SUPPLEMENTAL MATERIAL

Combined Cardiac MRI and C-Reactive Protein Levels Identify a Cohort at Low Risk for Defibrillator Firings and Death

Wu et al: Cardiac MRI and CRP for ICD Risk Stratification

SUPPLEMENTAL METHODS

Additional study population information

Exclusion criteria included: other indications for ICD placement (e.g. sustained ventricular arrhythmias, cardiac arrest, syncope); contraindications to CMR (e.g. existing cardiac device); New York Heart Association (NYHA) functional class IV; acute myocarditis or acute sarcoidosis or infiltrative disorders such as amyloidosis, or hemochromatosis, congenital heart disease, or hypertrophic cardiomyopathy; or renal insufficiency (creatinine clearance, CrCl<30 ml/min after July 2006; CrCl<60 ml/min after February 2007).

Blood sample collection and analysis

Blood samples were collected in EDTA at the time of ICD insertion and processed for long-term storage at -80°C. These plasma samples were thawed and assayed for hsCRP (Alpco) and NT-proBNP (Roche) using enzyme-linked immunosorbent assays. Other blood analytes (serum sodium, potassium, creatinine) were measured in the clinical laboratory.

Additional CMR imaging and analysis details

Short and long-axis cine images were acquired with a steady-state free precession sequence (TR=2.5-3.8; TE=1.1-1.6; flip angle=45-60°; temporal resolution 40-45 msec; average spatial resolution 1.5x2.4x8 mm). Two-dimensional LGE cross-sectional short- and long-axis images through the LV were acquired starting at approximately 15 minutes after intravenous administration of 0.15-0.20 mmol/kg of gadodiamide (Omniscan, GE Healthcare) or gadopentetate dimeglumine (Magnevist, Schering AG) using an inversion-recovery fast gradient-echo sequence (TR=5.4-8.3; TE=1.3-3.9; TI optimized for nulling of normal myocardium; spatial resolution 1.4-1.5x2.2-2.4x8 mm).

LV EF, volumes, and mass were quantified by standard methods.[1]

SUPPLEMENTAL RESULTS

Of the 18 nonischemic cardiomyopathy patients who sustained the primary endpoint, 14 occurred in patients with idiopathic cardiomyopathy.

Additional secondary endpoint occurrence

The secondary combined endpoint of HF hospitalizations, appropriate ICD firings, and cardiac death occurred in 67 patients (29%). Incidence rates in the low, medium, and high gray-CRP groups were 2.9%, 9.3%, and 23%/year, respectively, log-rank $p<0.001$.

ATP therapy alone (in the absence of ICD shocks) for ventricular arrhythmias was seen in 5 patients, all in the intermediate gray-CRP group. When ATP therapy was included as endpoint with appropriate ICD shocks and cardiac death, incidence rates by gray-CRP tertiles were 0.7%, 6.6%, and 16.0%/year, respectively, log-rank $p<0.001$ (Supplemental Figure 3).

There were 35 inappropriate firings (15%) with annual incidence rates of: 9.3% (low gray-CRP); 4.5% (intermediate); and 2.2% (high gray-CRP), log-rank $p=0.07$. This highlights the negative impact of the ICD in the low risk group. There were 20 device complications (8.5%), predominantly lead revisions for dislodgement or fractures, but also 2 system extractions for device infections and 1 pneumothorax requiring surgical pleurodesis and prolonged hospitalization.

SUPPLEMENTAL REFERENCES

1. Bellenger NG, Pennell DJ. Assessment of cardiac function. In: Manning WJ, Pennell DJ, eds. *Cardiovascular magnetic resonance*. 1st ed. Philadelphia, Pennsylvania: Churchill Livingstone; 2002:99-111.

