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Original Article

The Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) Trial—IMAGE HF Project 1A

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ABSTRACT

Background: The role of advanced (cardiac magnetic resonance [CMR] or positron emission tomography [PET]) vs single-photon emission computerized tomography (SPECT) ischemia imaging to guide management remains unclear in patients with ischemic heart failure (IHF). The primary aim was to determine the effect of imaging modality on a composite cardiovascular endpoint and cardiac death in patients with IHF who require ischemia assessment.

RÉSUMÉ

Contexte : Le rôle de l'imagerie avancée (résonance magnétique cardiaque [RMC] ou tomographie par émission de positons [TEP]) par rapport à la tomographie par émission monophotonique (TEMP) dans le diagnostic de l'ischémie pour guider la prise en charge reste incertain chez les patients atteints d'insuffisance cardiaque ischémique (ICI). L'objectif principal était de déterminer l'effet de la modalité d'imagerie sur un critère d'évaluation composite car-

Among patients with coronary artery disease (CAD) and heart failure (HF), mortality rates range from 10%-40% at 1 year.[1-8] Although early clinical trials and subsequent cohort studies have demonstrated a benefit of revascularization in patients with ischemic heart disease (IHD)and left ventricular (LV) dysfunction, these trials were limited by study design. In addition, advances in drug therapy, devices, imaging modalities, and options for intervention have rendered these studies less relevant in the current era. More-contemporary trials, including the **S**urgical **T**reatment for **Is**chemic **H**eart Failure **E**xtension **S**tudy (STICH[ES]), and **Rev**ascularization for **I**schemic **Ve**ntricular **D**ysfunction (REVIVED-BCIS2) trials[5,8] have provided further insight into the role of

Keywords: Heart failure; ischemic cardiomyopathy; revascularization; cardiac magnetic resonance imaging; positron emission tomography; nuclear cardiology

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Methods: Patients with IHF were randomized to advanced or SPECT imaging. A parallel registry also was performed. The primary endpoint was the composite of cardiac death, infarction, arrest, and cardiac rehospitalization. The key secondary endpoint was cardiac death.

Results: Patients in the randomized population (advanced imaging [PET or CMR; n = 64] or SPECT [n = 56]) had a cumulative incidence rate (CIR) for the primary endpoint of 33.1% and 33.0%, respectively (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.49, 1.80, P = 0.853). CIRs for cardiac death were 13.8% and 25.1%, respectively (HR 0.62, 95% CI 0.25, 1.80, P = 0.296).

In the parallel registry (n = 336 advanced; n = 216 SPECT), the primary endpoint CIRs were 31.2% and 35.3%, respectively (HR 0.81, 95% CI 0.56, 1.19, P = 0.284). CIRs for cardiac death were 11.0% and 16.6%, respectively (HR 0.53, 95% CI 0.27, 1.04, P = 0.066). Patients were followed for a median (interquartile range) of 24.1 (11.6, 27.5) months.

Pooled analysis from the randomized and registry populations revealed a significant benefit of advanced imaging for reduction of cardiac death (HR 0.56, 95% CI 0.33, 0.96, P = 0.04) with minimal heterogeneity (I^2 = 0%).

Conclusion: Among IHF patients assessed for ischemia, advanced imaging (PET or CMR) was not associated with reduced composite cardiac events, compared to SPECT.

Clinical Trial Registration: NCT01288560.

diovasculaire et la mortalité cardiaque chez les patients atteints d'ICI qui nécessitent une évaluation de l'ischémie.

Méthodologie : Les patients atteints d'ICI ont été randomisés pour recevoir une imagerie avancée ou une imagerie par TEMP. Un registre parallèle a également été établi. Le critère d'évaluation principal était le critère composite incluant le décès cardiaque, l'infarctus, l'arrêt cardiaque et la réhospitalisation pour cause cardiaque. Le critère d'évaluation secondaire d'intérêt était la mortalité cardiaque.

Résultats : Les patients de la population randomisée (imagerie avancée [TEP ou RMC] (n = 64) ou TEMP (n = 56)) présentaient un taux d'incidence cumulé (TIC) pour le critère d'évaluation principal de 33,1 % et 33,0 % respectivement (rapport de risque [RR] 0,94, indice de confiance [IC] à 95 % 0,49, 1,80, p = 0,853). Les TIC pour la mortalité cardiaque étaient respectivement de 13,8 % et 25,1 % (RR 0,62, IC à 95 % 0,25, 1,80, p = 0,296).

Dans le registre parallèle (n = 336 pour l'imagerie avancée ; n = 216 pour la TEMP), le TIC du critère d'évaluation principal était respectivement de 31,2 % et 35,3 % (RR 0,81, IC à 95 % 0,56, 1,19, p = 0,284). Les TIC pour la mortalité cardiaque étaient respectivement de 11,0 % et 16,6 % (RR 0,53, IC à 95 % 0,27, 1,04, p = 0,066). Les patients ont été suivis pendant une durée médiane (étendue interquartile) de 24,1 (11,6, 27,5) mois.

L'analyse combinée de la population du registre avec celle randomisée a montré un bénéfice significatif de l'imagerie avancée pour la réduction de la mortalité cardiaque (RR 0,56, IC à 95 % 0,33, 0,96, p = 0,04) avec une hétérogénéité minimale (I^2 = 0 %).

Conclusion : Parmi les patients atteints d'ICI évalués pour une ischémie, l'imagerie avancée (TEP ou RMC) n'était pas associée à une réduction des événements cardiaques composites par rapport à la TEMP.

Enregistrement de l'essai clinique : NCT01288560; https://clinicaltrials.gov/

revascularization for patients with ischemic HF (IHF), and research in this field is ongoing (**S**urgical **T**reatment for **Is**chemic **H**eart Failure [STICH3C] trial, NCT05427370). However, uncertainties remain regarding how and when to select HF patients who would benefit from revascularization.

