

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

1. Echocardiography Protocol

Doppler echocardiography studies were performed by an experienced echocardiographer in the specialist cardiovascular centre. The evaluation was blinded to subject treatment assignment and BNP. A Philips IE33 ultrasound scanner with standard adult probe was used for data acquisition.

Doppler echocardiography studies was performed in accordance with the American Society of Echocardiography recommendations. In particular

- Left ventricle systolic function used the Teichholz method.
- LV mass was calculated using the Devereux formula.
- Left Atrial (LA) volume was measured by area-length (A-L) method using apical 4-chamber (A4C) and apical 2-chamber (A2C) views at ventricular end systole (maximum LA size).
- LA volume and LVM was indexed to body surface area.
- Diastolic function study was analysed by evaluation of mitral inflow velocities, Tissue Doppler analysis of lateral and septal wall left atrial volume index and where possible pulmonary venous drainage flow velocities.

Procedure sequence:

1. Conventional Long axis view, 2 chamber and 4 chamber view of 2D,
2. M-mode study.
3. Doppler and tissue evaluation and hemodynamic study.

2. Healthcare System

The healthcare system in the Republic of Ireland is a mixed public/private funded system. Primary healthcare is free through the General Medical Services Scheme but only to those judged less able to pay and at the time of this study all those over 70 years of age. In 2005 29.63% of the total population were eligible for free primary healthcare through the General Medical Services Scheme. Registration with a primary care practice is required only if the patient belongs to the General Medical Services Scheme. Practices have few disease registers and no specific financial incentives for operating a recall system to monitor patient care. There are no national standardised chronic disease management strategies in primary care although pilot initiatives in ischaemic heart disease and diabetes have been undertaken. Free prescriptions are available only within the General Medical Services Scheme. Others pay the full costs of medicines up to a monthly limit of €120 (Approximately \$157) per family in 2010. The private cost of medications are based on the General Medical Services Scheme cost plus mark-up (typically 20%) and dispensing fee per item. Outpatient specialist visits are free to all and hospital inpatient stays are heavily subsidised. Primary care physicians are independent contractors to the State and can refer to any public or private hospital they desire. In this study area there were three independent private hospitals and three public hospital groups (consisting of five public hospitals) to which primary care physicians could refer patients for specialist assessment. Therefore, the investigators had no influence on patients being enrolled or clinical care outside of the intervention group with a BNP>50pg/ml which were followed up in the study center.

All major adverse events were classified based on the discharge summary from the hospitalization event and this information was obtained from the discharge summary provided to the primary care physician by a study nurse blinded to treatment allocation. There are 8 admitting hospitals in the catchment area of the 39 study centres and the vast majority of MACE events were admitted to

hospitals other than St. Vincent's University Hospital. The small number that came to St. Vincent's were under the care of the on-call medical team. Therefore the study investigators were not involved in the decision to admit.

3. Secondary Outcome Measures

The secondary outcome measures in the protocol are listed below. Those not reported in this paper are undergoing further analysis and will be subsequently reported.

1. Relative incident rates (per 1000 patient years) of unplanned/emergency cardiovascular hospitalisations for major adverse cardiovascular events (MACE); these events are heart failure, stroke (including transient ischaemic attack), myocardial infarction, arrhythmia or pulmonary embolism (including deep vein thrombosis) requiring hospitalisation;
2. Relative incident rates (per 1000 patient years) of unplanned/emergency all cause hospitalisations;
3. Relative incident rates (per 1000 patient years) of unplanned/emergency all cause hospitalisation and death;
4. Relative prevalence of HF and LVD and relative incident rates of unplanned/emergency hospitalisations in those patients with any recorded BNP equal to or above 50 pg/mL.
5. Covariate adjusted relative prevalence of HF and LVD and relative incident rates of unplanned/emergency hospitalisations. Covariates which will be included in the adjustment are: age, sex, hypertension, diabetes, vascular disease and obesity;
6. Relative effects of intervention in pre-specified subgroups: above and below median age; male female, hypertension, diabetes, vascular disease, structural cardiovascular disease, obesity;

7. Relative change over time of natriuretic peptides in all patients and those patients with at least two matching values; evaluation of the relationship between natriuretic peptides and severity of LVD, death, hospital admissions; Unadjusted and covariate adjusted analyses will be carried out and covariates which will be included in the adjustment are: age, sex, hypertension, diabetes, vascular disease and obesity;
8. Relative effects of the intervention on Health and Lifestyle questionnaire
9. Relative effects of the intervention on direct costs of care using microcosting approaches, direct and indirect costs of care and incremental cost-effectiveness of the intervention based on the primary and first three secondary endpoints;
10. Evaluation of the clinical, demographic, biochemical, pharmacological, genomic, proteomic, metabolomic determinants of natriuretic peptides.

