

**Supplementary Table 1: Rates of outcome according to high ( $\geq 29$ pg/ml) vs low NPY ( $< 29$ pg/ml) in each study cohort.**

	Low NPY <29pg/ml N = 561		High NPY $\geq 29$ pg/ml N = 272		P value for interaction
Cohort	Hospitalized Jan 13-Dec14 N=190	Ambulatory Dec 06-Dec 09 N=371	Hospitalized Jan 13-Dec14 N=42	Ambulatory Dec 06-Dec09 N=230	
<b>Cardiovascular death or heart failure hospitalization</b>					
No (%)	77 (40.5)	176 (47.4)	23 (54.8)	128 (55.7)	
Rate (95% CI)	29.6 (23.7, 37.0)	17.4 (15.1, 20.0)	44.8 (29.8, 67.4)	24.6 (20.7, 29.3)	
					0.71
<b>Cardiovascular death</b>					
No (%)	31 (16.3)	79 (21.3)	20 (47.6)	79 (34.3)	
Rate (95% CI)	9.5 (6.7, 13.5)	6.1 (4.9, 7.6)	33.1 (21.4, 51.4)	12.0 (9.6,14.9)	
					0.09
<b>Heart Failure Hospitalization</b>					
No (%)	63 (33.2)	132 (35.5)	12 (28.6)	91(39.6)	
Rate (95% CI)	24.2 (18.9, 31.0)	13.2 (11.1, 15.6)	23.4 (13.3, 41.1)	17.5 (14.3, 21.5)	
					0.40
<b>All cause death</b>					
No (%)	65 (34.2)	145 (39.1)	22 (52.3)	130 (56.5)	

Rate (95% CI)	19.9 (15.7,25.5)	11.2 (9.5,13.2)	36.5 (24.0,55.3)	9.9 (16.6,23.4)	
					0.87

**Supplementary Table 2: Baseline characteristics according to quartiles of NPY**

	Tertile 1	Tertile 2	Tertile 3	Tertile 4	p-value
	N=209	N=209	N=207	N=208	
NPY (pg/ml) median [IQR]	11.0 [7.2-13.1]	18.5 [16.7-20.5]	27.0 [24.6-29.4]	41.1 [36.0-51.3]	<0.001
<b>Demographics</b>					
Age, years	70.2(10.8)	71.6(10.7)	72.3(10.9)	72.8(10.4)	0.007
Women, n (%)	87 (41.6)	100 (47.8)	86 (41.5)	89 (42.8)	0.86
Race, n )%)					0.21
White	204 (97.6)	205 (98.1)	206 (99.5)	202 (97.1)	
Black	1 ( 0.5)	0 ( 0.0)	1 ( 0.5)	1 ( 0.5)	
South Asian	4 ( 1.9)	4 ( 1.9)	0 ( 0.0)	5 ( 2.4)	
BMI (kg/m <sup>2</sup> )	28.7 (6.9)	29.0 (6.8)	28.6 (7.3)	27.4 (5.8)	0.03
<b>Past Medical History</b>					
Cerebrovascular disease, n (%)	43 (20.6)	50 (23.9)	48 (23.2)	38 (18.3)	0.55
Previous MI, n(%)	76 (36.4)	93 (44.5)	93 (44.9)	92 (44.2)	0.11
Hypertension, n (%)	125 (59.8)	141 (67.5)	139 (67.1)	136 (65.4)	0.27

Atrial Fibrillation, n (%)	110 (52.6)	108 (51.7)	108 (52.2)	114 (54.8)	0.65
Diabetes, n (%)	61 (29.2)	71 (34.0)	66 (31.9)	61 (29.3)	0.91
COPD, n (%)	64 (30.6)	54 (25.8)	57 (27.5)	48 (23.1)	0.13
Rheumatoid arthritis, n (%)	7 ( 3.3)	7 ( 3.3)	4 ( 1.9)	5 ( 2.4)	0.40
Connective tissues disease, n (%)	4 ( 1.9)	7 ( 3.3)	3 ( 1.4)	2 ( 1.0)	0.26
Hypothyroidism, n (%)	22 (10.5)	21 (10.0)	19 ( 9.2)	17 ( 8.2)	0.38
Peripheral vascular disease, n (%)	31 (14.8)	31 (14.8)	41 (19.8)	26 (12.5)	0.86
Smoker, n (%)	125 (59.8)	133 (63.6)	132 (63.8)	135 (64.9)	0.30
Alcohol Excess, n (%)	43 (20.6)	31 (14.8)	35 (16.9)	27 (13.0)	0.07
<b>Vital Signs</b>					
Heart rate (beats/min)	80.3 (20.6)	81.1 (19.3)	78.9 (19.2)	78.6 (17.1)	0.40
Systolic Blood Pressure (mmHg)	133.2 (24.0)	135.7 (24.2)	130.4 (26.7)	131.2 (25.9)	0.09
<b>Heart Failure Characteristics</b>					
NYHA functional classification, n (%)					0.058
I	7 ( 3.3)	8 ( 3.8)	6 ( 2.9)	3 ( 1.4)	
II	103 (49.3)	118 (56.5)	130 (62.8)	103 (49.5)	