The primary objective of the **A**lternative **I**maging **Mo**dalities in **I**schemic **H**eart **F**ailure (AIMI-HF) study was to determine the impact of advanced imaging strategies with positron emission tomography (PET) or cardiac magnetic resonance (CMR) imaging, as compared to imaging using single-photon emission computerized tomography (SPECT), on a composite of cardiovascular (CV) outcomes in patients with HF who required further definition of ischemia or viability to guide management decisions regarding revascularization. This cohort of the AIMI-HF study focused on patients who required further definition of ischemia to guide decisions regarding revascularization. The results of the viability cohort will be addressed in a separate analysis.

Methods

Trial design and oversight

The design and conduct of this international pragmatic study were published previously.[9] This trial was approved by the ethics committee at each site, and all patients provided written informed consent. Subjects were enrolled from 15 centres in Canada, Finland, the US, Brazil, and Argentina.

Study participants

Adults aged > 18 years were eligible for inclusion if they had known or highly suspected CAD documented by coronary angiography, history of previous myocardial infarction (MI), or evidence of moderate ischemia or scar on prior imaging, and required further definition of ischemia to guide management decisions. Patients were required to have LV systolic dysfunction most likely attributable to IHD, with ejection fraction (EF) ≤ 45%, measured by acceptable means (echocardiography, radionuclide angiography, PET or SPECT perfusion, angiography, CMR) within the previous 6 months, and New York Heart Association (NYHA) class II-IV symptoms. Patients with IHD and NYHA class I symptoms were eligible if their baseline LVEF was ≤ 30%. Exclusion criteria included the following: medical conditions that would significantly affect the patient's outcome (eg, severe lung disease, active metastatic malignancy) precluding revascularization; < 4 weeks post ST-segment myocardial infarction; being otherwise unsuitable for revascularization or having an indication for emergency revascularization or concomitant valve surgery.

Randomization

In this pragmatic trial, patients were prospectively randomized to imaging modalities available at their site, including (SPECT) perfusion imaging vs advanced (PET or CMR) imaging.

Registry arm population

A separate registry cohort was created for patients who met inclusion criteria but could not be randomized due to either of the following: availability of only one imaging modality at the site at that time, or contraindication to one of the modalities available (eg, for CMR— having metallic device implants or glomerular filtration rate < 30 mL/min per 1.73 m^2; for any modality—having claustrophobia, or patient or clinician preference). Patients also were enrolled in the registry cohort when they met all other inclusion criteria and had already undergone standard or advanced imaging during the study period.

Clinical outcomes and follow-up

The primary objective of the AIMI-HF trial was to compare the effect of imaging strategies on the primary outcome, which was the time to the composite clinical endpoint. This endpoint included the following: cardiac death, MI, resuscitated cardiac arrest, and cardiac rehospitalization (for worsening HF, acute coronary syndrome, arrhythmia). Secondary outcomes included the following: (i) the event rates of the composite endpoint; (ii) cardiac death, and (iii) other individual components of the composite. The effect of imaging strategies on the incidence of revascularization procedures (percutaneous coronary intervention [PCI]; coronary artery bypass grafting [CABG]; none) and the interaction effect of the imaging strategy and revascularization on the primary outcome and CV death also were determined. Follow-up assessments were performed at 3, 12, 24, 36, and 48 months from baseline scans. All endpoints were independently and blindly adjudicated.

Imaging protocols

Standard imaging protocols were established using recognized protocols, per the American Society of Nuclear Cardiology guidelines (PET and SPECT) and the Canadian Society for Cardiovascular Magnetic Resonance guidelines for magnetic resonance imaging (MRI), as noted previously.[9-17] Imaging was performed whenever possible within 4 weeks after randomization and/or study enrollment. Sites reported imaging results, including extent of ischemia or scar, per imaging reporting standards.[9-17] A semiquantitative approach was used, with the percentage of ischemia and scar for each patient categorized into the following groups: < 5%, 5%-10%, 11%-20%, and > 20%, to define none, mild, moderate, or severe ischemia or scar, respectively. The same approach was used for SPECT and advanced modalities, including PET and CMR. All scanners were considered state-of-the-art at the time the study was conducted. Supplemental Table S1 lists the specific cameras used across regions.

Statistical analysis

Randomization was stratified by site, and permutated blocks of various sizes were used in the randomization. The baseline characteristics were presented for the advanced (PET or CMR) and SPECT imaging groups using mean and standard deviation for continuous variables, and frequencies and percentages for categorical variables. For the randomized trial population, standardized differences were used to identify possible differences between advanced vs SPECT subgroups. Baseline characteristics in the registry cohort were compared between 2 subgroups. Continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 test or Fisher's exact test. For the primary analysis, the cumulative incidence of the composite clinical endpoint of cardiac death, MI, cardiac arrest, and cardiac rehospitalization (for worsening HF, acute coronary syndrome, arrhythmia) were compared for the advanced vs standard SPECT imaging. A competing risk analysis was performed with noncardiac death as the competing risk. A cumulative incidence function was

Table 1. Baseline characteristics of patients for the randomized trial population