4. Power Calculations

It was assumed that an incident rate of HF and LVSD in the control group of 2.4% per annum. With an average follow up of 4 years, it was assumed that the incident rate could be modified by 39% based on the experience of the EUROPA study¹ resulting in a final study prevalence of 9.6% in the control group and 5.9% in the intervention group. With an OR = 0.59, alpha = .05 (two-tailed) and power = .80, the total required sample size was 1,644. To account for patient withdrawal over the the study period (5 years) and ensure adequate powering, we originally aimed to recruit 2,000 patients.

However, slower than expected recruitment rates resulted in an extension of the study in April 2009 and the redefinition of the primary endpoint to include significant left ventricular diastolic dysfunction as determined by $E/E' > 15$.

Sample size calculations for the revised primary endpoint were based on an assumption of prevalence of left ventricular dysfunction (systolic and diastolic) in the control group of 19.6% at study end and a treatment effect similar to that observed at 1 year with antihypertensive intervention in the LIFE study.² This would result in a prevalence of 13.4% in the intervention group and an absolute reduction of 6.2%.

With OR = 0.63, alpha = .05 (two-tailed) and power = .80, the total required sample size is 1129 with follow up of at least 1 year in all patients. It was agreed that the study would continue until sufficient number of patients were followed up for at least 1 year (accounting for known patient withdrawals) to exceed the numbers in the power calculation. Further assumptions were that allocation to control or intervention group is even and unbiased (i.e. group membership is an independent random binomial variable with $p = .5$) and that covariates account for 0% of the variation in probability of HF or left-ventricular dysfunction.