Supplemental Table: Characteristics of the Cohort by Etiology of Cardiomyopathy

	Nonischemic (n=98)	Ischemic (n=137)	p-value
Male (%)	62 (63)	117 (85)	<0.001
Age (mean ± SD) (years)	52±12	61±11	<0.001
% ≥ 70 years old	3	23	<0.001
Caucasian/African-American/ Other (%)	54 (56) / 40 (41) / 3 (3)	111 (81) / 22 (16) / 4 (3)	<0.001
Time from incident MI/ cardiomyopathy diagnosis	Median 1.05 years [IQR 0.3-5.4]	Median 4.4 years [IQR 0.9-10.7]	<0.001
NYHA Class I/ II/ III (%)	14 (14) / 45 (46) / 39 (40)	43 (31) / 51 (37) / 43 (31)	0.01
Risk factors (%)			
Hypertension	42 (43)	93 (68)	<0.001
Hypercholesterolemia	37 (38)	104 (76)	<0.001
Diabetes	14 (14)	46 (34)	0.001
Nicotine use	30 (31)	95 (69)	<0.001
Medication usage (%)			
ACE-inhibitor or ARB	87 (89)	121 (88)	0.91
Beta-blocker	91 (93)	129 (94)	0.69
Lipid-lowering	41 (42)	123 (90)	<0.001
Antiarrhythmics (amio)	6 (6)	11 (8)	0.58
Diuretics	59 (60)	79 (58)	0.70
Digoxin	27 (28)	21 (15)	0.02
Aldosterone inhibitor	25 (26)	25 (18)	0.18
Aspirin	48 (49)	125 (91)	<0.001
Electrophysiologic variables			
History of atrial fibrillation (%)	14 (14)	28 (20)	0.23
Heart rate	74±14 bpm	70±12 bpm	0.02
% with HR≥80 bpm	36	25	0.07
QRS duration	123±33 msec	117±27 msec	0.11
% with QRS>120 msec	45	32	0.05
Presence of LBBB	32 (33)	22 (16)	0.003
Received biventricular ICD	39 (40)	24 (18)	<0.001
Laboratory/biomarker variables			
Sodium (mEq/L)	139±3	139±3	0.80
Potassium (mEq/L)	4.2±0.4	4.3±0.4	0.39
Creatinine (mg/dL)	1.04±0.7	1.03±0.3	0.85
% with Cr>1.3	16 (8)	3 (7)	0.70
hsCRP (mg/L)	Median 3.2 [IQR 1.1-6.8]	Median 3.4 [IQR 1.3-8.8]	0.61
NT-proBNP (pg/ml)	Median 2080 [IQR 1480-3350]	Median 23700 [IQR 1470-3580]	0.31

Enrollment LVEF (non-CMR)	21±7%	25±7%	<0.001
CMR characteristics			
LVEF (mean±SD)	25±10%	28±8%	<0.001
% with LVEF≤20%	35 (36)	22 (16)	0.001
LV end-diastolic volume index (LVEDV/BSA)(ml/m^2)	135±50	120±36	0.01
LV end-systolic volume index (LVESV/BSA)(ml/m^2)	104±51	88±33	0.01
LV mass index (LV mass/BSA) (ml/m^2)	78±29	76±24	0.41
Hyperenhancement			
LGE present (%)	40 (41)	131 (95)	<0.001
Gray zone extent (grams)	Median 0 [IQR 0-2.3]	Median 14.5 IQR [7.4-22.4]	<0.001
Core region (grams)	Median 0 [IQR 0-3.1]	Median 19.2 IQR [14.1-27.6]	<0.001
Total (gray+core) (grams)	Median 0 IQR [0-5.4]	Median 36.1 IQR [21.0-47.4]	<0.001
Number of Primary Events (%)			
Total	18 (18)	27 (19)	0.80
Type of event			
Appropriate ICD firing	12 (12)	18 (13)	0.84
Cardiac death	6 (6)	9 (7)	0.97