III	85 (40.7)	76 (36.4)	59 (28.5)	90 (43.3)	
IV	14 ( 6.7)	7 ( 3.3)	12 ( 5.8)	12 ( 5.8)	
Previous HF admission, n (%)	57 (27.3)	56 (26.8)	72 (34.8)	75 (36.1)	0.02
Heart failure diagnosis within 2 years, n (%)	58 (27.8)	51 (24.4)	62 (30.0)	75 (36.1)	0.03
Permanent pacemaker, n (%)	9 ( 4.3)	9 ( 4.3)	14 ( 6.8)	11 ( 5.3)	0.43
CRT, n (%)	3 ( 1.4)	1 ( 0.5)	2 ( 1.0)	3 ( 1.4)	0.87
ICD, n (%)	6 ( 2.9)	1 ( 0.5)	3 ( 1.4)	4 ( 1.9)	0.63
Ischaemic aetiology, n (%)	93 (44.5)	111 (53.1)	105 (50.7)	114 (54.8)	0.07
<b>ECG/Echo</b>					
Sinus Rhythm, n (%)	115 (55.0)	124 (59.3)	120 (58.0)	117 (56.2)	0.88
LBBB, n (%)	45 (21.5)	45 (21.5)	44 (21.3)	46 (22.1)	0.91
QRS duration ms, median [IQR]	102.0 [92.0- 130.0]	102.0 [88.0- 124.0]	102.0 [90.0- 126.0]	103.0 [91.0-126.0]	0.94
Ejection Fraction (%)	40.1 (13.7)	41.8 (13.6)	39.1 (13.7)	39.3 (13.2)	0.35
<b>Medications</b>					

Diuretic, n (%)	166 (79.4)	176 (84.2)	186 (89.9)	196 (94.2)	<0.001
ACE inhibitor or ARB, n (%)	153 (73.2)	151 (72.2)	150 (72.5)	146 (70.2)	0.53
Beta Blocker, n (%)	126 (60.3)	119 (56.9)	135 (65.2)	148 (71.2)	0.006
Mineralocorticoid agonist, n (%)	21 (10.0)	22 (10.5)	28 (13.5)	29 (13.9)	0.15
Antiplatelet, n (%)	122 (58.3)	152 (72.7)	143 (69.1)	144 (69.3)	0.16
Warfarin, n(%)	75 (35.9)	69 (33.0)	79 (38.2)	80 (38.5)	0.39
<b>Bloods</b>					
BNP (pg/ml), median [IQR]	492.0 [260.0-883.0]	401.0 [216.0-798.0]	436.0 [232.0-960.0]	598.5 [266.5-1138.5]	0.01
Troponin I (ug/l)	0.2 (1.4)	0.1 (0.3)	0.2 (1.2)	0.1 (0.2)	0.60
Na mmol/l	138.1 (4.1)	138.3 (4.2)	138.9 (3.8)	138.7 (3.7)	0.03
Bilirubin mmol/l	13.8 (10.0)	13.4 (10.4)	13.5 (11.4)	14.0 (10.4)	0.65
AST mmol/l	26.3 (17.1)	25.0 (15.1)	32.1 (83.3)	30.4 (39.6)	0.28
ALT mmol/l	25.2 (23.9)	23.0 (18.7)	29.9 (93.9)	26.1 (41.4)	0.92
TSH mUI/l	2.0 (2.1)	2.3 (4.2)	2.0 (2.5)	2.8 (5.2)	0.003
T4 mmol/l	12.8 (5.3)	13.4 (5.3)	13.6 (4.5)	13.8 (4.1)	0.06

Haemoglobin g/dl	12.4 (1.9)	12.5 (1.9)	12.4 (2.0)	12.3 (2.0)	0.52
Lymphocytes x10 <sup>9</sup> /l	1.7 (1.0)	1.7 (0.7)	1.8 (1.3)	1.8 (1.9)	0.47
Urea mmol/l	8.3 (4.0)	9.3 (4.5)	10.3 (5.5)	11.5 (5.9)	<0.001
eGFR ml/min	54.2 (10.8)	52.0 (12.4)	49.6 (12.9)	46.0 (13.6)	<0.001
Albumin mmol/l	36.4 (4.5)	37.2 (4.6)	37.4 (4.8)	38.1 (4.3)	<0.001

Data are numbers (proportions) medians [interquartile range] or means  $\pm$  standard deviation. Percentages may not total 100 due to rounding. ACE, angiotensin converting enzyme. ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; HF heart failure; ICD, implantable cardiac defibrillator; IQR interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; Race was self reported by participants

**Supplementary Table 3: Pearsons correlations of NPY (log transformed)**

<b>Variable</b>	<b>r value</b>	<b>P value</b>
eGFR(per ml/min/1.73m <sup>2</sup> )	-0.22	<0.001
BNP (per log unit increase)	0.07	0.03
History of MI	0.06	0.10
History of AF	-0.05	0.89
Troponin (per log unit increase)	-0.03	0.47
Ejection fraction (%)	-0.02	0.59
History of CVA	-0.005	0.89

\*Adjusted for Age, Sex and eGFR.

