Otago Spotlight Series

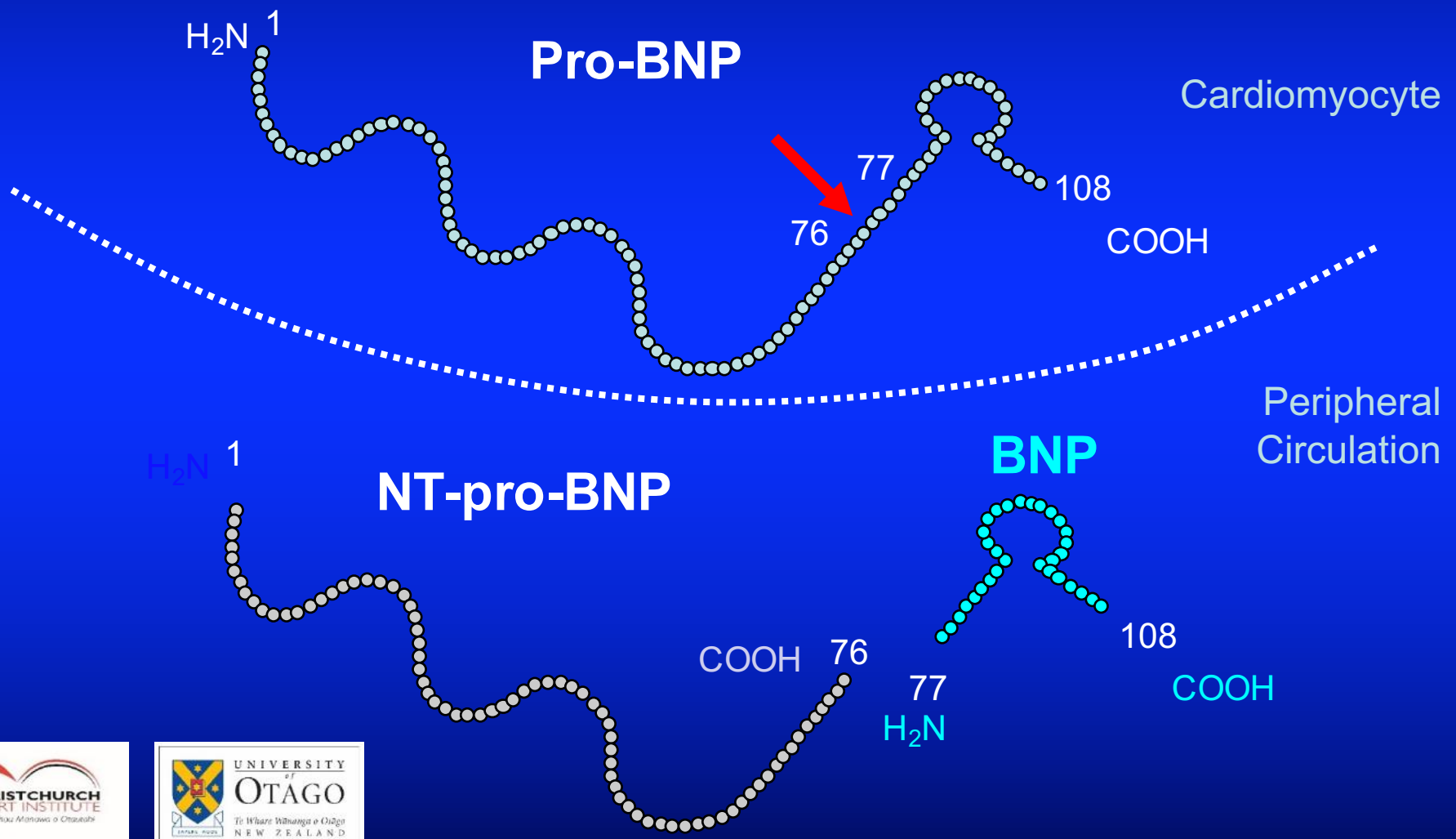
Cardiovascular Disease

Improving Diagnostic, Prognostic & Therapeutic **Biomarkers** in Heart Disease

Professor Mark Richards

Medicine, University of Otago, Christchurch

BNP / NT-ProBNP



Lam et al, JACC 2007; 49:1193

European Heart Journal Advance Access published November 17, 2005

European Heart Journal
doi:10.1093/eurheartj/ehi631

Clinical research

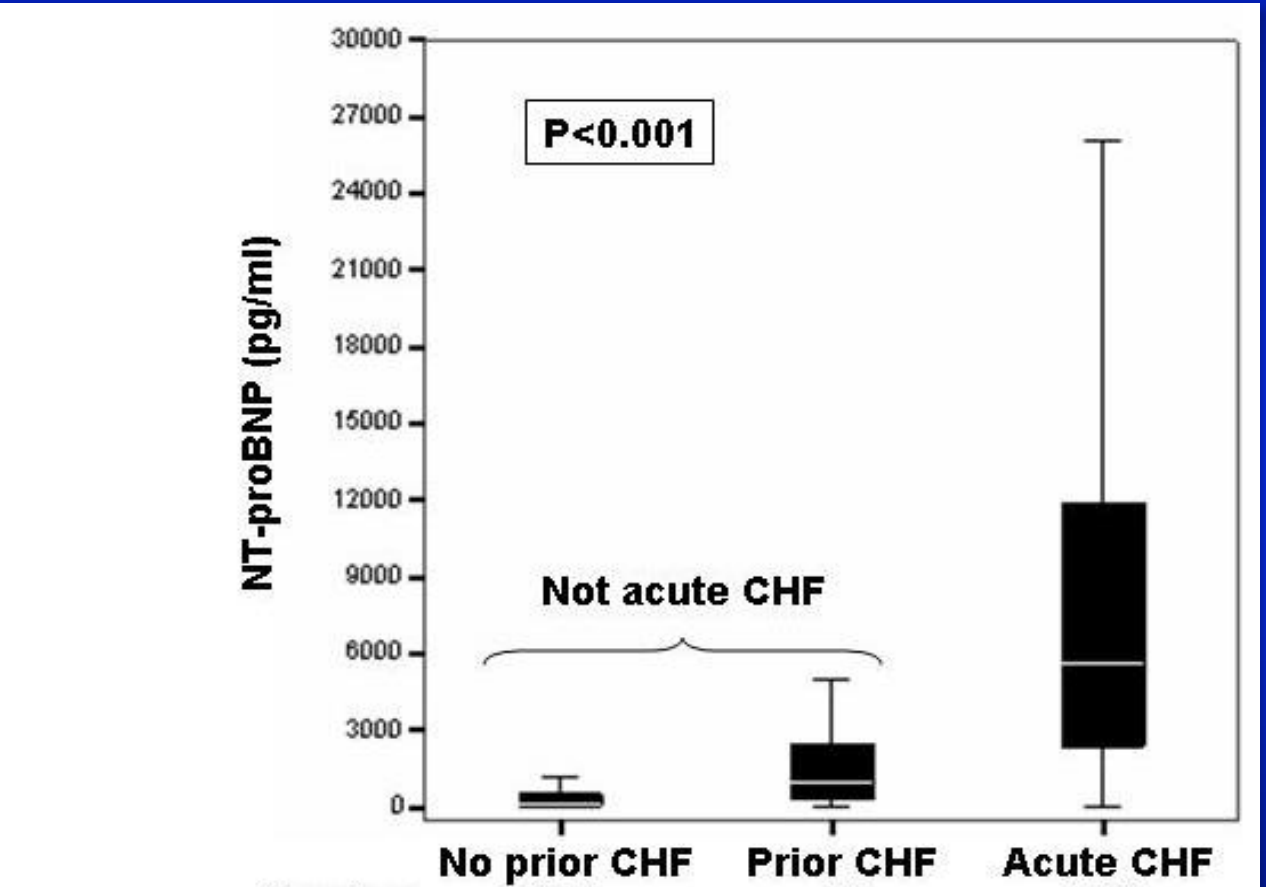
NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients

The International Collaborative of NT-proBNP Study

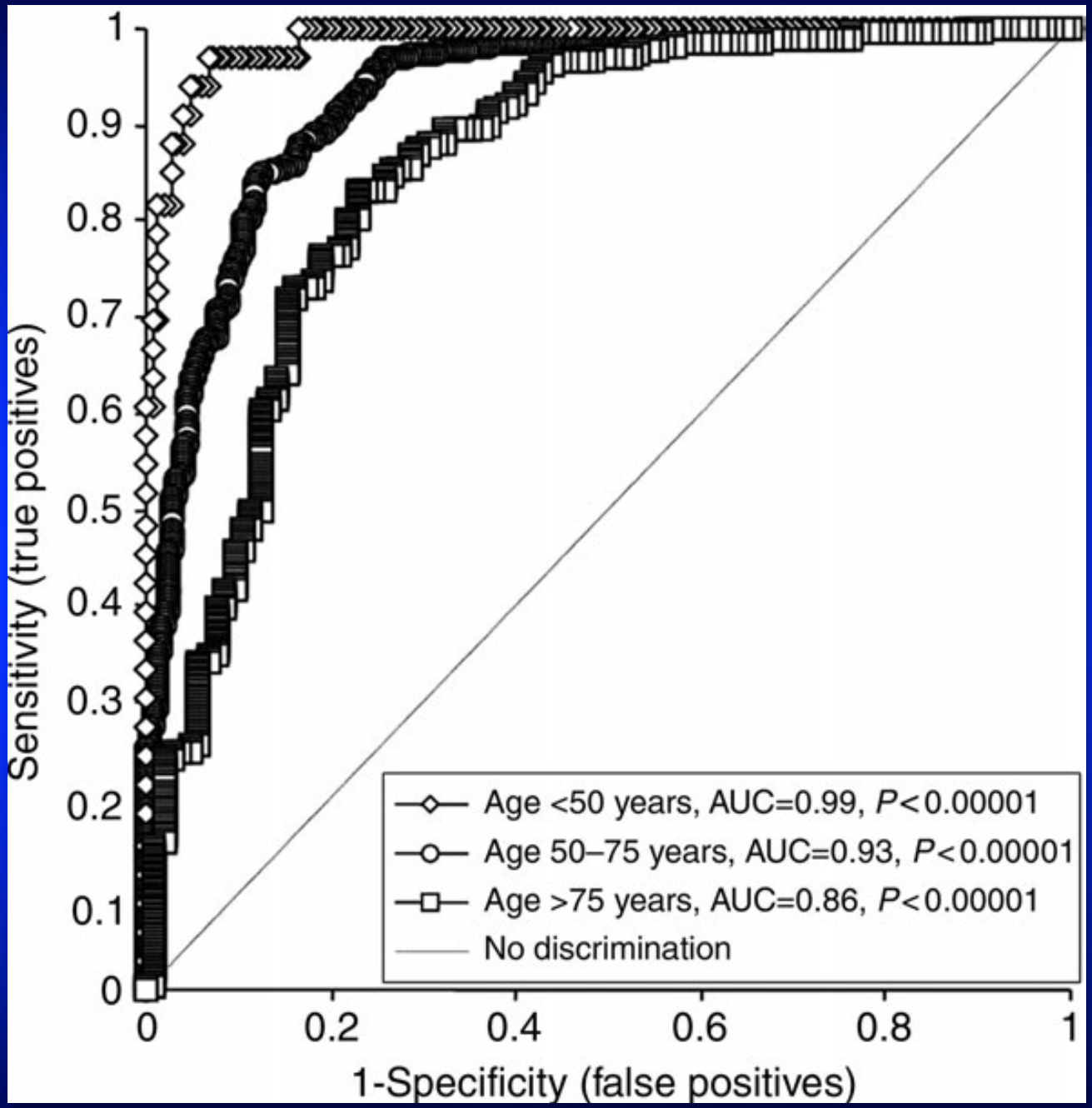
James L. Januzzi[1*†], Roland van Kimmenade[2†], John Lainchbury[3], Antoni Bayes-Genis[4], Jordi Ordonez-Llanos[5], Miguel Santalo-Bel[6], Yigal M. Pinto[2], and Mark Richards[3]

[1] *Cardiology Division, Massachusetts General Hospital, Yawkey 5984, 55 Fruit Street, Boston, MA 02114, USA;* [2] *Cardiology Department, University Hospital, Maastricht, The Netherlands;* [3] *Christchurch Cardioendocrine Research Group, Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand;* [4] *Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [5] *Biochemistry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; and* [6] *Emergency Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Diagnosis and NT-proBNP results



	No prior CHF	Prior CHF	Acute CHF
Number	481	55	720
NT-proBNP (pg/ml)	150	949	5669
NT-proBNP (pmol/L)	18	111	665



European Heart Journal (2006) 27, 330–337
doi:10.1093/eurheartj/ehi631

An almost perfect test in young patients..