eTable 1. Cardiovascular Risk Factor Management During the Study

	Control			Intervention			Inter-group difference (baseline to follow-up change) p
	Baseline	Follow-up	p	Baseline	Follow-up	p	
All Patients							
BNP, Mean (SD), pg/mL	44.77 (57.46)	54.29 (76.52)	<.001 ^w	48.18 (84.88)	53.64 (91.52)	.002 ^w	.47 ^w
BMI, Mean (SD), kg/m ²	27.97 (5.507)	28.45 (5.635)	<.001 ^w	27.73 (5.007)	28.24 (5.054)	<.001 ^w	.59 ^w
HR, Mean (SD), beats/minute	70.26 (12.22)	70.27 (11.98)	.69 ^t	69.72 (12.31)	68.55 (12.62)	.02 ^w	.16 ^w
SBP, Mean (SD), mmHg	147 (22.5)	137.8 (20.66)	<.001 ^t	144.7 (20.86)	134.8 (18.73)	<.001 ^w	.78 ^w
DBP, Mean (SD), mmHg	80.51 (11.92)	80.35 (11.96)	.64 ^w	81.12 (11.95)	80.2 (10.71)	.04 ^w	.18 ^w
Total Cholesterol, Mean (SD), mg/dL	182.1 (40.62)	182.6 (39.41)	.16 ^w	182.7 (39.94)	181.2 (36.61)	.47 ^t	.30 ^w
LDL, Mean (SD), mg/dL	101.4 (34.33)	101.4 (33.52)	.73 ^t	103.1 (36.44)	100.2 (32.1)	.10 ^t	.12 ^w
HDL, Mean (SD), mg/dL	50.52 (16.1)	51.8 (17.11)	.02 ^t	49.3 (15.74)	50.58 (17.38)	<.001 ^w	.97 ^w
Non-HDL, Mean (SD), mg/dL	131.6 (38.35)	130.8 (37.85)	.47 ^t	133.4 (38.19)	130.6 (35.58)	.08 ^t	.20 ^w
Triglycerides, Mean (SD), mg/dL	150.4 (78.81)	147.1 (86.32)	.02 ^w	156.7 (82.55)	154.7 (87.09)	.23 ^w	.55 ^w
Glucose, Mean (SD), mg/dL	109.6 (37.63)	110 (36.93)	.12 ^w	109.8 (37.79)	111 (40.15)	.40 ^w	.31 ^w
Creatinine, Mean (SD), mg/dL	0.95 (0.22)	0.96 (0.26)	.15 ^w	0.95 (0.23)	0.95 (0.23)	.04 ^w	.71 ^w
Hypertension†, N (%)	72.8%	48.4%	<.001 ^c	66.1%	43.2%	<.001 ^c	
Hypercholesterolaemia, N (%)	52.6%	54.9%	.41 ^c	50.6%	52.8%	.45 ^c	
BNP ≥ 50 pg/mL patients							
BNP, Mean (SD), pg/mL	86.55 (73.16)	110 (97.89)	<.001 ^t	91.6 (118)	104.1 (124.8)	<.001 ^w	.24 ^w
BMI, Mean (SD), kg/m ²	27.91 (6.063)	28.31 (6.162)	.002 ^w	27.35 (4.52)	27.96 (4.67)	<.001 ^t	.29 ^w
HR, Mean (SD), beats/minute	67.22 (12.24)	68.81 (12.61)	.06 ^t	66.94 (11.95)	65.95 (13.43)	.26 ^w	.09 ^w
SBP, Mean (SD), mmHg	148.7 (23.7)	136.5 (21.06)	<.001 ^t	147.1 (23.72)	135.3 (20.47)	<.001 ^w	.54 ^w
DBP, Mean (SD), mmHg	77.58 (12.26)	77.69 (11.56)	.93 ^w	78.95 (12.12)	78.9 (10.79)	.94 ⁿ	.79 ^w
Total Cholesterol, Mean (SD), mg/dL	174.9 (42.34)	178.1 (39.93)	.08 ^w	180.1 (40.36)	176.9 (34.34)	.33 ^t	.10 ^w
LDL, Mean (SD), mg/dL	95.73 (31.95)	98.06 (30.69)	.05 ^t	100.1 (34.99)	95.23 (29.14)	.07 ^t	.06 ^w
HDL, Mean (SD), mg/dL	50.64 (15.32)	52.4 (17.73)	.01 ^w	48.92 (15.26)	51.49 (18.35)	.004 ^w	.91 ^w
Non-HDL, Mean (SD), mg/dL	124.3 (39.79)	125.7 (38.14)	.42 ^t	131.2 (36.6)	125.4 (32.71)	.01 ^t	.06 ^w
Triglycerides, Mean (SD), mg/dL	140.2 (72.03)	134.8 (77.61)	.03 ^t	152.7 (82.86)	154.4 (85.5)	.95 ^w	.23 ^w
Glucose, Mean (SD), mg/dL	110.5 (40.15)	109.5 (38.93)	.90 ^w	108.8 (28.41)	108.7 (30.29)	.41 ^w	.48 ^w
Creatinine, Mean (SD), mg/dL	1.005 (0.26)	1.02 (0.32)	.73 ^w	0.97 (0.25)	0.97 (0.25)	.35 ^w	.98 ^w

eTable 1. Cardiovascular Risk Factor Management During the Study (continued)

	Control			Intervention			Inter-group difference (baseline to follow-up change)
	Baseline	Follow-up	p	Baseline	Follow-up	p	p
Hypertension†, N (%)	70.1	42.7	<.001 ^c	64.4	43.9	<.001 ^c	
Hypercholesterolaemia, N (%)	46.8	46.4	.99 ^c	46.4	48.3	.73 ^c	

BNP: B-type Natriuretic Peptide, BMI: Body Mass Index, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, LDL: Low-Density Lipoproteins, HDL: High-Density Lipoproteins, Non-HDL: Total Cholesterol less HDL, Hypertension: SBP > 140 or DBP > 90, †: analysis only includes patients with history of hypertension (N=852), Hypercholesterolaemia: Total Cholesterol > 173.75 mg/dL, ⁿ: two-tailed independent t-test, [†]: two-tailed independent t-test (data transformed to normal – p>.05 on Shapiro-Wilk test), ^w: two-tailed Wilcoxon rank sum test (Mann-Whitney), ^c: chi-square test