Variables	Advanced n = 64	SPECT n = 56
Age, y	68.5 ± 9.4	67.5 ± 9.2
Male	56 (87.5)	49 (87.5)
CHF	59 (92.2)	55 (98.2)
Previous PCI	26 (40.6)	21 (37.5)
Previous CABG	28 (43.8)	23 (41.1)
History of ventricular arrhythmias	12 (18.8)	13 (23.2)
Device		
Pacemaker only	0	5 (8.9)
ICD only	23 (35.9)	11 (19.6)
CRT any	3 (4.7)	5 (8.9)
Diabetes	24 (37.5)	28 (50.0)
HTN	38 (59.4)	37 (67.3)
Chronic renal dysfunction	18 (28.1)	16 (28.6)
PVD	11 (17.2)	9 (16.1)
Pulmonary disease	16 (25.0)	18 (32.1)
BMI (calculated)	29.0 ± 5.7	29.8 ± 5.6
NYHA class		
I or II	32 (50.0)	29 (51.8)
III or IV	32 (50.0)	27 (48.2)
CCS class		
0 or I or II	64 (100.)	51 (91.1)
III or IV	0	5 (8.9)
Systolic BP	119.5 ± 18.8	117.4 ± 16.8
HR	68.9 ± 12.2	76.4 ± 17.1
Beta-blocker	61 (95.3)	52 (92.9)
ACE and/or ARB	56 (87.5)	51 (91.1)
Diuretics	46 (71.9)	48 (85.7)
Spironolactone	19 (29.7)	21 (37.5)
Antiplatelet and/or ASA	55 (85.9)	44 (78.6)
Antiarrhythmic	7 (10.9)	5 (8.9)
Anticoagulants	29 (45.3)	27 (48.2)
Hemoglobin	129.4 ± 20.4	132.0 ± 21.1
Sodium	139.6 ± 2.9	138.7 ± 3.2
Potassium	4.2 ± 0.4	4.2 ± 0.6
Creatinine	113.0 ± 48.8	123.2 ± 81.8
EF at enrollment	28.7 ± 7.6	29.4 ± 8.0

Values are n (%) or mean ± standard deviation.

ACE, angiotensin- converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; EF, ejection fraction; HR, heart rate; HTN, hypertension; ICD, implantable cardiac device; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SPECT, single-photon emission computerized tomography.

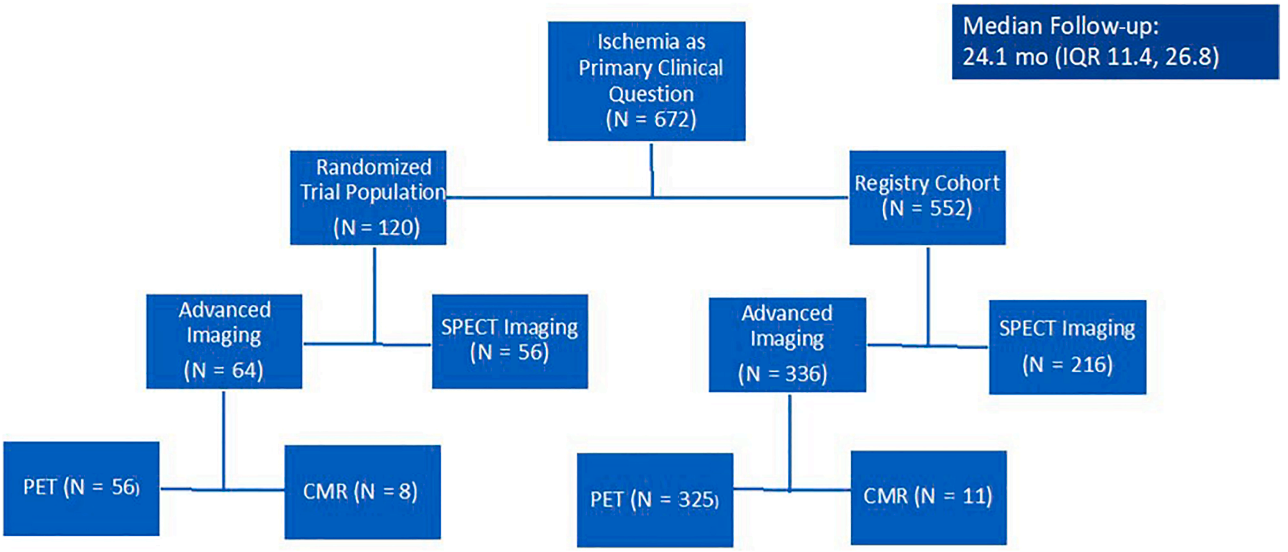


Figure 1. Flow of patient recruitment into Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) study. CMR, cardiac magnetic resonance; IQR, interquartile range; PET, positron emission tomography; SPECT, single-photon emission computerized tomography.

used in estimating the probability of the composite endpoints in the advanced and SPECT groups, and the 3-year cumulative incidence rate (CIR) was reported. The sub-distribution hazard model proposed by Fine and Gray was used to compare the cumulative incidence curves. The same analysis strategy was applied for cardiac death as the key clinically important secondary endpoint. For the all-cause death, the Kaplan-Meier product-limit estimates of the advanced vs SPECT imaging were compared using a log-rank test. The hazard ratio (HR) and associated 95% confidence interval (95% CI) were calculated using the Cox proportional hazard model. To adjust for possible effects of confounding variables on survival for advanced modality vs SPECT, all analyses were adjusted for baseline characteristics (Table 1) and site factor in the competing risk multivariable model and the Cox proportional hazards multivariable model. The same approach was applied to the early revascularization and no-revascularization subgroups in the registry cohort. All adjustment variables were prespecified.

A meta-analysis was used to pool the randomized and registry populations for primary outcome and cardiac death using an inverse-variance random-effect model. The heterogeneity between the randomized and registry populations was assessed using the I^2 statistic. The analysis was done on intention-to-treat data.

Results

Patients and follow-up

The entire AIMI-HF project enrolled 1390 subjects. This number included the enrollment of 672 patients between January 6, 2011 to November 5, 2019, for whom the clinical question for imaging was related to defining ischemia, which is the focus of this particular study. This study included 120 patients who were randomized to either advanced imaging (PET or CMR) (n = 64) or SPECT imaging (n = 56), and 552 patients who were enrolled in a parallel registry cohort (Fig. 1). Patients were followed for a median of 24.1 months (interquartile range 11.6, 27.5). A total of 10 patients (5 randomized and 5 registry; 1.5%) were lost to follow up at various timepoints of the study.