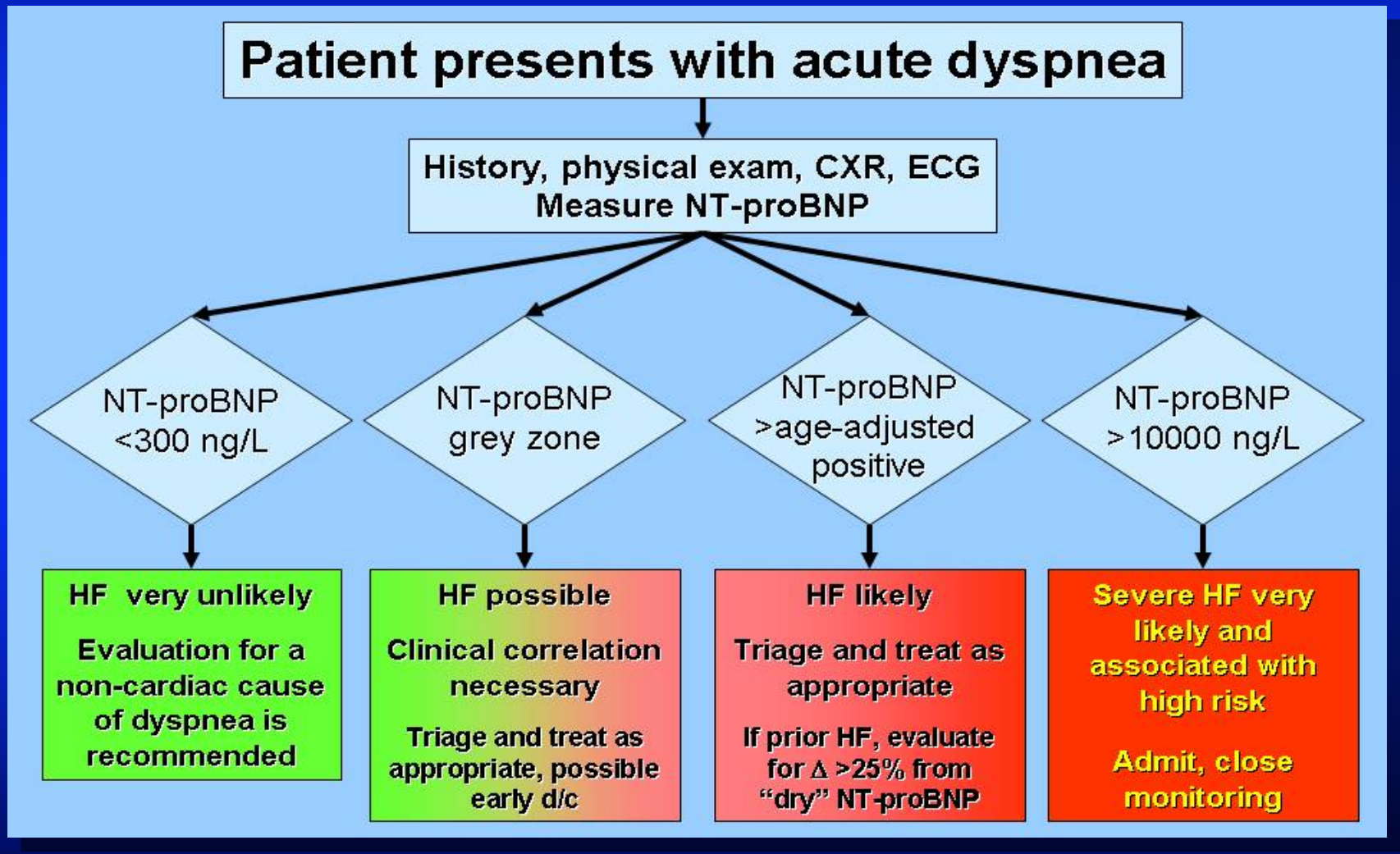
CHRISTCHURCH HEART INSTITUTE
Hangahau Manawa o Otautahi

UNIVERSITY OF OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

NT-proBNP
International Consensus Panel

CHRISTCHURCH HEART INSTITUTE

UNIVERSITY of OTAGO
NEW ZEALAND
CHRISTCHURCH



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2013 ACCF/AHA Guideline for the Management of Heart Failure : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Clyde W. Yancy, Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E. Casey, Jr, Mark H. Drazner, Gregg C. Fonarow, Stephen A. Geraci, Tamara Horwich, James L. Januzzi, Maryl R. Johnson, Edward K. Kasper, Wayne C. Levy, Frederick A. Masoudi, Patrick E. McBride, John J.V. McMurray, Judith E. Mitchell, Pamela N. Peterson, Barbara Riegel, Flora Sam, Lynne W. Stevenson, W.H. Wilson Tang, Emily J. Tsai and Bruce L. Wilkoff

Circulation. published online June 5, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

Class I

1. **In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (217-223).** ***(Level of Evidence: A)***
2. **Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (222, 224-229).** ***(Level of Evidence: A)***

NEW DEFINITION OF HEART FAILURE REQUIRES ELEVATED PLASMA NP --for HFPEF and HFmrEF

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

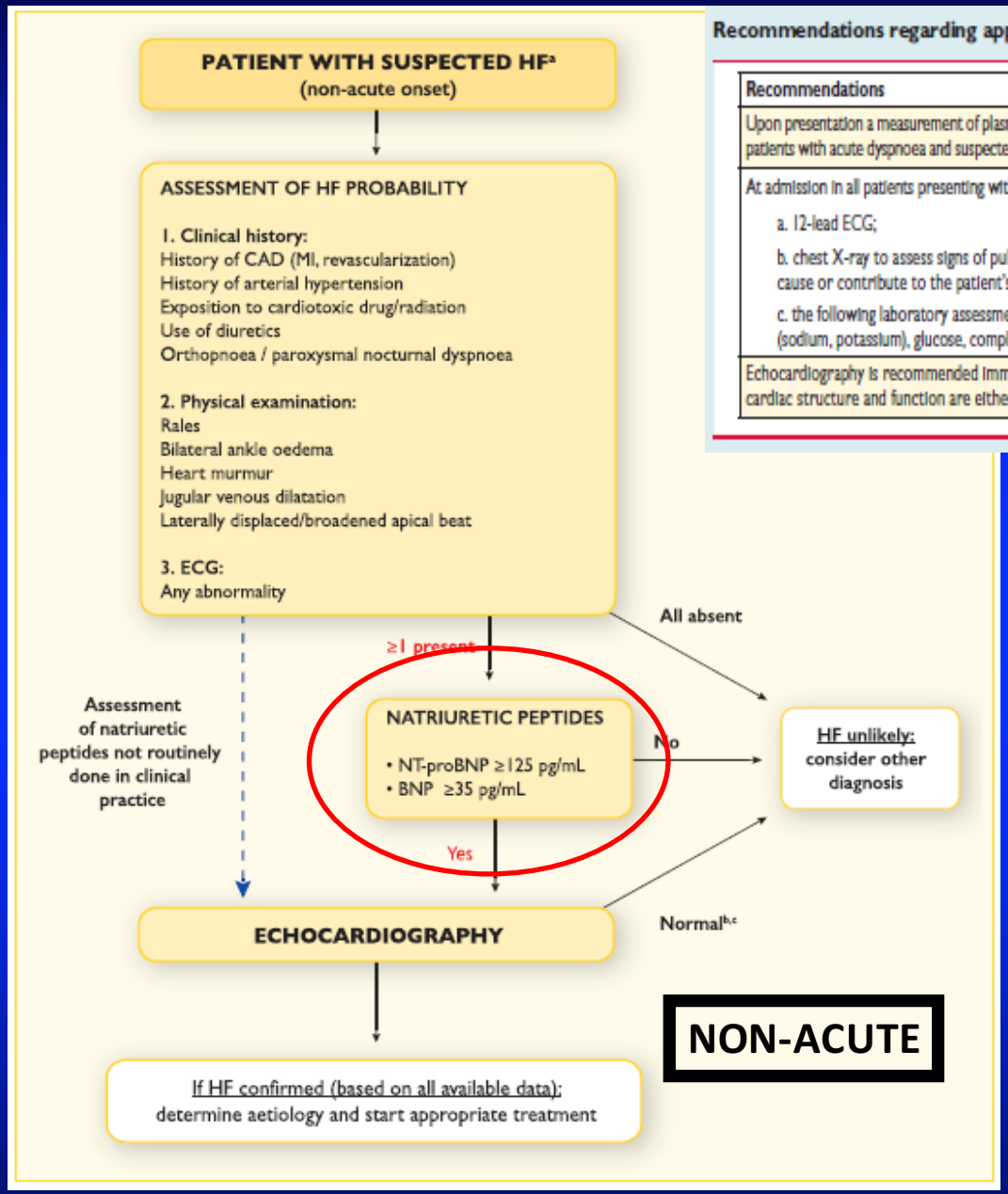
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP >35 pg/ml and/or NT-proBNP >125 pg/mL

