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Appendix E1

Study Design and Cohort

Clinical events of all subjects were assessed by an interrogation of Social Security Death Index of the United States, detailed review of all available electronic medical records and scripted telephone interview.

^{82}Rb/*N*-13 Ammonia MPI: Hybrid PET/CT-Additional Details

Myocardial perfusion was assessed at rest and during pharmacological stress with either adenosine, dipyridamole, dobutamine, or regadenoson. Regional myocardial perfusion was assessed at rest after the administration of 46.5 ± 8.5 mCi (1718.7 ± 316.1 MBq) of ^{82}Rb or 25.2 ± 4.4 mCi (932 ± 164.2 MBq) of *N*-13 ammonia. Following the initial radionuclide injection, a 7 to 20 minute rest emission scan (^{82}Rb and *N*-13 ammonia respectively) was acquired in a list mode. During maximal hyperaemia from a pharmacological stress infusion, a second dose of ^{82}Rb (mean 46.5 ± 8.6 mCi, 1718.4 ± 317.2 MBq) or 25.6 ± 4.3 mCi (946.0 ± 159.4 MBq) of *N*-13 ammonia was administered, and a stress emission scan was acquired in the same manner followed by a second transmission CT scan for attenuation correction of the stress perfusion data. The PET list mode data were reconstructed into dynamic images for myocardial blood flow quantification, and into static images for qualitative myocardial ischemia assessment. PET images were reconstructed using ordered subsets expectation maximization (OSEM) (30 iterations and 2 subsets), and a 3-dimensional PET filter was used (Butterworth filter cut-off frequency 10, order of 5). Rest and stress LV ejection fraction (EF) were calculated from gated myocardial perfusion images using commercially available software (Corridor4DM, INVIA Medical Imaging Solutions, Ann Arbor, Michigan).

Assessment of NAFLD

We performed a validation of hepatic HU measurement on CTAC by measuring mean hepatic HU (by the same method as described in this study) in 32 patients who had both MPI hybrid PET/CT and a diagnostic-quality noncontrast abdominal CT. This demonstrated strong positive correlation for mean hepatic HU measurement (R = 0.72).

Assessment of Clinical Outcomes

Outcomes and vital status were assessed by a combination of examining the electronic medical record, follow-up telephone interviews and integrating data from the Social Security Death Index, the National Death Index, and the Partners Health care Research Patient Data Registry, as previously described.(14) Myocardial infarction was defined by elevation of serum troponin consistent with myocardial injury, along with symptoms of chest pain or ECG changes. Heart failure events were defined by admission to an inpatient unit or emergency department for at least 12 hours for new or worsening symptoms compatible with heart failure. For the survival analysis, MACE was the outcome variable and patients who did not experience MACE were

censored at the date of last followup. That date was defined as date of followup by electronic medical record or by phone call, whichever occurred last.

Table E1: Univariable and Multivariable Association With NAFLD

Parameters	Univariable		Multivariable	
	β coeff. ± SE.	*P*	β coeff. ± SE.	*P*
Age	–0.003 ± 0.002	0.001	—	—
Female	0.006 ± 0.050	0.795	—	—
BMI, kg/m2	0.018 ± 0.002	<0.001	0.015 ± 0.03	<0.001
Systolic BP, mm Hg	0.0008 ± 0.001	0.07	—	—
Diastolic BP, mm Hg	–0.0001 ± 0.002	0.90	—	—
Heart rate, bpm	0.003 ± 0.002	<0.001	0.002 ± 0.002	0.03
CVD Risk Factors				
Hypertension	0.061 ± 0.173	0.019	—	—
Diabetes	0.131 ± 0.050	<0.001	—	—
Dyslipidemia	0.019 ± 0.085	0.418	—	—
Smoking	–0.018 ± 0.079	0.647	—	—
Fam Hx of premature CAD	0.002 ± 0.056	0.941	—	—
Morise score	0.016 ± 0.026	<0.001	—	—
Medications				
ACEI	0.072 ± 0.194	0.005	—	—
Betablockers	–0.008 ± 0.046	0.724	—	—
Statins	0.069 ± 0.184	0.003	—	—
ASA	–0.013 ± 0.045	0.575	—	—
Diuretics	0.046 ± 0.051	0.069	—	—
Oral hypoglycemic agents	0.245 ± 0.069	<0.001	0.16 ± 0.07	<0.001
Insulin	0.107 ± 0.076	0.006	—	—
Rest ECG				
Normal	0.107 ± 0.09	0.019	—	—
AF	–0.036 ± 0.131	0.591	—	—
LBBB	0.006 ± 0.130	0.927	—	—
RBBB	–0.101 ± 0.144	0.170	—	—
Left ventricular volumes and ejection fraction				
LVEF stress, %	–0.001 ± 0.002	0.308	—	—
LVEF Rest. %	0.0004 ± 0.003	0.736	—	—
LV mass, g	0.002 ± 0.001	<0.001	0.002 ± 0.001	0.04
LVEDVI, stress, mL/m2	–0.006 ± 0.0016	0.438	—	—
LVEDVI, rest, mL/m2	–0.0008 ± 0.0017	0.375	–0.004 ± 0.003	0.003

AF = atrial fibrillation; ASA = aspirin; ACEI = angiotensin converting enzyme inhibitors; BMI = body mass index; BP = blood pressure; CFR = coronary flow reserve; CAD = coronary artery disease; coeff. = coefficient; DM = diabetes mellitus; ECG = electrocardiograph; Fam = family; HU = Hounsfield units; Hx = history; HR = hazard ratio; LVEF = left ventricular ejection fraction; LBBB = left bundle branch block; LVEDVI = indexed left ventricular end diastolic volume; MBF = mean myocardial blood flow; NAFLD = nonalcoholic fatty liver disease; PET = positron emission tomography; RBBB = right bundle branch block; bpm = beats per minute. Only significant variables are shown in the multivariable models.

Table E2: MACE in the study cohort stratified by NAFLD annualized event rate

Events	NAFLD *n* = 125	FU time (days)	AER (%)	No NAFLD *n* = 761	FU time (days)	AER (%)
Death (all cause)	4	1913 ± 1004	0.5	80	1817 ± 963	1.9
Nonfatal MI	8	1120 ± 835	2.1	32	1057 ± 739	1.5
Heart failure hospitalization	9	1310 ± 846	2	36	1170 ± 882	1.5
Coronary revascularization	5	1081 ± 1018	1.4	16	914 ± 710	0.8
MACE	18	1755 ± 1031	3	115	1733 ± 977	3.2

AER = annualized event rate; FU = follow-up; MI = myocardial infarction; MACE = major adverse cardiac events; NAFLD = nonalcoholic fatty liver disease.