SUPPLEMENTAL FIGURE LEGENDS

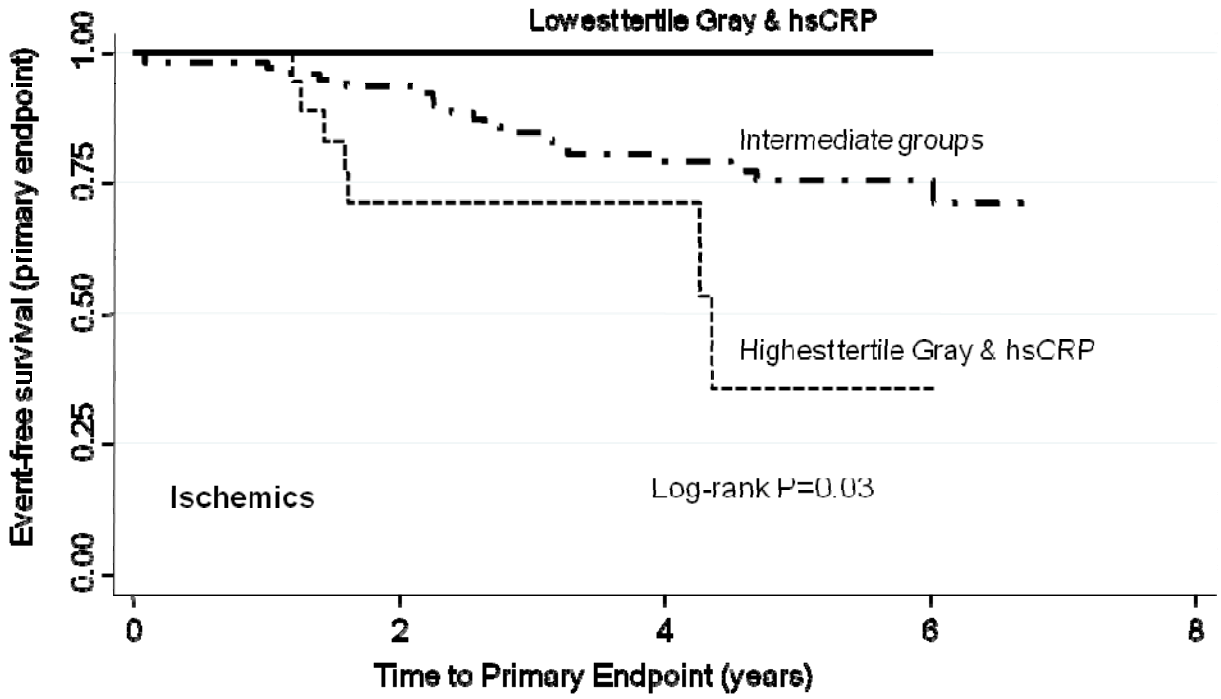
Supplemental Figure 1: Kaplan-Meier curves for the primary endpoint in the ischemic (Panel A) and nonischemic subgroups (Panel B).

Supplemental Figure 2: Forest plot showing hazard ratios (95% CI) for the primary endpoint associated with each 10 gram increment of GZ by patient subgroups. HRs were stratified for etiology of cardiomyopathy, except when etiology was specifically assessed. The area of each data marker is proportional to the inverse of the HR variance (i.e. larger-sized markers connote smaller variances). The non-significant p-values across all categories indicate that: (1) the association between GZ and the primary outcome persisted across all subgroups; and (2) there is no interaction between GZ and any other variable, including hsCRP.

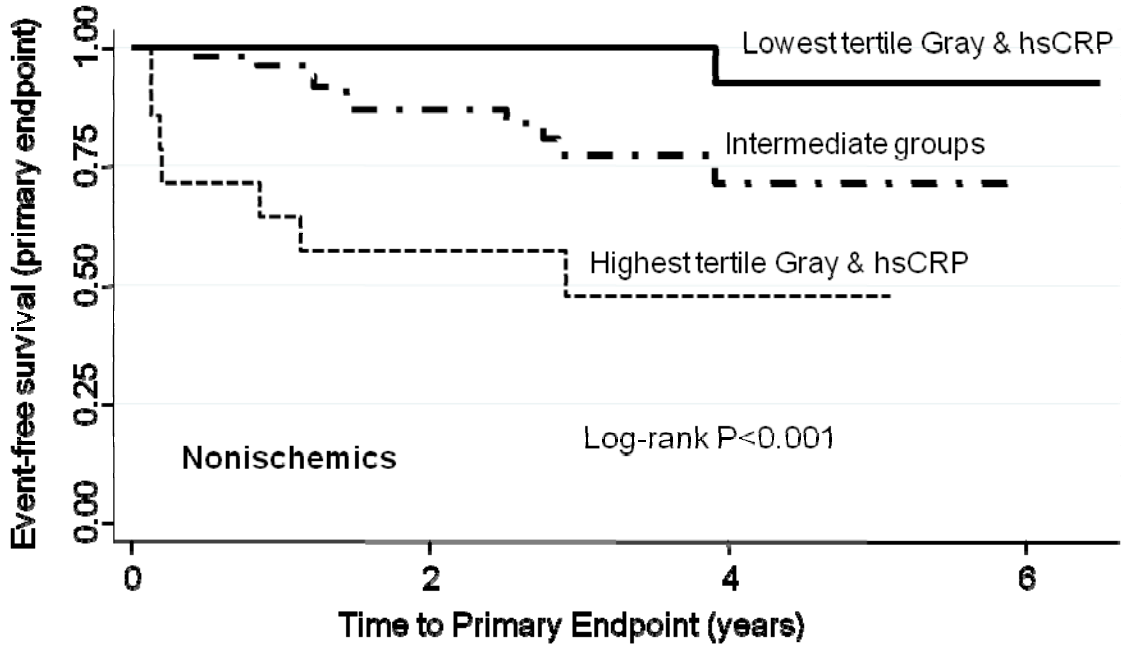
Supplemental Figure 3: Kaplan-Meier curves for the secondary endpoint of appropriate ATP therapy, appropriate ICD shocks, and cardiac death.

