CAC score on diagnostic performance of machine learning based-FFR_{CT}	314	482	CAC ≥ 400: Per patient = 87 Per vessel = 76	CAC ≥ 400: Per patient = 91 Per vessel = 85	CAC ≥ 400: Per patient = 68 Per vessel = 63	CAC ≥ 400: Per patient = 93 Per vessel = 78	CAC ≥ 400: Per patient = 60 Per vessel = 74	CAC ≥ 400: Per patient = 0.71 Per vessel = 0.71	Diagnostic accuracy with increasing calcium score is also reflected in poor correlation between CT-FFR and invasive FFR in vessels with CAC ≥ 400 (r=0.35)
Xu et al.[74]	Effect of CCTA image quality on machine learning based-FFR_{CT} diagnostic performance	437	570	–	Per lesion = 82	Per lesion = 93	–	–	High quality images = 0.93 Low quality images = 0.80	Retrospective multicenter study. The diagnostic performance of FFR_{CT} is affected by image quality, vessel enhancement and heart rate.

Meta-analysis										
Gonzalez et al.[29]	Meta-analysis compared the diagnostic performance of FFR_{CT}, CCTA and CTP for assessing the functional significance of coronary stenosis in patients with known or suspected CAD	662 (FFR_{CT})	714 (FFR_{CT})	–	Per patient = 90 Per vessel = 83	Per patient = 72 Per vessel = 77	Per patient = 70 Per vessel = 63	Per patient = 90 Per vessel = 91	–	FFR_{CT} improves the specificity of CCTA for detecting hemodynamically significant lesions.
Zhuang et al.[75]	Meta-analysis for reliable assessment of the diagnostic performance of FFR_{CT} compared with CCTA using invasive FFR as reference	1852	2731	–	Per patient = 89 Per vessel = 71	Per patient = 85 Per vessel = 82	–	–	–	FFR_{CT} has higher specificity for anatomical and physiological assessment of coronary artery stenosis compared with CCTA
Li et al.[76]	Meta-analysis of NXT Trial, DISCOVER-FLOW study and DeFACTO	609	1050	–	Per patient = 89 Per vessel = 83	Per patient = 71 Per vessel = 78	Per patient = 70 Per vessel = 61	Per patient = 90 Per vessel = 92	Per patient = 0.89 Per vessel = 0.88	

	study									
Deng et al.[77]	Meta-analysis of the diagnostic performance of FFR_{CT}	706	1165	–	Per patient = 90 Per vessel = 83	Per patient = 72 Per vessel = 78	–	–	Per patient = 0.94 Per vessel = 0.91	FFR_{CT} demonstrated a high diagnostic performance compared with invasive FFR in detecting lesions causing ischemia

ACS = acute coronary syndrome; AUC = area under the curve; CAC = coronary artery calcium; CAD = coronary artery disease; CCTA = coronary CT angiography; CFD = computational fluid dynamics; CTP = CT perfusion; FFR = fractional flow reserve; FFR_{CT} = fractional flow reserve derived from CCTA; ICA = invasive coronary angiography; NPV = negative predictive value; PPV = positive predictive value; STEMI = ST-elevation MI.

Supplementary Material Table 2: Key Studies of Impact of FFR_{CT} on Clinical Decision-making and Outcome

Citation/Study	Objectives	Study type and no. patients	Results
Hlatky et al.[16]; Douglas et al.[6,15]; PLATFORM	1-year clinical, economic, and quality-of-life outcomes using FFR_{CT} instead of usual care in patients with stable, new-onset chest pain	Prospective, multicenter (n = 584)	• ICA was deferred in 61% of the patients based on the CCTA/FFR_{CT} strategy and were event free • MACE rate was low in the usual care and CCTA/FFR_{CT} arm in ≤90 days. • Infrequent clinical events at 1-year follow-up • In the ICA planned patients, mean cost was 33% lower with FFR_{CT} ($8,127 versus $12,145 for usual care; p<0.0001)
Nørgaard et al.[10]	Real-world clinical utility of FFR_{CT} for decision-making in patients with stable CAD.	Observational, single center (n=185)	• No serious adverse cardiac events reported in patients who were deferred from ICA based on FFR_{CT} results (66%) during a median follow-up period of 12 months. • 29% were referred to ICA based on FFR_{CT}
Curzen et al.[53]; RIPCORD study	The effect of adding FFR_{CT} to CCTA alone for assessment of lesion-specific severity and patient management in patients with chest pain	Retrospective (NXT trial data), multicenter (n=200)	• 30% reduction in PCI and 18% change in the target vessel for PCI • FFR_{CT} reallocated management category from OMT to PCI in 12% • The availability of non-invasive FFR_{CT} changed the allocated management plans in 44% of the study population
Jensen et al.[11]	Short-term safety of frontline CCTA + selective FFR_{CT} in stable patients with typical angina pectoris and its influence on downstream rate of ICA	Prospective, multicenter (n=774)	• Deferring the ICA in patients with FFR_{CT} >0.80 had a favorable short-term prognosis and was associated with a high rate of cancellation of planned ICA (63% in the high-risk versus 23% in the low–intermediate-risk group) • No MACEs were reported in high-risk patients in whom ICA was cancelled in ≤90 days of follow-up.
Nørgaard et al.[78]	Clinical outcomes and safety utilizing a diagnostic strategy including first line CCTA and selective FFR_{CT}	Single-center, observational (n= 3,674)	• Similar clinical outcomes were observed in the patients with FFR_{CT} >0.80 and patients without obstructive disease on CCTA (<30%). • After a median follow-up of 24 months, higher rates of MACEs were reported in patients with FFR_{CT} <0.80 if treated medically than patients treated medically with FFR_{CT} >0.80 (9.4% versus 3.8%, p=0.07)

