

Supplemental Table 1: Completed or ongoing randomized trials and clinical studies using biomarkers as surrogate endpoints

Study	Condition	Modality	Variables used	Findings
COURAGE trial nuclear substudy(1)	Obstructive CAD	Tc99m/Thallium SPECT MPI	%Ischemic TPD	PCI + OMT led to a greater reduction in ischemia compared to OMT alone. Patients with $\geq 5\%$ ischemia reduction had lower unadjusted risk for death or myocardial infarction.
BARI-2D trial nuclear substudy(2)	Obstructive CAD	SPECT MPI	%Stress TPD, Rest TPD, % Ischemic TPD	Patients randomized to revascularization had lower stress perfusion abnormalities at 1 year compared to those randomized to medical therapy. 1 year stress TPD was associated with an increased hazard of cardiac death or MI
INSPIRE trial(3)	Obstructive CAD	Tc-99m SPECT MPI	Change in total and ischemic TPD	Similar and comparable reductions in TPD and Ischemic TPD in IMT and Revascularization (PCI or CABG) arms. Ischemia suppression was achieved in 80% of patients randomized to either strategy.
ADVANCE trial(4)	Obstructive CAD	Tc-99m SPECT MPI	Stress TPD, Ischemic TPD	Scintigraphic results including size and severity of perfusion abnormalities and extent of ischemia were similar among patients randomized to use of regadenoson as a stressor compared to adenosine.
Mahmari et al 1994(5)	Obstructive CAD	Tl-201 SPECT	Change in Stress TPD	Significant reduction in total perfusion defect size with nitroglycerin patch vs. placebo
ACME trial substudy(6)	1 and 2 vessel obstructive CAD	Tl-201 SPECT		Patients with ischemia on SPECT present at 6 months in either arm had higher mortality vs. those without ischemia (18% vs.8%, $p=0.02$). Patients with higher % ischemia had higher mortality
Burns et al 2001(7)	Obstructive CAD and refractory angina	Tc-99m SPECT	Stress TPD, Ischemic TPD	No difference in perfusion defect between transmural laser revascularization and control arms
Grines et al 2003(8)	Obstructive CAD, Stable angina	Tc99m SPECT	Change in ischemic TPD	Intracoronary injection of adenoviral gene for fibroblast growth factor (Ad5FGF-4) overall did not improve myocardial perfusion, but showed a trend towards improved perfusion compared to placebo

VIVA trial(9)	Obstructive CAD stable angina	Tc99m SPECT	Summed Stress Score	Low or high dose recombinant human vascular endothelial growth factor protein did not improve perfusion vs. placebo at 60 days.
Aqel et al. 2008(10)	Obstructive HCM	Rest Tc-99mSPECT	Rest perfusion defect size	Alcohol septal ablation leads to small basal septal infarct and perfusion defect, which improves with time.
Venkatraman et al. 2011(11)	Obstructive CAD	Tc-99m SPECT	Stress TPD, Ischemic TPD	Ranolazine does not improve myocardial perfusion
Bober et al 2019(12)	Stable obstructive CAD	Rb-82 PET	Stress MBF	Stress MBF improved when revascularization targeted to regions with reduced CFC and relative perfusion abnormalities on baseline PET, but not when revascularization was performed among patients without reduced CFC or abnormal perfusion at baseline.
PACIFIC substudy(13)	Obstructive CAD	O15-H2O PET	Stress MBF, MBFR,	Stress MBF and MBFR improved post revascularization, Improvement in stress MBF and MBFR paralleled improvement in FFR. PCI led to a greater improvement of regional stress MBF vs. CABG.
deWinter et al 2022(14)	Stable obstructive CAD	[¹⁵ O]H ₂ O PET	Stress MBF, MBFR, CFC	Stress MBF, MBFR, CFC increased with successful revascularization (PCI or CABG), an increase in CFC was independently associated with lower rates of death and non-fatal MI
Parodi O et al. Circ 1999(15)	Hypertension	N13NH3 PET	Stress MBF	Stress MBF improved in patients randomized to verapamil but not enalapril
Buus NH et al. 2004(16)	Hypertension	PET	MBFR	Patients randomized to perindopril had improvement in MBFR after 1 year but not those randomized to atenolol
Yokoyama I et al 2004(17)	Hyperlipidemia	N13 NH3 PET	Stress MBF	Stress MBF improved with simvastatin but not pravastatin
Akinboboye O et al. 2002(18)	Hypertension and LVH	O15-H2O PET	Stress MBF and MBFR	MBFR and stress MBF improved with lisinopril but not losartan.
Baller D et al. 1999(19)	Hyperlipidemia and Microvascular Dysfunction	N13-NH3 PET	MBFR	Simvastatin for 6 months improves CFR