New ESC GUIDELINES May 2016 European Heart Journal

CHRISTCHURCH HEART INSTITUTE

UNIVERSITY of OTAGO NEW ZEALAND CHRISTCHURCH



Recommendations regarding applied diagnostic measurements

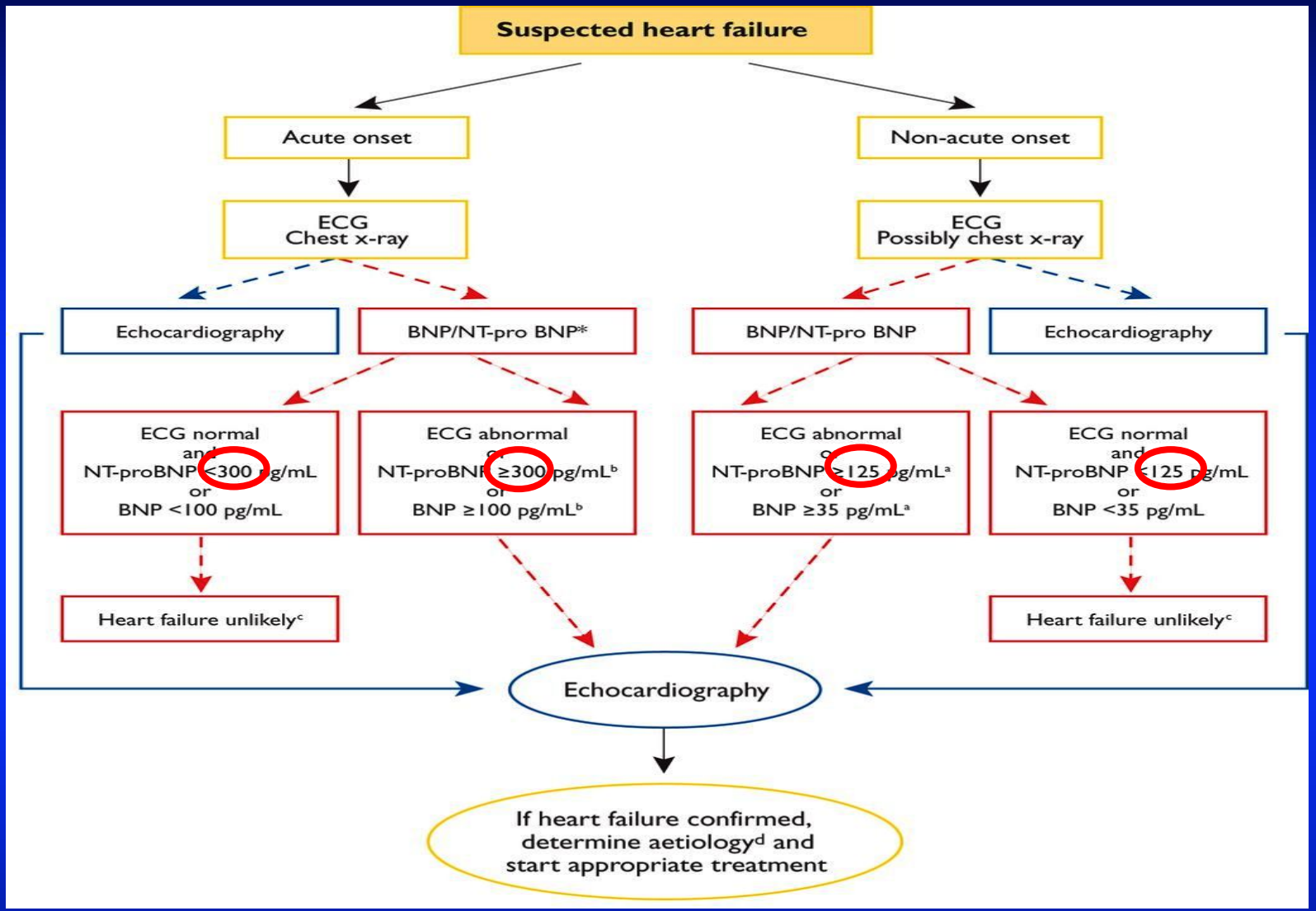
Recommendations	Class[a]	Level[b]	Ref[c]
Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.	I	A	531–534
At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended:			
a. 12-lead ECG;	I	C	
b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms;	I	C	
c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.	I	C	
Echocardiography is recommended immediately in haemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.	I	C	

ACUTE

Upon presentation measurement of plasma NT-proBNP is recommended in ALL cases with acute dyspnea and suspected Acute Heart Failure

