

End of Study Report

Full title of study: BNP for Personalised Primary Prevention in Diabetes (4P Study)

Research Sponsor: University of Dundee and NHS Tayside

R&D reference number: 2013DM14

Name of REC: East of Scotland Research Ethics Service (EoSRES)

REC reference number: 15/ES/0042

ISRCTN No: ISRCTN12700399

Date study commenced: 5/8/2015

Date study ended: 8/6/2017

Number of participants recruited: 246

Total number of screening: 289

Details of Chief Investigator

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This End of Study Report contains the key summary findings of the 4P Study, in the form of figures and statistics. The definition of cardiac target organ damage (cTOD), except myocardial ischaemia, is according to Nadir et al (JACC 2012) and the updated American Society of Echocardiography (ASE) guideline in 2016. The results are then analysed based on these 2 definitions.

The key difference between definition of echocardiographic findings between Nadir et al (JACC 2012) and ASE Guideline (Updated 2016)

Echocardiographic Findings	Nadir et al (JACC 2012)	ASE Guideline (2016)
LVH	No difference	No difference
LVSD	LVSD (EF<50)	LVSD (EF<52 in M; <54 in F)
LVDD	LVDD (E/Eat'>15)	LVDD (e' vel, E/E', LA vol/BSA, TR PG)
LAE	LAE (LA vol/BSA>28)	LAE (LA vol/BSA >34)

Below is the summary of Echocardiographic findings of 4P Study according to Nadir et al (JACC 2012)

cTOD	Number (%)
LVH	70 (28.46%)
LVSD	1 (0.41%)
LVDD	13 (5.28%)
LAE	106 (43.09%)
Ischaemia	8 (3.25%)

Below is the summary of Echocardiographic findings of 4P Study according to ASE Guideline (Updated 2016)

cTOD	Number (%)
LVH	70 (28.46%)
LVSD	4 (1.63%)
LVDD	11 (4.47%)
LAE	46 (18.7%)
Ischaemia	8 (3.25%)

Conclusion

NT-proBNP, Trop T and Trop I (pico) appear to perform better as cardiac biomarkers in detecting cTOD according to the definition by Nadir et al (JACC 2012). Trop I (pico) performs best as cardiac biomarker in detecting cTOD according to the definition by ASE Guideline (Updated 2016). We are at the finalising stage of statistical analysis and hope to publish soon.

Below is the summary of findings of 4P Study (Demographics, Past Medical History, Blood Pressure, Medicines, Blood Test Results, ECG Findings, Biomarker Results)

PARAMETER	Overall (n=244)	
	Mean	SD
Age	66.14	8.69
Male: n/%	154	63.11%
BMI	30.83	5.3
Height	1.69	0.1
Weight	87.8	17.11
BSA	1.98	0.21
Duration of DM	10.12	6.18
Hypertension	155	0.635246
Dyslipidemia	127	0.520492
RA	3	0.012295
Any smoking Hx	128	0.52459
Current smoker	19	0.077869
Alcohol consumption	5.19	9.44
SBP	126.59	11.91
DBP	72.06	6.49
Heart Rate	69.66	12.05
Diet Controlled DM	58	23.77%
Metformin	160	65.57%
SU	59	24.18%
TZD	14	5.74%
GLP-1	17	6.97%
DPP4 Inh	26	10.66%
SGLT-2 Inh	13	5.33%
Insulin	29	11.89%
Asp	35	14.34%
Clop	1	0.41%
Statin	183	75.00%
Ezetimibe	6	0.25%
Fibrate	4	1.64%
ACE-i	107	43.85%
ARB	44	18.03%
MRA	4	1.64%
B blocker	29	11.89%
A blocker	15	6.15%
CCB	81	33.20%
Thiazide	52	21.31%