eTable 2. Cardiovascular Investigations During the Study

	Tests (per 1000 patient-years)				Number (%) of patients tested		
	Control	Intervention	p-value		Control	Intervention	p-value
All Patients							
<i>Patient-years</i>	2898.26	2917.16		<i>N</i>	677	697	
Exercise Stress Test	70 (24.2)	106 (36.3)	.01		58 (8.6%)	86 (12.3%)	.02
Holter	88 (30.4)	78 (26.7)	.41		69 (10.2%)	48 (6.9%)	.03
Electrocardiogram	367 (126.6)	591 (202.6)	<.001		217 (32.1%)	273 (39.2%)	.01
Angiogram	85 (29.3)	111 (38.1)	.07		71 (10.5%)	89 (12.8%)	.19
ABPM	228 (78.7)	464 (159.1)	<.001		140 (20.7%)	205 (29.4%)	<.001
Cardiac Imaging	347 (119.7)	942 (322.9)	<.001		224 (33.1%)	320 (45.9%)	<.001
Chest X-ray	217 (74.9)	159 (54.5)	.002		131 (19.4%)	109 (15.6%)	.07
Carotid Ultrasound	35 (12.1)	27 (9.3)	.30		32 (4.7%)	20 (2.9%)	.07
BNP ≥ 50 pg/mL patients							
<i>Patient-years</i>	1051.17	1150.29		<i>N</i>	235	263	
Exercise Stress Test	31 (29.5)	58 (50.4)	.02		24 (10.2%)	45 (17.1%)	.03
Holter	56 (53.3)	62 (53.9)	.95		42 (17.9%)	36 (13.7%)	.20
Electrocardiogram	188 (178.8)	415 (360.8)	<.001		104 (44.3%)	167 (63.5%)	<.001
Angiogram	43 (40.9)	74 (64.3)	.02		38 (16.2%)	56 (21.3%)	.15
ABPM	99 (94.2)	340 (295.6)	<.001		53 (22.6%)	130 (49.4%)	<.001
Cardiac Imaging	165 (157)	745 (647.7)	<.001		101 (43%)	179 (68.1%)	<.001
Chest X-ray	123 (117)	100 (86.9)	.03		64 (27.2%)	68 (25.9%)	.73
Carotid Ultrasound	16 (15.2)	17 (14.8)	.93		15 (6.4%)	12 (4.6%)	.37

ABPM: Ambulatory Blood Pressure Monitor; Cardiac Imaging: transthoracic echocardiography, transesophageal echocardiography and cardiac magnetic resonance imaging

eTable 3. Prescribed Drugs at Baseline and Follow-up

Medication class	Baseline		Follow up		Chi-square p-values	
	Control	Intervention	Control	Intervention	Baseline	Follow up
All Patients	677	697	677	697		
Alpha Blockers, N (%)	15 (2.2%)	24 (3.4%)	24 (3.5%)	28 (4.0%)	.23	.75
Beta Blockers, N (%)	169 (25.0%)	187 (26.8%)	198 (29.2%)	219 (31.4%)	.47	.41
Calcium Channel Blockers, N (%)	102 (15.1%)	113 (16.2%)	147 (21.7%)	166 (23.8%)	.61	.39
Statins, N (%)	355 (52.4%)	368 (52.8%)	405 (59.8%)	421 (60.4%)	.94	.87
Anti-Platelet, N (%)	267 (39.4%)	296 (42.5%)	290 (42.8%)	317 (45.5%)	.28	.35
Diuretics, N (%)	141 (20.8%)	128 (18.4%)	203 (30%)	207 (29.7%)	.28	.95
AA, N (%)	3 (0.4%)	3 (0.4%)	4 (0.6%)	6 (0.9%)	-	-
ARB, N (%)	126 (18.6%)	155 (22.2%)	167 (24.7%)	226 (32.4%)	.11	.002
ACEI, N (%)	167 (24.7%)	157 (22.5%)	180 (26.6%)	177 (25.4%)	.38	.66
Any AA, ARB or ACEI, N (%)	282 (41.7%)	299 (42.9%)	336 (49.6%)	394 (56.5%)	.68	.01
BNP ≥50 pg/mL Patients	235	263	235	263		
Alpha Blockers, N (%)	6 (2.6%)	14 (5.3%)	9 (3.8%)	15 (5.7%)	.18	.44
Beta Blockers, N (%)	87 (37.0%)	117 (44.5%)	115 (48.9%)	133 (50.6%)	.11	.78
Calcium Channel Blockers, N (%)	47 (20.0%)	54 (20.5%)	64 (27.2%)	81 (30.8%)	.97	.44
Statins, N (%)	137 (58.3%)	149 (56.7%)	155 (66.0%)	179 (68.1%)	.78	.69
Anti-Platelet, N (%)	117 (49.8%)	143 (54.4%)	123 (52.3%)	151 (57.4%)	.35	.30
Diuretics, N (%)	67 (28.5%)	69 (26.2%)	98 (41.7%)	106 (40.3%)	.64	.82
AA, N (%)	2 (0.9%)	2 (0.8%)	2 (0.9%)	4 (1.5%)	-	-
ARB, N (%)	50 (21.3%)	77 (29.3%)	65 (27.7%)	116 (44.1%)	.05	<.001
ACEI, N (%)	66 (28.1%)	79 (30.0%)	76 (32.3%)	86 (32.7%)	.70	.99
Any AA, ARB or ACEI, N (%)	112 (47.7%)	147 (55.9%)	134 (57.0%)	195 (74.1%)	.08	<.001