In the randomized trial population, the average patient age was 68.0 ± 9.3 years, with 12.5% female patients enrolled. The majority of patients (95.0%) had NYHA functional class II or III symptoms, and the mean baseline LVEF was 29.0% ± 7.8% (Table 1). The baseline characteristics for the patients in the registry cohort are presented in Table 2.

In the entire ischemia cohort, a total of 17 patients did not get the intended imaging modality anticipated (9 patients had an alternative mode of imaging, and 8 patients had no imaging).

Primary outcome and secondary outcome of cardiac death

Randomized trial population. After a follow-up duration of 3 years, the CIR for the primary outcome in the randomized trial population occurred in 33.1% of patients in the advanced imaging group and 33.0 % of patients who had SPECT imaging, with no difference between the groups (HR 0.94, 95% CI 0.49, 1.80, $P = 0.853$; Fig. 2). The CIR for cardiac death occurred in 13.8% of patients who had advanced imaging, and 25.1% of patients who had SPECT imaging (HR 0.62, 95% CI 0.25, 1.52, $P = 0.296$; Table 3; Fig. 2). Correspondingly, other components of the composite were not different for advanced vs SPECT imaging.

Registry cohort. Among the 552 patients enrolled in a parallel registry arm, the CIR for the primary endpoint occurred in 31.2% of patients who had advanced imaging and 35.3% of patients who had SPECT imaging at 3 years (HR 0.81, 95% CI 0.561, 1.19, $P = 0.284$ after adjustment for baseline characteristics and site factor). In the prespecified secondary endpoint of cardiac death, the CIR was 11.0%, vs

Table 2. Baseline characteristics of patients in the registry cohort

Variables	Advanced n = 336	SPECT n = 216	*P*
Age, y	67.1 ± 9.3	69.1 ± 10.2	0.024
Male	282 (83.9)	186 (86.1)	0.486
CHF	270 (80.4)	186 (86.1)	0.082
Previous PCI	154 (45.8)	111 (51.4)	0.202
Previous CABG	112 (33.3)	90 (41.7)	0.047
History of ventricular arrhythmias	33 (9.8)	48 (22.2)	< 0.001
Device			0.005
Pacemaker only	11 (3.3)	10 (4.6)	
ICD only	49 (14.6)	53 (24.5)	
CRT any	17 (5.1)	17 (7.9)	
Diabetes	166 (49.4)	98 (45.4)	0.354
HTN	239 (71.1)	173 (80.1)	0.018
Chronic renal dysfunction	82 (24.4)	78 (36.1)	0.003
PVD	48 (14.3)	49 (22.7)	0.011
Pulmonary disease	106 (31.6)	62 (28.7)	0.479
BMI (calculated)	30.2 ± 6.7	28.7 ± 5.3	0.008
NYHA class			0.121
I or II	194 (57.7)	139 (64.4)	
III or IV	142 (42.3)	77 (35.7)	
CCS class			0.378
0 or I or II	285 (84.8)	189 (87.5)	
III or IV	51 (15.2)	27 (12.5)	
Systolic BP	123.2 ± 20.3	123.7 ± 20.5	0.791
HR	74.5 ± 16.9	72.3 ± 15.1	0.127
Beta-blocker	291 (86.6)	193 (89.4)	0.338
ACE and/or ARB	240 (71.4)	173 (80.1)	0.022
Diuretics	186 (55.4)	141 (65.3)	0.021
Spironolactone	83 (24.7)	74 (34.3)	0.015
Antiplatelet and/or ASA	270 (80.4)	163 (75.5)	0.172
Antiarrhythmic	28 (8.3)	33 (15.3)	0.011
Anticoagulants	117 (34.8)	93 (43.1)	0.052
Hemoglobin	127.7 ± 20.6	127.2 ± 19.6	0.784
Sodium	138.7 ± 3.3	138.7 ± 3.5	0.820
Potassium	4.1 ± 0.5	4.2 ± 0.4	0.448
Creatinine	134.0 ± 116.9	136.9 ± 110.6	0.784
EF at enrollment	29.8 ± 8.2	31.5 ± 7.6	0.015

Values are n (%) or mean ± standard deviation.

ACE, angiotensin- converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; EF, ejection fraction; HR, heart rate; HTN, hypertension; ICD, implantable cardiac device; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SPECT, single-photon emission computerized tomography.

16.6% for advanced vs SPECT (HR 0.53, 95% CI 0.27, 1.04, $P = 0.066$ after adjustment for baseline characteristics and site factor; Table 4; Fig. 3). The results from the multivariable models for primary outcome and cardiac death are included in Supplemental Tables S2 and S3.

Pooled analyses of randomized and registry trial populations

Given the similarities in directionality of results, we conducted a post hoc analysis of the randomized and registry populations pooled in a meta-analysis, to evaluate the net effect of advanced vs SPECT imaging on the primary outcome and the secondary outcome of cardiac death. The data were analyzed to 3 years of follow up. The degree of ischemia and scar identified on imaging is noted in Supplemental Table S4. No significant difference was observed between advanced and SPECT imaging for the primary outcome (HR 0.84, 95% CI 0.61, 1.17, $P = 0.30$), with minimal heterogeneity in the results between the 2 populations ($\chi^2 = 0.15$, $P = 0.70$, $I^2 = 0\%$). However, a significant reduction occurred in cardiac death for advanced imaging vs SPECT imaging (HR 0.56, 95% CI 0.33, 0.96, $P = 0.04$), with minimal heterogeneity in the results between the 2 populations ($\chi^2 = 0.07$, $P = 0.78$, $I^2 = 0\%$; Fig. 4).

We also evaluated all-cause death. The randomized and registry all-cause death outcomes paralleled the findings for cardiac death. In the pooled meta-analysis, a trend occurred, which did not meet statistical significance, in all-cause death for advanced imaging vs SPECT imaging (HR 0.65, 95% CI 0.42, 1.00, $P = 0.05$) with minimal heterogeneity in the results between the 2 populations ($\chi^2 = 0.21$, $P = 0.65$, $I^2 = 0\%$).