Safdar B et al 2017(20)	Coronary microvascular Dysfunction	Rb-82 PET	MBFR	Ranolazine improved MBFR at 30 days by 17% vs. placebo. Mean change in MBFR similar with ranolazine vs. placebo
Cheng K et al.(21) (pre-post)	Refractory angina and CAD	Rb-82 PET	Change in MBFR, change in stress MBF, change in rest MBF	Overall, there was no change in MBF, rest or stress MBF with coronary sinus reducer therapy. However, patients with baseline MBFR <1.8 had an improvement in stress MBF and MBFR, but patients with baseline MBFR >=1.8 did not.
LiiRA study (pre- post)(22) <i>NCT02714881</i>	Rheumatoid Arthritis	N13 NH3 PET MPI	Change in global MBFR	No change in MBFR with TNF-alpha inhibitor treatment over 24 weeks
CIRT-CFR trial(23) <i>NCT02786134</i>	Previous MI or multivessel CAD	N13-NH3 or Rb 82 PET	Change from baseline MBFR	There was no change in MBFR from baseline in either patients randomized to methotrexate or placebo.
Leccisotti L et al. 2022(24)	Type 2 DM	N13-NH3 PET	MBFR	Dapagliflozin significantly improved MBFR vs. placebo.
SIMPLE trial(25)	Type 2 DM at high CV risk	Rb-82 PET	MBFR	No change in MBFR from baseline either with empagliflozin or placebo
<i>SALTIRE II,</i> <i>NCT02132026</i>	Aortic stenosis	18F-NaF PET	Microcalcification activity	Denosumab and alendronic acid did not affect the calcification activity within the aortic valve
BASIK-2, <i>NCT02917525</i>	Aortic stenosis	18F-NaF PET	Microcalcification activity	The effects of Vitamin K2 on the calcification activity within the aortic valve
ECAV, <i>NCT03217786</i>	Cardiac transplant	Rb 82 PET	PET MBF	Change in percent intimal volume and myocardial blood flow
MARINER <i>NCT06089486</i>	Cardiac transplant	Rb 82 PET	PET MBF	Surveillance strategy using surrogate biomarker (PET MBF) vs. invasive angiography with intracoronary imaging
NEURO- TTRansform <i>NCT04136184</i>	Cardiac amyloidosis	Technetium pyrophosph ate		Change in volumetric heart to lung ratio

Evuzamitide <i>NCT05635045</i>	Cardiac amyloidosis	124I-evuzamitide PET	Quantitative uptake	Change in radiotracer activity after one year of treatment
I-CARE <i>NCT05776212</i>	Cardiac Amyloidosis	18F-NaF PET	Microcalcification activity	Baseline measures and change in uptake in 18F-NaF PET activity
ADMIRE-HF <i>NCT00126425</i>	Heart failure with LVEF $\leq 35\%$	I123 MIBG	heart to mediastinum ratio	Prospective validation of the prognostic utility of heart to mediastinum ratio
CHASM CS-RCT <i>NCT03593759</i>	Active cardiac sarcoidosis	FDG and perfusion PET	Summed rest score	Low-dose prednisone/methotrexate combination will have no inferior efficacy to standard dose prednisone with respect to endpoints

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