AA – Aldosterone Antagonists, ARB – Angiotensin Receptor Blockers, ACEI – Angiotensin-Converting-Enzyme Inhibitors

eTable 4. End-Point Prevalence Analysis in BNP <50 pg/mL Subgroup

	Ctl. (442)	Int. (434)	Arm (unadjusted)		Arm (adjusted)	
			IRR [CI ₉₅]	p-value	IRR [CI ₉₅]	p-value
<i>HF or LVD, N (%)</i>	15 (3.4%)	12 (2.8%)	0.81 [0.37,1.75]	0.59	0.92 [0.42,2.01]	0.83
<i>HF or LVSD, N (%)</i>	4 (0.9%)	6 (1.4%)	1.54 [0.43,5.48]	0.51	1.84 [0.50,6.82]	0.36
<i>Asymptomatic LVSD, N (%)</i>	2 (0.5%)	4 (0.9%)	2.05 [0.37,11.23]	0.41	2.19 [0.39,12.23]	0.37
<i>Asymptomatic LVDD, N (%)</i>	11 (2.5%)	6 (1.4%)	0.55 [0.20,1.50]	0.24	0.60 [0.21,1.65]	0.32
<i>Asymptomatic LVD, N (%)</i>	13 (2.9%)	10 (2.3%)	0.78 [0.34,1.79]	0.56	0.84 [0.36,1.97]	0.70
<i>Arrhythmia, N (%)</i>	6 (1.4%)	3 (0.7%)	0.51 [0.13,2.04]	0.34	0.62 [0.15,2.57]	0.51
<i>Heart Failure, N (%)</i>	2 (0.5%)	2 (0.5%)	1.02 [0.14,7.26]	0.99	1.64 [0.21,12.76]	0.64
<i>Myocardial Infarction, N (%)</i>	5 (1.1%)	6 (1.4%)	1.23 [0.37,4.04]	0.74	1.24 [0.36,4.23]	0.73
<i>PE or DVT, N (%)</i>	5 (1.1%)	2 (0.5%)	0.40 [0.08,2.10]	0.28	0.37 [0.07,1.99]	0.25
<i>Stroke or TIA, N (%)</i>	14 (3.2%)	4 (0.9%)	0.28 [0.09,0.87]	0.03	0.23 [0.07,0.77]	0.02
<i>MACE, N (%)</i>	26 (5.9%)	16 (3.7%)	0.61 [0.32,1.16]	0.13	0.60 [0.31,1.16]	0.13