Impact of revascularization

Overall, early revascularization (within 6 months of an imaging study) occurred in 17.4% of patients being evaluated for ischemia, and at a greater frequency in patients who had advanced imaging vs SPECT (21.8% vs 11.0%, respectively, $P = 0.0003$). To better understand the impact of revascularization, further analysis was undertaken. This analysis focused on the registry, given that the randomized control trial was underpowered. Among those in the registry cohort,

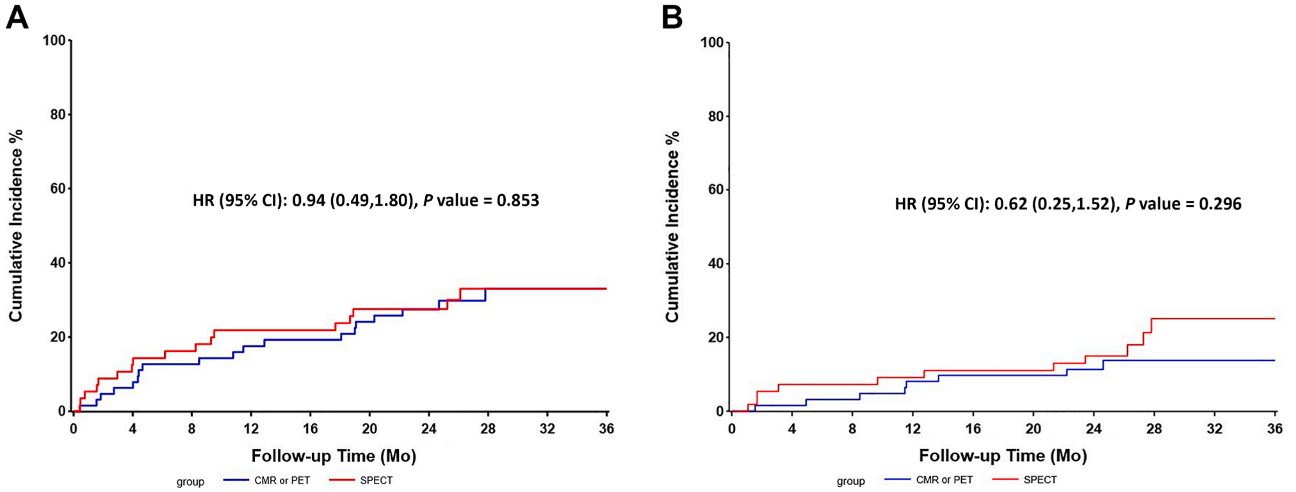


Figure 2. Cumulative incidence of (**A**) primary composite outcome and (**B**) cardiac death in randomized trial population. CI, confidence interval; CMR, cardiac magnetic resonance; HR, hazard ratio; PET, positron emission tomography; SPECT, single-photon emission computerized tomography.

early revascularization occurred more frequently in the advanced imaging group vs the SPECT group (23.5% vs 10.7%, $P = 0.0001$). The majority of the revascularization in the registry cohort was achieved with PCI (55.6%), whereby 40.2% of patients with early revascularization had CABG, and 3.9% had both CABG and PCI.

In the registry cohort, among patients who had early revascularization, the CIR for the primary outcome was significantly lower in patients who had advanced imaging (28.4% vs 56.7%, advanced vs SPECT, HR 0.19, 95% CI, 0.05, 0.77, $P = 0.02$ after adjustment for variables in the baseline characteristics and site factor). No significant differences occurred in the CIR for the primary endpoint for advanced vs SPECT imaging in those who did not have early revascularization among the registry cohort, after adjustment for baseline characteristics and site factor (32.0% vs 32.5%, advanced vs SPECT, HR 0.91, 95% CI, 0.60, 1.37, $P = 0.641$).

Discussion

Decisions relating to revascularization in IHF remain complex. This randomized and registry trial is the largest of its kind designed to pragmatically evaluate the impact of imaging modalities for ischemia in patients with IHF. No significant differences occurred in the primary outcome for advanced vs SPECT imaging in either the randomized trial population or the registry cohort. A significant reduction in the cumulative incidence of cardiac death was observed for advanced imaging when the randomized and registry populations were pooled in a meta-analysis.

The role of revascularization in patients with HF continues to be debated. The main **S**urgical **T**reatment for **Isc**hemic **H**eart Failure (STICH) trial did not demonstrate that routine CABG reduced mortality for patients with ischemic LV dysfunction at 5 years; however, a survival benefit for revascularization was apparent in the extended (10-year) follow-up period.[1,2,8,18] In addition, a selective benefit was observed in particular cohorts, including those aged < 60 years, those with 3-vessel disease, and those with significantly impaired EF.[19] A recent systematic review identified a statistically significant benefit of revascularization on all-cause mortality that was neither substantial nor robust, and was limited by significant bias across numerous randomized controlled trials.[20] More recently, the REVIVED-BCIS 2 study demonstrated that revascularization with PCI, vs optimal medical therapy, failed to result in a lower incidence of death or HF hospitalization in patients with ischemic LV dysfunction.[5] Differences in baseline characteristics limit the ability to make direct comparisons between STICH and REVIVED-BCIS,[1,2,5] and these trials did not evaluate ischemia imaging per se. REVIVED-BCIS published

Table 3. Outcomes in the randomized trial population

3 y outcome	Event rates	Advanced N = 64	SPECT N = 56	HR (95% CI)*	P*
Primary outcome	N (%)	19 (29.7)	17 (30.4)		
	CIR, %	33.1	33.0	0.94 (0.49,1.80)	0.853
Cardiac death	N (%)	8 (12.5)	11 (19.6)		
	CIR, %	13.8	25.1	0.62 (0.25,1.52)	0.296
All death	N (%)	9 (14.1)	14 (25.0)		
	Kaplan-Meier event rate, %	17.1	33.2	0.55 (0.24,1.26)	0.150

CI, confidence interval; CIR, cumulative incidence rate; HR, hazard ratio; SPECT, single-photon emission computerized tomography.