	testing in real-world symptomatic patients with suspected stable CAD.		• FFR_{CT} <0.8 referred for ICA appeared to have a lower risk of non-fatal MI (1.3%)
Fairbairn et al.[26] and Patel et al.[79]; ADVANCE Registry	The real-world utility and clinical impact of using FFR_{CT} on decision-making	Prospective, multicenter (n=5,083)	• No MACEs were reported in ≤90 days in patients with FFR_{CT} >0.80 (0%) compared with FFR_{CT} <0.80 (0.3%). • 19 MACEs (HR 19.75; 95% CI [1.19–326]; p=0.0008) and 14 deaths or MI (HR 14.68; 95% CI [0.88–246]; p=0.039) occurred in subjects with FFR_{CT} ≤0.80. • FFR_{CT} modified the recommended treatment strategies based on CCTA in approximately two-thirds of the study population. • At 1 year, the patients with negative FFR_{CT} reported a low rates of revascularization, MACE and significantly low cardiovascular death or MI rate compared with the patients with abnormal FFR_{CT}
Collet et al.[8] & Andreini et al.[7]; SYNTAX III Revolution	Impact of FFR_{CT} on therapeutic clinical decision-making and selection of vessels for revascularization in patients with 3-vessel CAD.	Prospective, multicenter (n= 223)	• Decision-making with CCTA + FFR_{CT} was feasible. • 7% change in the proposed treatment recommendation • 12% change in the target vessels for PCI • Reclassified 14% of patients from intermediate and high to low risk. • FFR_{CT} AUC was 0.85 (95% CI [0.79–0.90]), with 95% sensitivity and 61% specificity in patients with triple-vessel disease (n=77).
Park et al.[80]; EMERALD Study	The anatomical, plaque, and hemodynamic characteristics of high-risk non-obstructive coronary lesions that caused ACS	Case–control study, (n=132 lesions)	• FFR_{CT} predicts the risk of ACS in non-obstructive lesions. • Prediction model including ΔFFR_{CT}, low-attenuation plaque and plaque volume showed the highest ability in ACS prediction (AUC 0.725; 95% CI [0.724–0.727])
Qiao et al.[81]	Impact of machine learning-based FFR_{CT} compared with ICA for therapeutic decision-making and patient outcome in patients with stable chest pain	Retrospective (n=1,121)	• Proposed treatment regimen was modified in 14.9% of patients based on $FFR_{CT.}$ • Over a 26-month median follow-up, FFR_{CT} ≤0.80 was significantly associated with MACE compared with FFR_{CT} >0.80 (HR 6.84; 95% CI [3.57–13.11]; p<0.001) • Positive FFR_{CT} prior to ICA could have reduced the rate of ICA by 54.5%, leading to 4.4% less PCI

Crawley et al.[82]	Introduction of FFR_{CT} in a large district general hospital and its impact on clinical assessment of CAD	Single-center (n=584)	• With FFR_{CT} ≤0.8, a total of 44.5% required either PCI (34.7%) or coronary artery bypass grafting (9.8%) and 55.5% were managed with OMT. • With FFR_{CT} >0.80, 98.3% received OMT and only 4.7% (n=8) required ICA (only 3 patients underwent PCI) • The lowest risk of MACE was observed in patients with FFR_{CT} >0.80 treated with OMT (1.8%). • FFR_{CT} ≤0.80 significantly associated with MACE compared with FFR_{CT} >0.80 (HR 6.84; 95% CI [1.24–2.73], p=0.002)
Nørgaard et al.[83]	Outcomes following a normal FFR_{CT} result in patients with moderate stenosis and coronary artery calcification, and the relationship between the extent of calcification, stenosis, and FFR_{CT}	– (n=975)	• Lower incidence of MACEs at 4.2 years in patients with any CAC and FFR_{CT} >0.80 versus FFR_{CT} ≤0.80 (3.9% and 8.7%, p=0.04) • A negative relationship between CAC scores and FFR_{CT} irrespective of stenosis severity was demonstrated

ACS = acute coronary syndrome; CAC = coronary artery calcium; CAD = coronary artery disease; CCTA = coronary CT angiography; FFR = fractional flow reserve; FFR_{CT} = fractional flow reserve derived from CCTA; ICA = invasive coronary angiography; MACE = major adverse cardiac event; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

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