eTable 5. Event Rate Analysis in BNP <50 pg/mL Subgroup

	Number of Events		Person-years		Events per 1000 person-years		Arm (unadjusted)		Arm (adjusted)	
	Ctl.	Int.	Ctl.	Int.	Ctl.	Int.	IRR [CI ₉₅]	p-value	IRR [CI ₉₅]	p-value
<i>Arrhythmia</i>	7	4	1847.09	1766.87	3.8	2.3	0.56 [0.17,2.02]	.40	0.76 [0.21,2.70]	.67
<i>Heart Failure</i>	2	3	1847.09	1766.87	1.1	1.7	1.55 [0.26,9.29]	.63	2.62 [0.40,17.15]	.31
<i>Myocardial Infarction</i>	5	6	1847.09	1766.87	2.7	3.4	1.24 [0.38,4.07]	.72	1.23 [0.36,4.17]	.74
<i>PE or DVT</i>	6	2	1847.09	1766.87	3.2	1.1	0.34 [0.07,1.71]	.19	0.34 [0.07,1.70]	.19
<i>Stroke or TIA</i>	15	4	1847.09	1766.87	8.1	2.3	0.28 [0.09,0.83]	.02	0.25 [0.08,0.78]	.02
<i>MACE</i>	35	19	1847.09	1766.87	18.9	10.8	0.56 [0.32,0.98]	.04	0.57 [0.32,1.00]	.05

eTable 6. End-Point Patient Prevalence Analysis by Last Observation Carried Forward

	Cnt.	Int.	OR [CI₉₅]	p-value	Adj. OR [CI₉₅]	p-value
All Patients	677	697				
<i>HF or LVD, N (%)</i>	59 (8.7%)	37 (5.3%)	0.59 [0.38, 0.90]	.01	0.62 [0.40,0.96]	.03
<i>HF or LVSD, N (%)</i>	33 (4.9%)	23 (3.3%)	0.67 [0.39, 1.15]	.14	0.69 [0.40,1.21]	.19
<i>Asymptomatic LVSD, N (%)</i>	19 (2.8%)	16 (2.3%)	0.81 [0.41, 1.60]	.55	0.85 [0.43,1.69]	.65
<i>Asymptomatic LVDD, N (%)</i>	26 (3.8%)	14 (2.0%)	0.51 [0.27, 0.99]	.05	0.58 [0.30,1.13]	.11
<i>Asymptomatic LVD, N (%)</i>	45 (6.6%)	30 (4.3%)	0.63 [0.39, 1.02]	.06	0.67 [0.41,1.08]	.10
<i>Arrhythmia, N (%)</i>	29 (4.3%)	21 (3%)	0.69 [0.39, 1.23]	.21	0.75 [0.42,1.35]	.34
<i>Heart Failure, N (%)</i>	14 (2.1%)	7 (1.0%)	0.48 [0.19, 1.20]	.12	0.53 [0.21,1.33]	.17
<i>Preserved EF, N (%)</i>	8 (1.3%)	6 (1.0%)	0.72 [0.25, 2.10]	.55	0.88 [0.30,2.63]	.83
<i>Reduced EF, N (%)</i>	6 (1.0%)	1 (0.2%)	0.16 [0.02, 1.34]	.09	0.16 [0.02,1.33]	.09
<i>Myocardial Infarction, N (%)</i>	11 (1.6%)	8 (1.1%)	0.70 [0.28, 1.76]	.45	0.69 [0.27,1.75]	.43
<i>PE or DVT, N (%)</i>	10 (1.5%)	4 (0.6%)	0.38 [0.12, 1.23]	.11	0.35 [0.10,1.14]	.08
<i>Stroke or TIA, N (%)</i>	28 (4.1%)	13 (1.9%)	0.44 [0.23, 0.86]	.02	0.46 [0.23,0.91]	.03
<i>MACE, N (%)</i>	71 (10.5%)	51 (7.3%)	0.67 [0.46, 0.98]	.04	0.70 [0.47,1.03]	.07
BNP ≥50 pg/mL patients	235	263				
<i>HF or LVD, N (%)</i>	44 (18.7%)	25 (9.5%)	0.46 [0.27, 0.77]	.003	0.49 [0.29,0.85]	.01
<i>HF or LVSD, N (%)</i>	29 (12.3%)	17 (6.5%)	0.49 [0.26, 0.92]	.03	0.53 [0.27,1.02]	.06
<i>Asymptomatic LVSD, N (%)</i>	17 (7.2%)	12 (4.6%)	0.61 [0.29, 1.31]	.21	0.69 [0.31,1.53]	.36
<i>Asymptomatic LVDD, N (%)</i>	15 (6.4%)	8 (3%)	0.46 [0.19, 1.11]	.08	0.53 [0.22,1.31]	.17
<i>Asymptomatic LVD, N (%)</i>	32 (13.6%)	20 (7.6%)	0.52 [0.29, 0.94]	.03	0.57 [0.31,1.03]	.06
<i>Arrhythmia, N (%)</i>	23 (9.8%)	18 (6.8%)	0.68 [0.36, 1.29]	.24	0.70 [0.36,1.36]	.30
<i>Heart Failure, N (%)</i>	12 (5.1%)	5 (1.9%)	0.36 [0.12, 1.04]	.06	0.40 [0.13,1.18]	.10