Loop diuretic	8	3.28%
Warfarin	4	1.64%
DOAC	0	0.00%
Allopurinol	5	2.05%
Haemoglobin	139.53	14.71
eGFR	95.51	92.41
Creat	71.86	16.17
Total Chol	4.06	0.94
HDL	1.23	0.39
Chol/HDL	3.49	1.04
LDL	2.09	0.74
HbA1c	55.57	11.03
HbA1c 1yr	53.99	9.4
uACR	1.39	4.8
ecg.LVH	11	4.51%
LBBB	7	2.87%
RBBB	15	6.15%
IVCD	44	18.03%
LAD	55	22.54%
1st Deg AVB	40	16.39%
Poor R prog	29	11.89%
Normal ECG	123	50.41%
BNP mean	24.64	29.8
BNP median	16.4	23.15
NT-proBNP mean	433.89	768.07
NT-proBNP median	195.11	351.51
Trop I mean	2.67	2.63
Trop I median	2	2.35
Trop I pico mean	1.81	2.31
Trop I pico median	1	2
Trop T mean	8.24	6.01
Trop T median	7.18	5.77

Below is the summary of findings of 4P Study (Demographics, Past Medical History, Blood Pressure, Medicines, Blood Test Results, ECG Findings, Biomarker Results) using cTOD defined by Nadir et al (JACC 2012)

PARAMETER	No cTOD (n=104)		cTOD (n=140)		p-val
	Mean	SD	Mean	SD	
Age	65.07	9.02	66.94	8.38	NS
Male: n/%	69	66.34%	85	60.71%	NS
BMI	30.02	4.53	31.42	5.75	0.03433
Height	1.7	0.09	1.67	0.1	0.01731
Weight	87.14	14.74	88.31	18.7	NS
BSA	1.98	0.19	1.97	0.23	NS
Duration of DM	9.57	5.95	10.52	6.34	NS
Hypertension	62	59.62%	93	66.43%	NS
Dyslipidemia	55	52.88%	72	51.43%	NS
RA	0	0.00%	3	2.14%	NS
Any smoking Hx	56	53.85%	72	51.43%	NS
Current smoker	9	8.65%	10	7.14%	NS
Alcohol consumption	5.58	9.94	4.9	9.07	NS
SBP	124	11.67	128.52	11.75	0.003168
DBP	72.97	6.02	71.38	6.75	0.05363
Heart Rate	71.76	11.72	68.09	12.09	0.01814
Diet Controlled DM	27	25.96%	31	22.14%	NS
Metformin	67	64.42%	93	66.43%	NS
SU	22	21.15%	37	26.43%	NS
TZD	4	3.85%	10	7.14%	NS
GLP-1	5	4.81%	12	8.57%	NS
DPP4 Inh	12	11.54%	14	10.00%	NS
SGLT-2 Inh	9	8.65%	4	2.86%	0.04618
Insulin	9	8.65%	20	14.29%	NS
Asp	20	19.23%	15	10.71%	0.06054
Clopidogrel	0	0.00%	1	0.71%	NS
Statin	78	75.00%	105	75.00%	NS
Ezetimibe	3	2.89%	3	2.14%	NS
Fibrate	4	3.85%	0	0.00%	0.0193
ACE-i	47	45.19%	60	42.86%	NS
ARB	15	14.42%	29	20.71%	NS
MRA	2	1.92%	2	1.43%	NS
B blocker	11	10.58%	18	12.86%	NS