NON-ACUTE

2016 ESC GUIDELINES
May 2016
European Heart Journal
2016doi:10.1093/eurheartj/ehw128

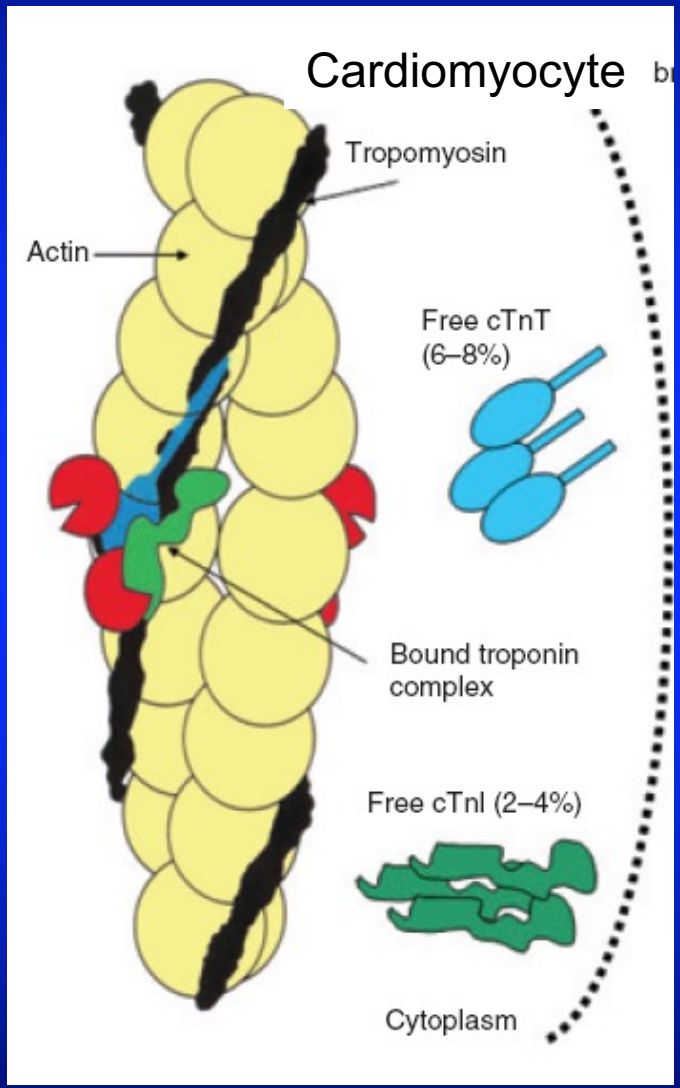


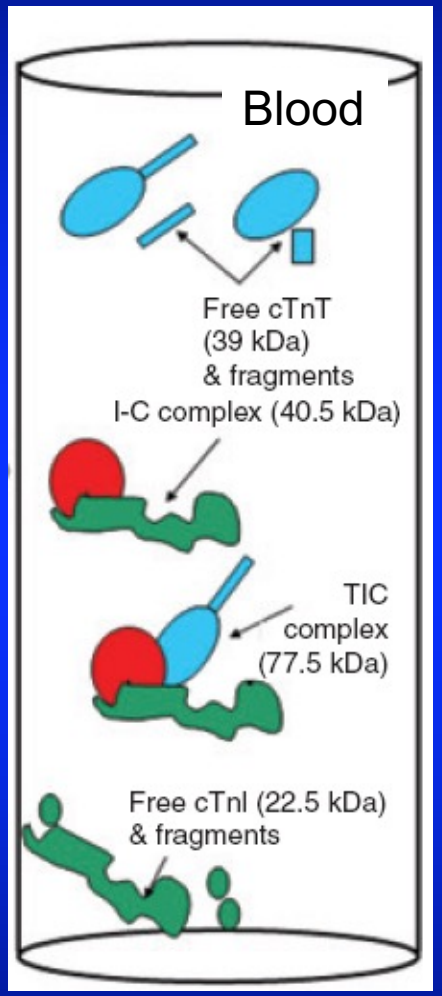
ESC Guidelines for diagnosis and treatment of HF 2012

CHRISTCHURCH HEART INSTITUTE
Hungahungatoroa Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

Troponin intra and extra-cellular locations





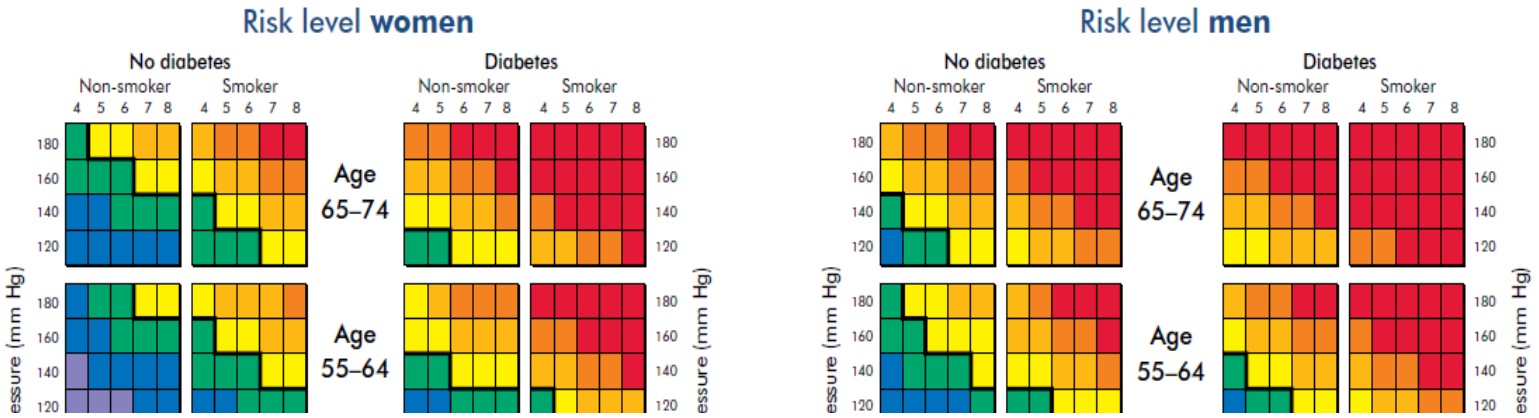
Gaze et al. Ann Clin Bioch 2008

CHRISTCHURCH HEART INSTITUTE

UNIVERSITY of OTAGO
CHRISTCHURCH

New Zealand Cardiovascular Risk Charts

www.nzgg.org.nz



Can biomarker(s) improve current Risk Stratification and treatment decisions/efficacy ?

Key

5-year cardiovascular disease (CVD) risk (fatal and non-fatal)

- Very high: >30%, 25–30%, 20–25%
- High: 15–20%
- Moderate: 10–15%
- Mild: 5–10%, 2.5–5%, <2.5%

Using the Charts

- Identify the chart relating to the person's sex, diabetic status, smoking history and age.
- Within the chart choose the cell nearest to the person's age, systolic blood pressure (SBP) and total cholesterol (TC) TC:HDL ratio. People who fall exactly on a threshold between cells are placed in the cell indicating higher risk.

Note: The risk charts now include values for SBP alone, as this is the most informative of conventionally measured blood pressure parameters for cardiovascular risk. Diastolic pressures may add some predictive power, especially at younger ages (eg, a diastolic pressure consistently >100 mm Hg in a patient with SBP values between 140 and 170 mm Hg).

Certain groups may have CVD risk underestimated using these charts. See Cardiovascular Guidelines Handbook (2009 Edition) for details.