Supplemental Figure 1

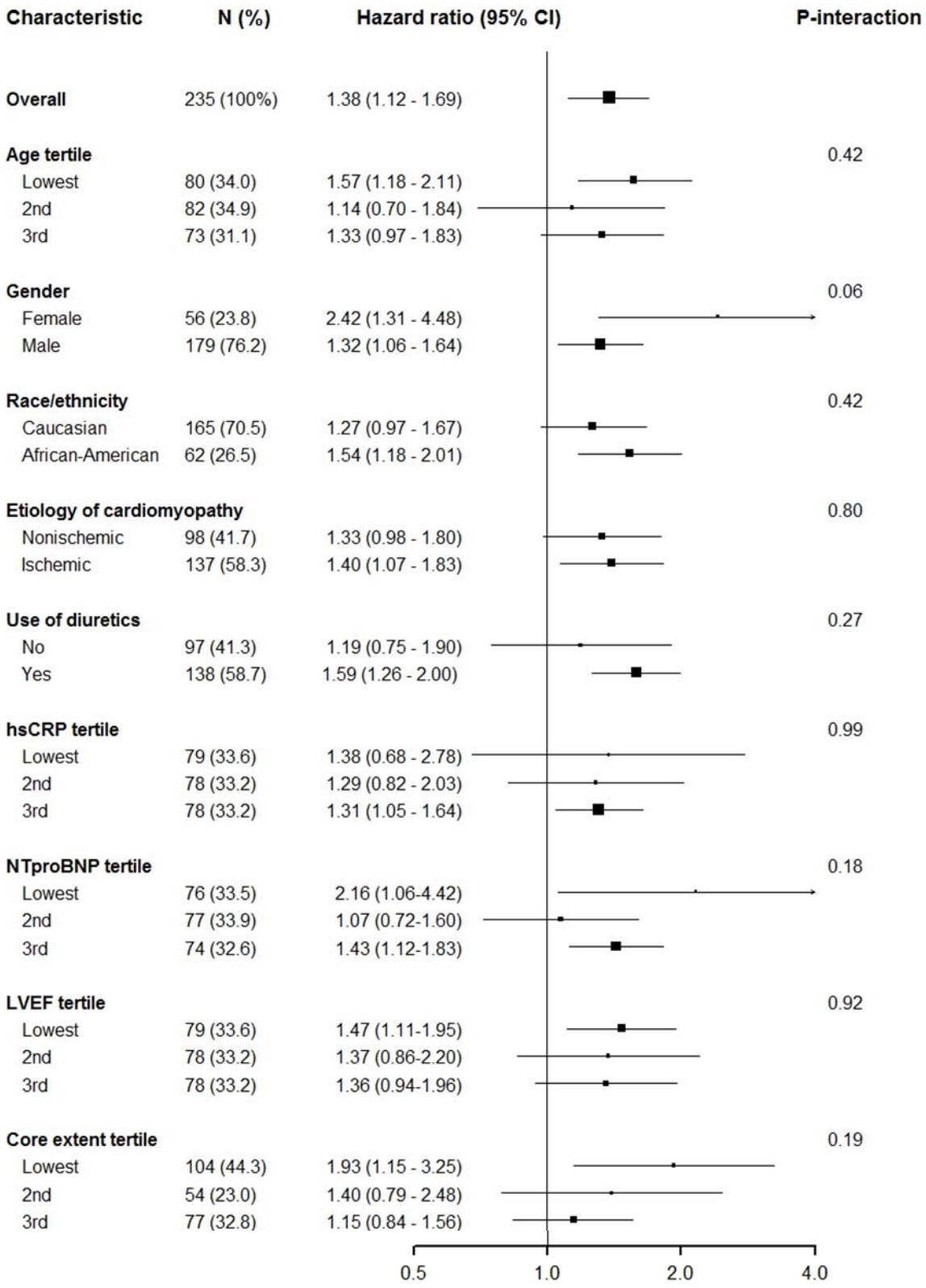
Panel A: Ischemic cohort



Panel B: Nonischemic cohort



Supplemental Figure 2



Supplemental Figure 3