eTable 6. End-Point Patient Prevalence Analysis by Last Observation Carried Forward (continued)

	Cnt.	Int.	OR [CI₉₅]	p-value	Adj. OR [CI₉₅]	p-value
All Patients	677	697				
<i>Preserved EF, N (%)</i>	7 (3.0%)	4 (1.5%)	0.50 [0.14, 1.72]	.27	0.61 [0.17,2.17]	.45
<i>Reduced EF, N (%)</i>	5 (2.2%)	1 (0.4%)	0.17 [0.02, 1.49]	.11	0.16 [0.02,1.46]	.11
<i>Myocardial Infarction, N (%)</i>	6 (2.6%)	2 (0.8%)	0.29 [0.06, 1.46]	.13	0.27 [0.05,1.38]	.12
<i>PE or DVT, N (%)</i>	5 (2.1%)	2 (0.8%)	0.35 [0.07, 1.83]	.22	0.37 [0.07,2.05]	.26
<i>Stroke or TIA, N (%)</i>	14 (6.0%)	9 (3.4%)	0.56 [0.24, 1.32]	.18	0.66 [0.27,1.60]	.36
<i>MACE, N (%)</i>	45 (19.1%)	35 (13.3%)	0.65 [0.40, 1.05]	.08	0.69 [0.42,1.13]	.14

HF: Heart Failure, LVD: Left ventricular dysfunction, LVSD: Left ventricular systolic dysfunction, LVDD: Left ventricular diastolic dysfunction, EF: Ejection Fraction, PE: Pulmonary Embolism, DVT: Deep vein thrombosis, TIA: Transient Ischaemic Attack, MACE: Major Cardiovascular Event (Arrhythmia, Heart Failure, Myocardial Infarction, PE/DVT or Stroke/TIA)

eTable 7. Event Rate Analysis by Last Observation Carried Forward

	Cnt.	Int.	IRR [CI₉₅]	p-value	Adj. IRR [CI₉₅]	p-value
All Patients						
<i>Patient-years</i>	2898.26	2917.16				
<i>Arrhythmia, Events (per 1000 patient-years)</i>	45 (15.5)	29 (9.9)	0.64 [0.40, 1.02]	.06	0.70 [0.44, 1.12]	.14
<i>Heart Failure, Events (per 1000 patient-years)</i>	18 (6.2)	8 (2.7)	0.44 [0.19, 1.02]	.05	0.49 [0.21, 1.15]	.10
<i>Myocardial Infarction, Events (per 1000 patient-years)</i>	11 (3.8)	8 (2.7)	0.72 [0.29, 1.80]	.48	0.70 [0.28, 1.75]	.44
<i>PE / DVT, Events (per 1000 patient-years)</i>	11 (3.8)	4 (1.4)	0.36 [0.12, 1.13]	.08	0.33 [0.10, 1.06]	.06
<i>Stroke / TIA, Events (per 1000 patient-years)</i>	32 (11.0)	16 (5.5)	0.50 [0.27, 0.91]	.02	0.55 [0.30, 1.01]	.06
<i>MACE, Events (per 1000 patient-years)</i>	117 (40.4)	65 (22.3)	0.55 [0.41, 0.75]	<.001	0.59 [0.44, 0.80]	<.001
BNP ≥50 pg/mL Patients						
<i>Patient-years, Events (per 1000 patient-years)</i>	1051.17	1150.29				
<i>Arrhythmia, Events (per 1000 patient-years)</i>	38 (36.2)	25 (21.7)	0.60 [0.36, 1.00]	.05	0.60 [0.36, 1.00]	.05
<i>Heart Failure, Events (per 1000 patient-years)</i>	16 (15.2)	5 (4.3)	0.29 [0.10, 0.78]	.01	0.31 [0.11, 0.86]	.02
<i>Myocardial Infarction, Events (per 1000 patient-years)</i>	6 (5.7)	2 (1.7)	0.30 [0.06, 1.51]	.15	0.26 [0.05, 1.34]	.11
<i>PE / DVT, Events (per 1000 patient-years)</i>	5 (4.8)	2 (1.7)	0.37 [0.07, 1.88]	.23	0.42 [0.08, 2.31]	.32
<i>Stroke / TIA, Events (per 1000 patient-years)</i>	17 (16.2)	12 (10.4)	0.65 [0.31, 1.35]	.24	0.78 [0.37, 1.66]	.52
<i>MACE, Events (per 1000 patient-years)</i>	82 (78.0)	46 (40.0)	0.51 [0.36, 0.74]	<.001	0.54 [0.37, 0.78]	.001