* No adjustment for baseline characteristics variables.

Table 4. Outcomes in registry cohort

3 y outcome	Event rates	Advanced N = 336	SPECT N = 216	HR (95% CI)*	*P**
Primary outcome	N (%)	91 (27.1)	71 (32.9)		
	CIR, %	31.2	35.3	0.81 (0.56, 1.19)	0.284
Cardiac death	N (%)	35 (10.4)	28 (13.0)		
	CIR, %	11.0	16.6	0.53 (0.27, 1.04)	0.066
All death	N (%)	49 (14.6)	38 (17.6)		
	Kaplan-Meier event rate, %	15.5	21.6	0.69 (0.42, 1.15)	0.158

CI, confidence interval; CIR, cumulative incidence rate; HR, hazard ratio; SPECT, single-photon emission computerized tomography.

* Adjustment for variables in Table 2 and site factor.

a post hoc analysis on ischemia detection, and this did not demonstrate an association between ischemic burden and clinical outcomes.[21] However, differences in study design, population, and methodology limit the ability to directly compare the results to those of the current study. Notwithstanding this limitation, the data support the notion of using a selective approach to revascularization in patients with IHF. Observational data have demonstrated that methods to define ischemia, viability, and scar can identify high-risk patients who are likely to benefit (or not) from revascularization. The long-term impact of newer or "alternative" imaging strategies used for revascularization decision processes have not been well evaluated in large cohorts of patients with HF.

The current study demonstrated that in patients being evaluated for ischemia burden, the imaging modality did not significantly affect the primary composite endpoint in either the randomized trial population or the registry cohort. However, in a post hoc analysis, a significant reduction in cardiac death was observed in patients who had advanced imaging vs SPECT, in a pooled meta-analysis. In addition, among the registry cohort who had early revascularization, a significant reduction occurred in the primary endpoint in patients who had advanced imaging (Central Illustration). This finding suggests that advanced imaging may more appropriately direct patients to revascularization or medical therapy. However, this possibility must be confirmed in subsequent studies. Recent data from the **I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness With **M**edical and **I**nvasive **A**pproaches Trial (ISCHEMIA) study confirmed the beneficial effect of complete revascularization on cardiac outcomes in patients with stable CAD and no heart failure who were assigned to the invasive strategy.[19]

Cardiac PET imaging (which was the dominant advanced technology in our cohort) has advantages over SPECT imaging as a more accurate marker for ischemia.[22-24] The findings in this study also extend previous work suggesting a relationship between revascularization benefit and presence of ischemia on cardiac imaging in patients with ischemic cardiomyopathy. The higher scar score with SPECT may be a reflection of attenuation artifact. Attenuation correction was not a requirement of the protocol, reflecting the SPECT practices at the time, nor is it universally applied today. In addition, data comparing PET to SPECT has demonstrated greater accuracy even with attenuation correction.[25,26] The substudy of the ISCHEMIA trial observed improved outcomes following revascularization, compared to medical therapy, in patients with inducible ischemia, a history of HF, and an EF of 35%-45%.[27] More recently, Ródenas-Alesina and colleagues evaluated a contemporary cohort of patients with ischemic cardiomyopathy and demonstrated that the beneficial effects of early revascularization were mediated by the percentage of ischemia.[28] In IHF patients, the use of ischemia testing, particularly with advanced imaging, may better select patients who would benefit from a strategy of

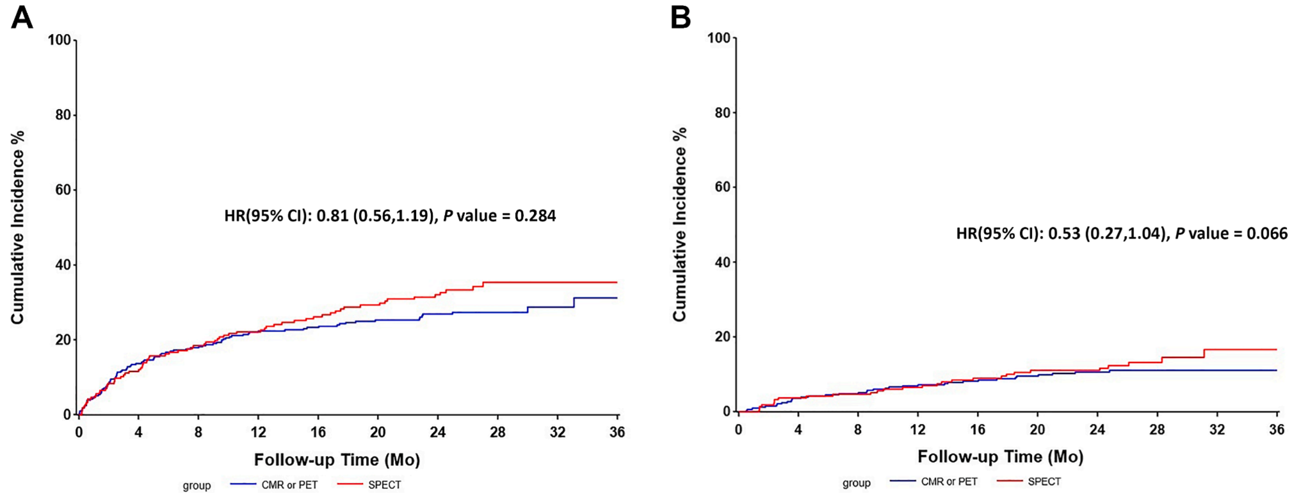


Figure 3. Cumulative incidence of (**A**) primary composite outcome and (**B**) cardiac death in registry cohort. CI, confidence interval; CMR, cardiac magnetic resonance; HR, hazard ratio; PET, positron emission tomography; SPECT, single-photon emission computerized tomography.