A blocker	4	3.85%	11	7.86%	NS
CCB	28	26.92%	53	37.86%	NS
Thiazide	22	21.15%	30	21.43%	NS
Loop diuretic	2	1.92%	6	4.29%	NS
Warfarin	0	0.00%	4	2.86%	NS
DOAC	0	0.00%	0	0.00%	NS
Allopurinol	2	1.92%	3	2.14%	NS
Haemoglobin	142.88	13.33	137.04	15.22	0.001643
eGFR	95.24	19.73	95.72	21.94	NS
Creat	72.9	16.77	71.09	15.73	NS
Total Chol	4.16	0.99	3.99	0.9	NS
HDL	1.22	0.36	1.23	0.42	NS
Chol/HDL	3.64	1.15	3.39	0.93	NS
LDL	2.14	0.73	2.06	0.74	NS
HbA1c	56.69	10.55	54.73	11.33	NS
HbA1c 1yr	54.03	9.76	53.96	9.15	NS
uACR	0.73	1.56	1.88	6.19	0.04185
ecg.LVH	1	0.96%	10	7.14%	0.02137
LBBB	3	2.88%	4	2.86%	NS
RBBB	4	3.85%	11	7.86%	NS
IVCD	16	15.38%	28	20.00%	NS
LAD	23	22.12%	32	22.86%	NS
1st Deg AVB	15	14.42%	25	17.86%	NS
Poor R prog	14	13.46%	15	10.71%	NS
Normal ECG	58	55.77%	65	46.43%	NS
BNP mean	18.4	18.22	29.27	35.44	0.002065
BNP median	12.9	19.52	19.25	25.88	0.007534
NT-proBNP mean	287.43	352	543.73	956.3	0.003951
NT-proBNP median	152.97	315.03	237.33	429.11	0.004212
Trop I mean	1.99	2	3.18	2.92	0.000201
Trop I median	1.7	1.6	2.5	2.9	0.000274
Trop I pico mean	1.17	1.42	2.29	2.71	4.42E-05
Trop I pico median	1	2	1.5	2	5.25E-05
Trop T mean	7.11	5.23	9.08	6.42	0.008969
Trop T median	5.9	5.31	7.56	6.2	0.005887

Below is the summary of findings of 4P Study (Demographics, Past Medical History, Blood Pressure, Medicines, Blood Test Results, ECG Findings, Biomarker Results) using cTOD defined by ASE Guideline (Updated 2016)

PARAMETER	No cTOD (n=144)		cTOD (n=100)		p-val
	Mean	SD	Mean	SD	
Age	65.54	9.26	67	7.75	NS
Male: n/%	92	63.89%	62	62.00%	NS
BMI	29.78	4.65	32.34	5.81	0.000324
Height	1.69	0.09	1.68	0.1	NS
Weight	85.37	14.97	91.34	19.32	0.0102
BSA	1.96	0.2	2	0.23	NS
Duration of DM	10.03	6.47	10.25	5.77	NS
Hypertension	87	60.42%	68	68.00%	NS
Dyslipidemia	80	55.56%	47	47.00%	NS
RA	2	1.39%	1	1.00%	NS
Any smoking Hx	74	51.39%	54	54.00%	NS
Current smoker	12	8.33%	7	7.00%	NS
Alcohol consumption	5.49	9.63	4.76	9.19	NS
SBP	125.48	12.24	128.2	11.28	0.0749
DBP	72.48	6.6	71.45	6.31	NS
Heart Rate	70.94	11.27	67.84	12.91	NS
Diet Controlled DM	32	22.22%	26	26.00%	NS
Metformin	96	66.67%	64	64.00%	NS
SU	33	22.92%	26	26.00%	NS
TZD	4	2.78%	10	10.00%	0.01705
GLP-1	6	4.17%	11	11.00%	0.03922
DPP4 Inh	12	0.083333	14	14.00%	NS
SGLT-2 Inh	10	6.94%	3	3.00%	NS
Insulin	15	10.42%	14	14.00%	NS
Asp	24	16.67%	11	11.00%	NS
Clopidogrel	0	0.00%	1	1.00%	NS
Statin	113	78.47%	70	70.00%	NS
Ezetimibe	4	2.78%	2	2.00%	NS
Fibrate	4	2.78%	0	0.00%	NS
ACE-i	61	42.36%	46	46.00%	NS
ARB	26	18.06%	18	18.00%	NS
MRA	2	1.39%	2	2.00%	NS
B blocker	13	9.03%	16	16.00%	NS
A blocker	6	4.17%	9	9.00%	NS
CCB	47	32.64%	34	34.00%	NS