Risk level: 5-year CVD risk (fatal and non-fatal)	Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)		
	1 intervention (25% risk reduction)	2 interventions (45% risk reduction)	3 interventions (55% risk reduction)
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

NNT = Number needed to treat

Based on the conservative estimate that each intervention: aspirin, BP treatment (lowering SBP by 10 mm Hg) or lipid modification (lowering LDL-C by 20%) reduces cardiovascular risk by about 25% over 5 years.

Note: Cardiovascular events are defined as myocardial infarction, new angina, ischaemic stroke, transient ischaemic attack (TIA), peripheral vascular disease, congestive heart failure and cardiovascular-related death.

Kidney Health · Stroke Foundation · diabetes new zealand · Heart Foundation · New Zealand Guidelines Group · Ministry of Health

Source: New Zealand Guidelines Group. *New Zealand Cardiovascular Guidelines Handbook: A summary resource for primary care practitioners.* 2nd ed. Wellington: New Zealand Guidelines Group; 2009.

Biomarkers in Heart Disease:

-the non-acute setting-

- There are TWO Cardinal Established Clinical CV Biomarkers
  - cardiac troponins
  - cardiac B type natriuretic peptides

Both established in acute cardiac disease -acute heart failure
-acute heart attack (AMI)

Both increasingly recognized as sensitive predictors of CV Prognosis in pre-clinical and non-acute settings

CHRISTCHURCH HEART INSTITUTE
Rangahau Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

High sensitivity troponins – submerging evidence

- AMI
- Myocarditis
- Pulmonary embolism
- Acute heart failure
- ESRD
- AVNRT

- Small NSTEMI or type II MI
- Myocardial injury:
- Chemotoxic
- Hypertensive crisis
- Earlier stages of CKD
- Marathon run
- Chronic PAH
- Chronic heart failure
- Stable CAD
- Tachycardia
- Myocardial ischemia ?
- General population middle-aged
- Community Screening ?

Conventional Sensitive cTn

Contemporary sensitive

Hs-cTn

Level 4 Level 3 Level 2 Level 1

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2014) **35**, 268–270
doi:10.1093/eurheartj/eht479

EDITORIAL

Highly sensitive troponins knocking at the door of primary prevention

Evangelos Giannitsis* and Hugo A. Katus

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

Biomarkers applied in the general population ?

- **NT-proBNP** Amino-terminal pro-B type natriuretic peptide
- **TnT:** Measured with a new highly sensitive assay - lower detection limit (3 pg/mL)
- GDF-15: Growth differentiation factor-15
- sFLT-1: fms-tyrosine kinase-1(VEGF receptor-1)
- PLGF: Placental growth factor

CHRISTCHURCH HEART INSTITUTE
Rangahau Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

MONICA 10 … reported 2009

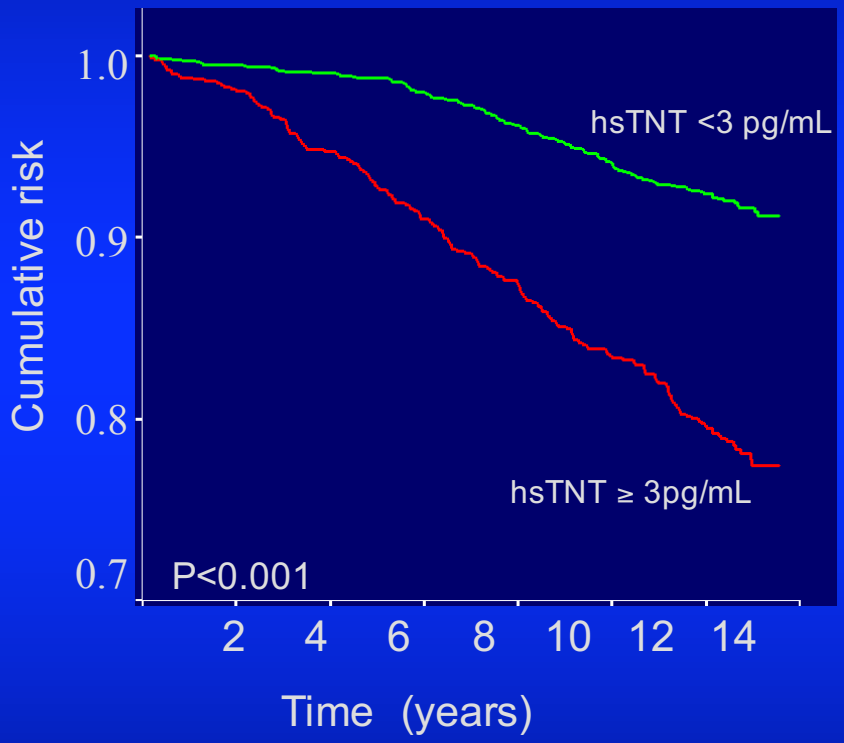
- In 1982-1984: a random sample of 4807 individuals, aged 30, 40, 50 or 60 years were invited to participate in the Danish MONICA program
- In 1993-1994: 3785 former participants were re-invited to participate in the MONICA 10 program
- To evaluate the value of **NT-proBNP, hs cTnT**, GDF-15,PLGF, and sFLT-1 for predicting first major cardiovascular events and death in the general population

CHRISTCHURCH HEART INSTITUTE

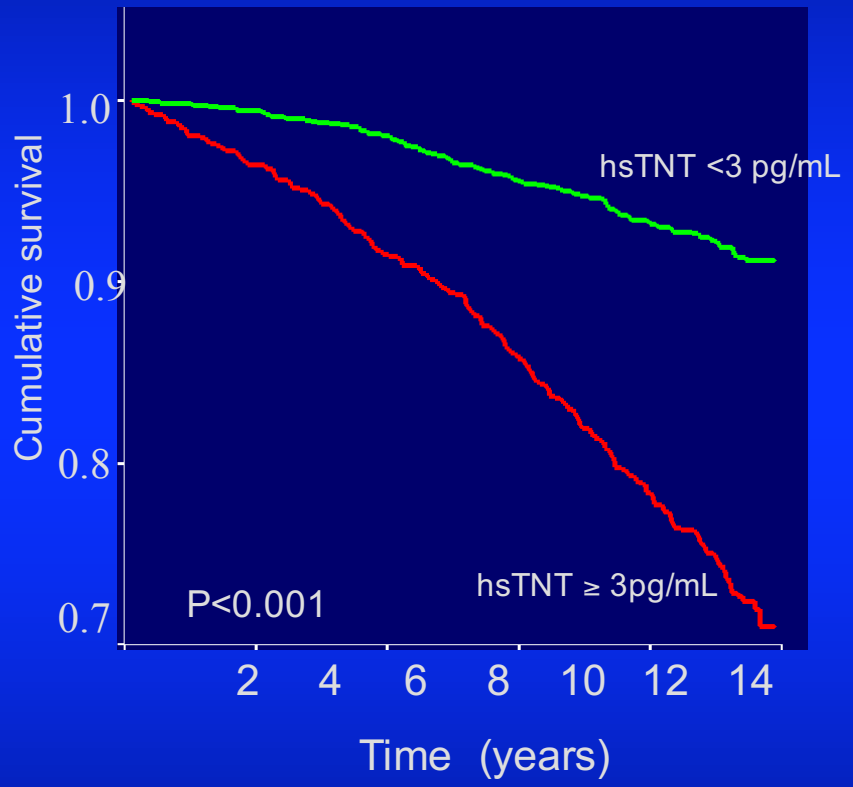
UNIVERSITY of OTAGO NEW ZEALAND CHRISTCHURCH