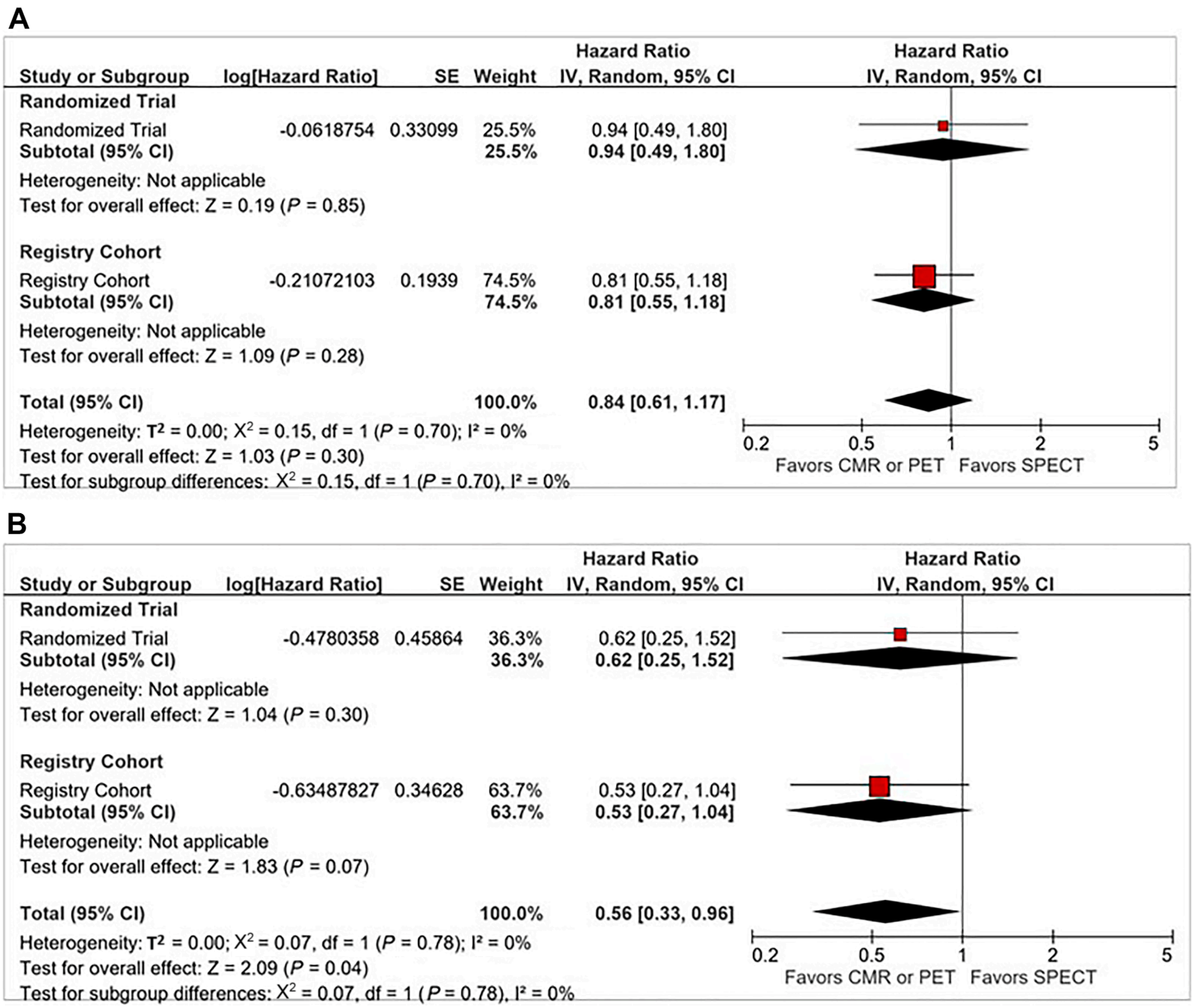
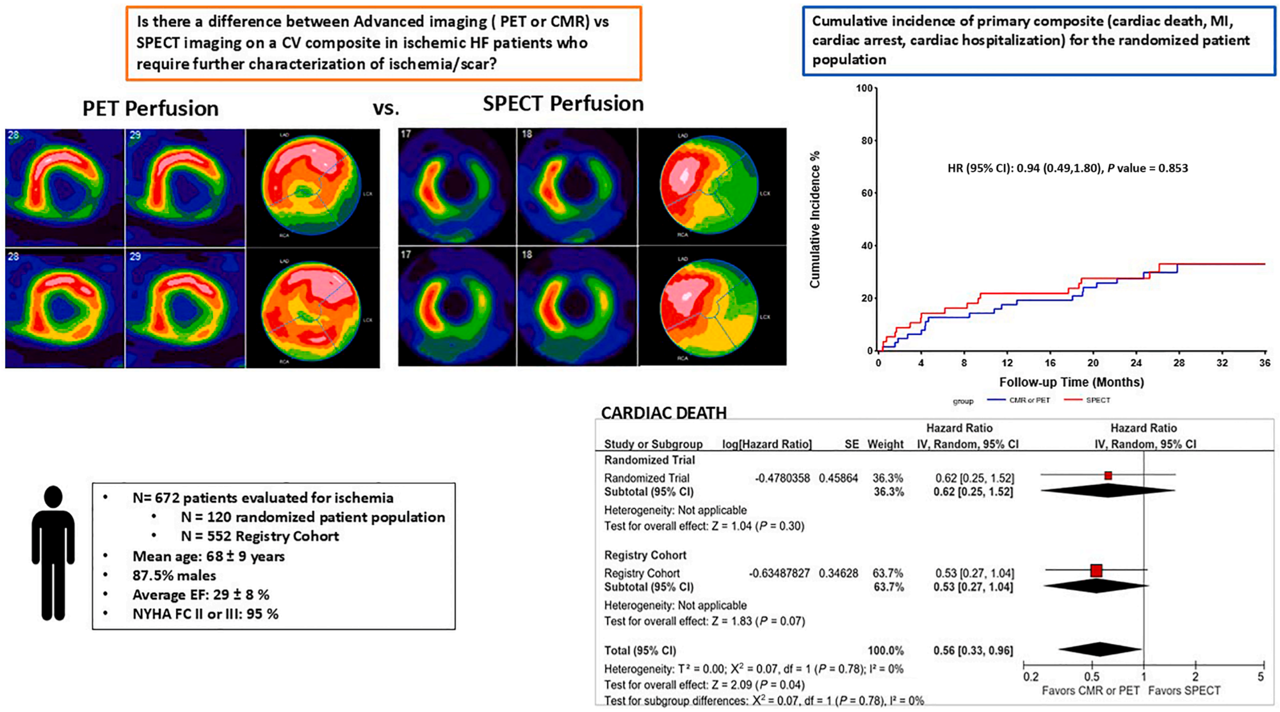