Thiazide	29	20.14%	23	23.00%	NS
Loop diuretic	2	1.39%	6	6.00%	0.04668
Warfarin	2	1.39%	2	2.00%	NS
DOAC	0	0.00%	0	0.00%	NS
Allopurinol	4	2.78%	1	1.00%	NS
Haemoglobin	141.88	13.82	136.16	15.35	0.003258
eGFR	95.63	18.77	95.34	23.91	NS
Creat	71.72	15.69	72.07	16.91	NS
Total Chol	4.14	1.01	3.94	0.83	NS
HDL	1.24	0.4	1.2	0.38	NS
Chol/HDL	3.55	1.14	3.41	0.88	NS
LDL	2.11	0.76	2.07	0.71	NS
HbA1c	55.99	9.7	54.96	12.72	NS
HbA1c 1yr	54.18	9.42	53.72	9.42	NS
uACR	1.48	5.82	1.25	2.85	NS
ecg.LVH	4	2.78%	7	7.00%	NS
LBBB	5	3.47%	2	2.00%	NS
RBBB	4	2.78%	11	11.00%	0.008547
IVCD	24	16.67%	20	20.00%	NS
LAD	33	22.92%	22	22.00%	NS
1st Deg AVB	19	13.19%	21	21.00%	NS
Poor R prog	18	12.50%	11	11.00%	NS
Normal ECG	77	53.47%	46	46.00%	NS
BNP mean	20.98	21	29.91	38.02	0.0356
BNP median	14.95	21.3	17.35	27.25	0.1292
Trop I mean	2.28	2.46	3.23	2.77	0.006876
Trop I median	1.7	1.9	2.65	2.73	0.000938
Trop T mean	7.5	5.82	9.3	6.15	0.02235
Trop T median	6.36	5.05	7.66	6.43	0.006686

Log regression models for all 5 cTOD according to Nadir et al (JACC 2012)

	BNP	NT-proBNP	Trop T	Trop I	Trop I (pico)
p-val	0.00731	0.02372	0.0264	0.000735	0.000441
AUC	0.599931	0.6604082	0.646259	0.635852	0.681565
Sensitivity	0.8857	0.7643	0.7571	0.7214	0.7071
Specificity	0.1731	0.4762	0.4571	0.4327	0.5048
PPV	0.5905	0.6605	0.6503	0.6312	0.6556
NPV	0.5294	0.6024	0.5854	0.5357	0.5638
Note all current models are using correction for age, sex, gfr and BMI					
AUC					
Male		0.6947899	0.682185		0.706555
Female		0.7454545	0.72052		0.739221
High wt		NS	NS		0.740815
Low wt		0.7079349	NS		NS
High BMI		NS	0.662287		0.729941
Low BMI		0.6865672	NS		0.658316
**High weight is > 87. Low wt is 87 or less					

Log regression models for all 5 cTOD according to ASE Guideline (Updated 2016)

	BNP	NT-proBNP	Trop T	Trop I	Trop I (pico)
p-val	0.02929	0.058402	0.023928	0.00797	0.015027
AUC	0.557049		0.602276	0.624201	0.668621
Sensitivity	0.14		0.11	0.21	0.14
Specificity	0.95139		0.93103	0.91667	0.93793
PPV	0.66667		0.52381	0.63636	0.6087
NPV	0.61435		0.60268	0.62559	0.61261
***Note BNP & Trop T not sig when corrected for age, sex, gfr and BMI					
***Note Trop I (pico) done with corrected model					
AUC					
Male		NS	NS		NS
Female		NS	0.741397		0.772267
High wt		NS	NS		NS
Low wt		0.7205215	NS		NS
High BMI		NS	0.663707		0.710519
Low BMI		NS	NS		NS
**High weight is > 87. Low wt is 87 or less					