**Supplementary Table 4: Hazard ratio of incremental NPY values relative to median value of 22.6pg/ml for each outcome of interest**

NPY Level (pg/ml)	HR relative to median value (22.6pg/ml)
All cause death	
5	1.46 (0.99-2.14)
10	1.25 (0.85-1.84)
20	0.97 (0.91-1.02)
22.6	1
30	1.52 (1.12-2.06)
40	1.56 (1.12-2.17)
45	1.53 (1.10-2.12)
50	1.48 (1.07-2.05)
Cardiovascular death	
5	1.22 (0.72-2.07)
10	1.03 (0.61-1.75)
20	0.92 (0.85-0.99)

22.6	1
30	1.49 (1.11-2.00)
40	1.70 (1.11-2.60)
45	1.62 (1.06-2.47)
50	1.51 (0.99-2.32)
Heart failure hospitalization or cardiovascular death	
5	1.25 (0.87-1.79)
10	1.16 (0.82-1.64)
20	1.00 (0.94-1.06)
22.6	1
30	1.12 (0.91-1.38)
40	1.23 (0.91-1.67)
45	1.27 (0.93-1.72)
50	1.29 (0.95-1.74)
Heart failure hospitalization	
5	1.29 (0.86-1.92)

10	1.13 (0.76-1.68)
20	1.01 (0.95-1.08)
22.6	1
30	1.00 (0.79-1.27)
40	1.05 (0.74-1.50)
45	1.08 (0.76-1.55)
50	1.12 (0.78-1.59)

**Supplementary Table 5: Incremental value of NPY to the MAGGIC risk score as a binary variable.**

	<u>NPY as binary variable (&gt;=29 pg/ml)</u>			
	<b>Harrells C statistic (95% CI)</b>			
<b>Outcome</b>	<b>NPY</b>	<b>MAGGIC</b>	<b>MAGGIC + NPY</b>	<b>P value</b>
<b>CV death/HFH</b>	0.53 (0.51-0.56)	0.61 (0.58-0.64)	0.61 (0.58-0.64)	0.854
<i>IDI: 0.002 (-0.007-0.022) p 0.647 NRI 0.580 (-0.645-0.672) p 0.675</i>				
<b>HFH</b>	0.52 (0.49-0.55)	0.60 (0.56-0.64)	0.60 (0.56-0.64)	0.706
<i>IDI: 0.004 (-0.011-0.026) p 0.669 NRI 0.330 (-0.343-0.395) p 0.689</i>				
<b>CV death</b>	0.56 (0.53-0.59)	0.66 (0.61-0.70)	0.67 (0.62-0.72)	0.337
<i>IDI: 0.029 (-0.007-0.091) p 0.076 NRI 0.290 (0.016-0.652) p 0.044</i>				
<b>All cause death</b>	0.56 (0.53-0.59)	0.67 (0.63-0.70)	0.67 (0.64-0.70)	0.773
<i>IDI: 0.009 (-0.002-0.033) p 0.202 NRI 0.203 (-0.163-0.338) p 0.116</i>				

**Supplementary Table 6: Incremental value of NPY to the MAGGIC risk score as a continuous variable.**

<u>NPY as continuous variable (log transformed)</u>				
<b>Harrells C statistic (95% CI)</b>				
<b>Outcome</b>	<b>NPY</b>	<b>MAGGIC</b>	<b>MAGGIC + NPY</b>	<b>P value</b>
<b>CV death/HFH</b>	0.54 (0.51-0.57)	0.61 (0.58-0.64)	0.61 (0.58-0.65)	0.790
<i>IDI: 0.002 (-0.008-0.021) p 0.679 NRI 0.580 (-0.629-0.684) p 0.699</i>				
<b>HFH</b>	0.52 (0.49-0.56)	0.60 (0.56-0.64)	0.60 (0.56-0.64)	0.345
<i>IDI: 0.002 (-0.004-0.010) p 0.723 NRI 0.536 (-0.581-0.637) p 0.515</i>				
<b>CV death</b>	0.56 (0.53-0.60)	0.66 (0.61-0.71)	0.67 (0.62-0.71)	0.142
<i>IDI: 0.010 (-0.011-0.045) p 0.222 NRI 0.264 (-0.234-0.475) p 0.202</i>				
<b>All cause death</b>	0.56 (0.53-0.60)	0.67 (0.64-0.70)	0.67 (0.64-0.70)	0.192
<i>IDI: 0.002 (-0.004-0.016) P 0.549, NRI: 0.180 (0.301-0.344) p 0.498</i>				