eTable 8. Number of BNP Tests ≥ 50 pg/ml in Those Admitted to Hospital With New Onset Heart Failure

BNPs ≥ 50 pg/mL	0	1	2	3	4	5	6	Total patients	Total tests
Control	2	5	2	1	2	2	0	14	30
Intervention	2	1	0	2	0	1	1	7	18

¹Fox, K.M., Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*, 2003. 362(9386): p. 782-8

²Wachtell K. et al. Change in Diastolic Left Ventricular Filling After One Year of Antihypertensive Treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study, *Circulation* 2002;105:1071-1076.

eTable 9. Number of Noncardiovascular Emergency Admissions

Non-CV emergency admissions	No data	0	1	2	3	4	5+	Patients with events	Events
Control	155	403	82	24	4	4	5	119	192
Intervention	164	410	81	23	11	4	4	123	204

eTable 10. Number of Major Adverse Cardiovascular Event (MACE) Hospital Admissions

MACE (inc.PE/DVT)	No data	0	1	2	3	4	5+	Patients with events	Events
Control	155	451	46	16	2	3	4	71	117
Intervention	164	482	41	7	2	1	0	51	65

eTable 11. Number of Hospital Admissions and Outpatient Contacts

	Control, n	Intervention, n
Primary Care Practitioner visits	2,533	3,383
Natriuretic peptide testing	1,938	2,328
STOP-HF referral center visits	-	1,052
Primary Care and STOP-HF clinic CV testing	595	1,055
CV Elective outpatient/day-case procedures	268	314
CV Hospitalizations (Elective)	49	59
CV Hospitalizations (Emergency)	117	65
Non-CV Elective outpatient/day-case procedures	350	405
Non-CV Hospitalizations (Elective)	133	119
Non-CV Hospitalizations (Emergency)	192	204
Total	6,175	8,984

eTable 12. Type of Noncardiovascular and Cardiovascular Hospital Admissions and Outpatient Contacts

Emergency Noncardiovascular Hospitalizations	Control, n	Intervention, n
Respiratory system	37	38
Digestive system	24	31
Musculoskeletal system and injuries	43	36
Endocrine system	2	4
Renal system	7	19
Skin, subcutaneous system and breast	10	10
Reproductive system	1	5
Nervous system	8	10
Hepatobiliary system	4	8
Others	56	43
Total	192	204
Elective Hospitalizations and outpatient/day-case Noncardiovascular		
	Control, n	Intervention, n
Respiratory system	16	14
Digestive system	146	200
Musculoskeletal system and injuries	64	48
Endocrine system	5	2
Renal system	43	42
Skin, subcutaneous system and breast	62	50
Reproductive system	24	27
Nervous system	15	18
Hepatobiliary system	8	5
Others	100	118
Total	483	524
	Control, n	Intervention, n
Arrhythmia	45	29
Heart Failure	18	8
Myocardial Infarction	11	8
Pulmonary Embolism/DVT	11	4
Stroke/TIA	32	16
	Control, n	Intervention, n
Angiography	88	111
Angioplasty	10	17
CABG	9	4
Other	36	39
Other major CV surgery	2	3
Pacemaker, ICD, Ablation	8	9
Peripheral Vascular Procedures	6	6
Exercise Stress Test	70	106
Holter monitor	88	78
Cardiac Imaging	347	942
Chest X-ray	217	159
Carotid Ultrasound	35	27
Total	317	373