TNT and Outcome

First CV event



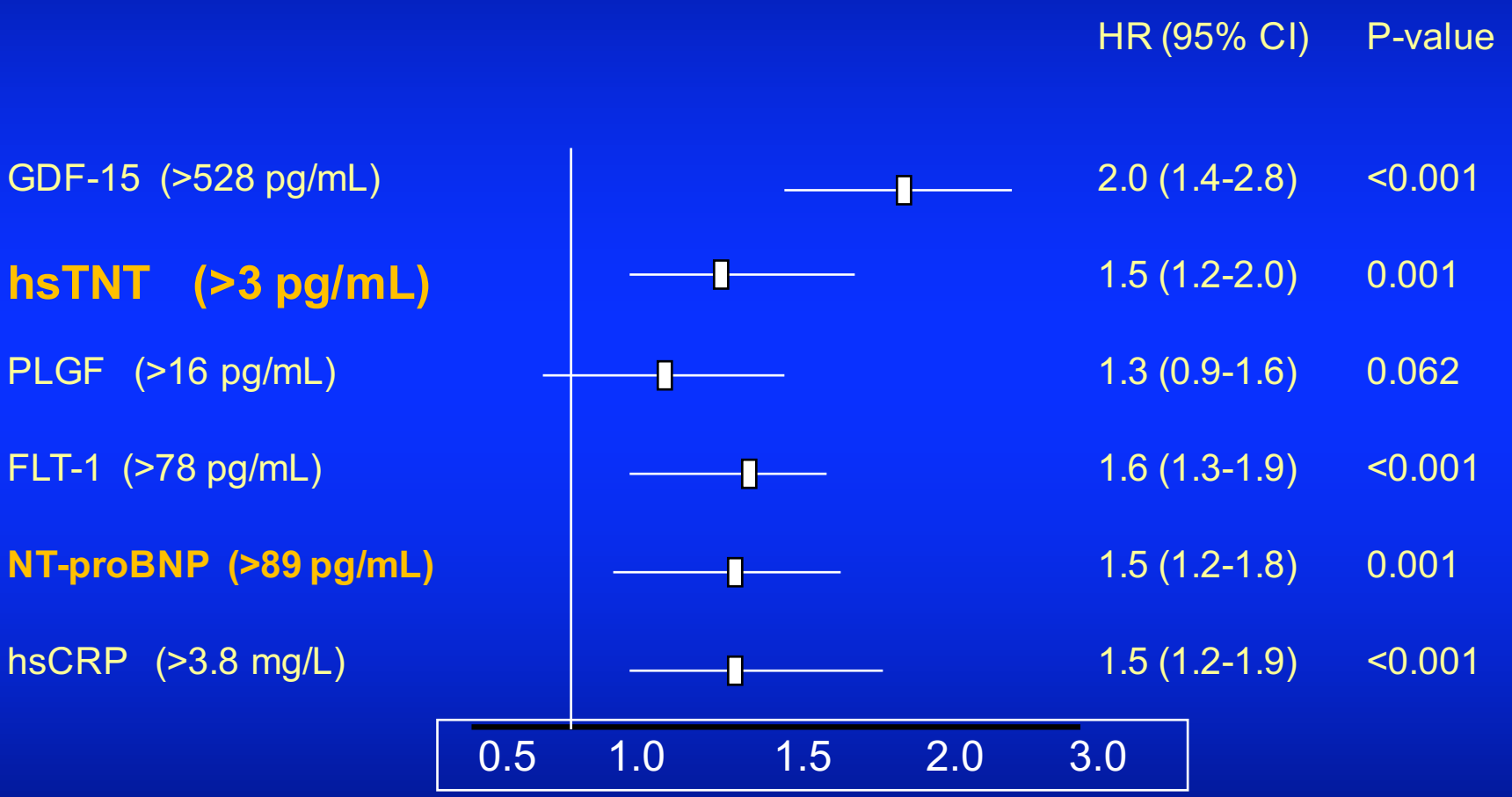
Overall mortality



CHRISTCHURCH HEART INSTITUTE

UNIVERSITY of OTAGO
NEW ZEALAND
CHRISTCHURCH

Adjusted HR for overall mortality



HR adjusted for age, gender, diabetes, current smoking, systolic BP, hypertensive medication, serum total-cholesterol, serum HDL-cholesterol

Contribution of 30 Biomarkers to 10-Year Cardiovascular Risk Estimation in 2 Population Cohorts

The MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) Biomarker Project

Stefan Blankenberg, MD; Tanja Zeller, PhD; Olli Saarela, MSc; Aki S. Havulinna, MSc; Frank Kee, MD; Hugh Tunstall-Pedoe, MD; Kari Kuulasmaa, PhD; John Yarnell, MD; Renate B. Schnabel, MD; Philipp S. Wild, MD; Thomas F. Münzel, MD; Karl J. Lackner, MD; Laurence Tiret, PhD; Alun Evans, MD*; Veikko Salomaa, MD*; for the MORGAM Project

Circulation 2010;121:2388-97.