Figure 4. Pooled estimate effects for randomized trial population and registry cohort for (**A**) primary outcome and (**B**) cardiac death. CI, confidence interval; CMR, cardiac magnetic resonance; df, degrees of freedom; PET, positron emission tomography; SE, standard error; SPECT, single-photon emission computerized tomography.

revascularization and subsequent improved clinical outcomes. These data suggest that advanced imaging−guided revascularization better prevents long-term adverse cardiac events.

We acknowledge limitations in our study. Primarily, the randomized trial population was underpowered to detect differences in the primary and secondary endpoints. However, given the similarities in directionality of results, and the fact that the populations were sufficiently similar, the randomized and registry populations were pooled in a post hoc meta-analysis and demonstrated significant reduction in cardiac death for patients undergoing advanced imaging (PET or CMR). The registry population was designed minimizing biases associated with observational studies, in particular confounding using propensity-score methods. The risk of bias associated with an observational study was minimized, as assessed by the Risk of Bias In Non Randomized Studies of Interventions (ROBINS-I) tool,[29] and the algorithm to decide whether to combine a randomized and observational study is satisfied in that an insufficient number of randomized studies address the question, and the observational study is without critical risk of bias and addresses the question with respect to the protocol-specified interventions.[30] The combined result was similar in magnitude, but with the greater precision, the result was statistically significant.

As with any study evaluating a diagnostic imaging test, the impact of that test on an outcome depends on the subsequent decision-making from the results. Although challenging, this study design simulates real-world scenarios in which clinicians use imaging to make decisions. The disadvantage is that performance and detection bias can occur, and the dependence on the effectiveness of the treatment selected. In this population, a reasonable expectation is that the degree of ischemia and scar detected would be fairly similar. However, the incidence of ischemia was greater in the advanced imaging arm, and more scar was seen with SPECT. Although some bias in patient selection is possible and is not evident, this difference most likely reflects the known superior accuracy of advanced imaging, which overcomes some of the limitations of SPECT



Central Illustration. Graphical summary of the study population and main findings of the Ischemia arm of the Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) Study. No significant differences occurred in the cumulative incidence of the primary composite endpoint (cardiac death, myocardial infarction [MI], cardiac arrest, cardiac rehospitalization) for the randomized patient population. Pooling the results from the randomized and registry populations demonstrated a significant reduction in cardiac death (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.33, 0.96) for advanced (cardiac magnetic resonance [CMR] or positron emission tomography [PET]) imaging over single-photon emission tomography (SPECT) imaging. CV, cardiovascular; EF, ejection fraction; HF, heart failure; NYHA FC, New York Heart Association functional class; SE, standard error.

imaging.[25,26,31,32] This superiority may in part explain the improved outcomes for the advanced imaging arm over SPECT for the combined randomized and registry data set.

Stress MRI was underrepresented in the advanced imaging arm. The potential advantages of stress MRI may include its ability to evaluate myocardial viability and differentiate nonischemic cardiomyopathies; we were unable to assess this possibility in this study, as use of stress MRI was underrepresented in the advanced imaging arm.

This study did not include patients with IHF and preserved EF. Recent data suggest that these patients may have greater short-term risk post-revascularization but improved long-term survival, compared to patients with reduced EF.[33] Whether ischemia imaging could help better select patients with HF with preserved EF for revascularization needs to be confirmed in additional studies.

The AIMI-HF study compared advanced cardiac imaging, with either PET or CMR, to SPECT perfusion imaging in patients with IHF. No statistically significant differences occurred in the primary composite for advanced vs SPECT imaging in either the randomized or the registry trial populations. At a pragmatic level, when cardiac imaging is used to evaluate ischemia and/or scar in patients with IHF, the choice of imaging modality does not appear to have a significant impact on a composite of CV endpoints. The sample size of the randomized cohort was underpowered, so results do need to be interpreted with caution. However, when the 2 study populations were pooled in a meta-analysis, a significant reduction occurred in cardiac death, suggesting potential benefit for advanced imaging in this population. In addition, among registry patients who had early revascularization, the cumulative incidence rate for the primary outcome was significantly lower in patients who had advanced imaging vs SPECT. Whether this finding suggests that advanced imaging may better select those who may or may not benefit from revascularization should be interpreted with caution and needs to be confirmed in future studies.

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Given their role as Associate Editor, David Ian Paterson had no involvement in the peer review of this article and has no access to information regarding its peer review.

Ethics Statement

This trial was approved by the ethics committee at each site

Patient Consent

All patients provided written informed consent.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2025.06.023.