30 Markers
7915 from FINRISK 97
-538 incident CV events over 10y

2552 men
Belfast PRIME cohort
-260 events

Developed score cTnI, NT-proBNP, CRP

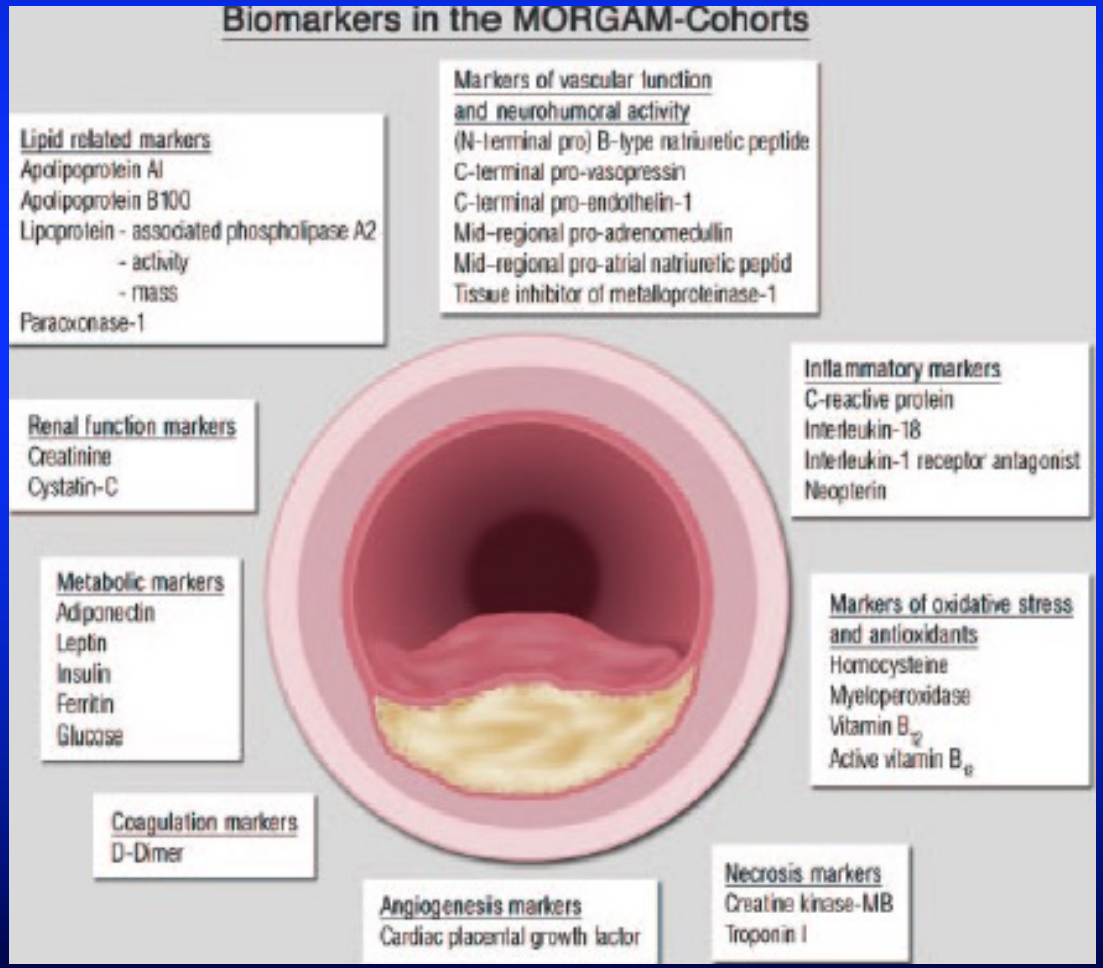
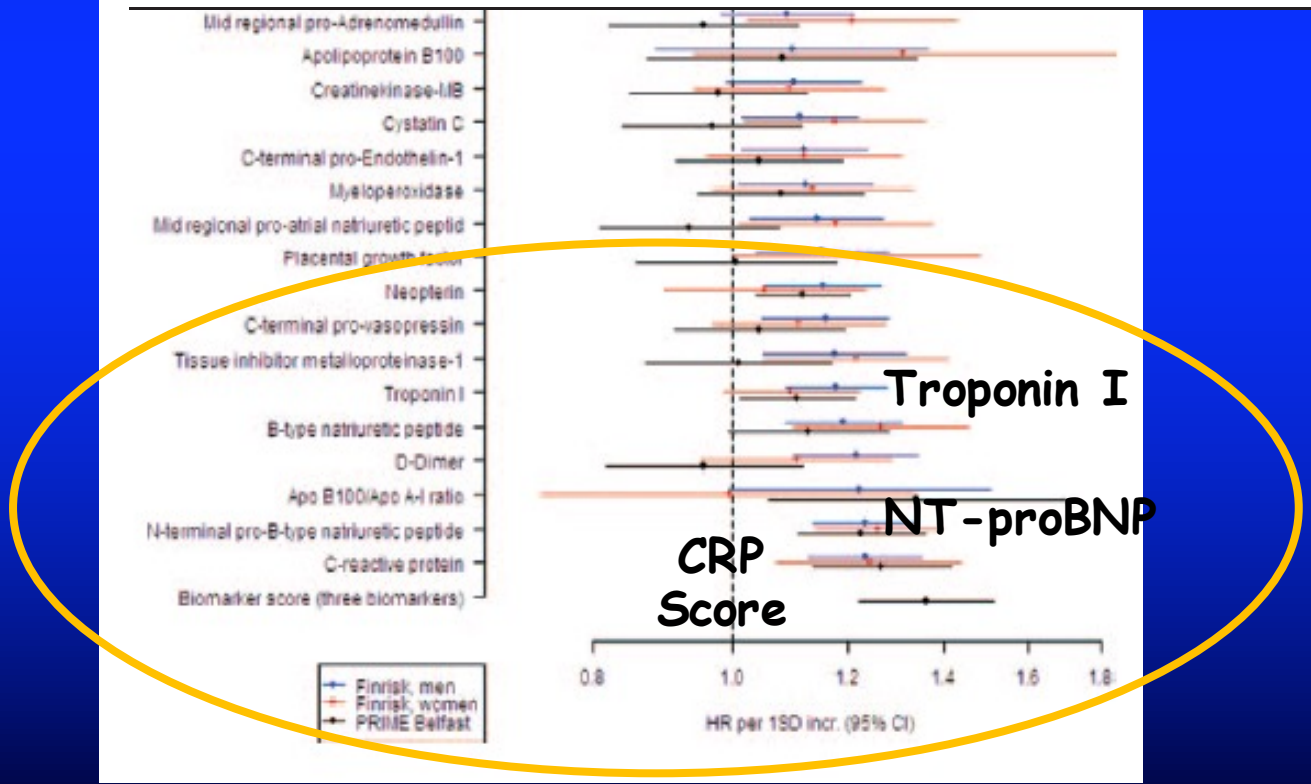


Table 3. HRs of Future Cardiovascular Events According to Optimal Cut Points

Biomarker	FINRISK 97 Men: Data-Derived Optimal Cut Point*	FINRISK 97 Men: Percentile	Belfast PRIME Men: Percentile	Belfast PRIME Men: HR (95% CI)	Belfast PRIME Men: *P*
C-reactive protein	6.81 mg/L	93.1	91.0	1.948 (1.392–2.726)	0.0004
NT-proBNP	187 pg/mL	94.5	97.2	2.289 (1.393–3.759)	0.0011
Troponin I	0.008 ng/mL	91.9	97.6	1.870 (1.017–3.438)	0.0440
Score: $0.38468 \times \text{C-reactive protein}^{1/3} + 0.11005 \times \text{NT-proBNP}^{1/3} + 1.27006 \times \text{troponin I}^{1/3}$	1.35686	92.5	95.7	2.346 (1.564–3.520)	<0.0001



Circulation 2010;121:2388-97

Figure 2. Fully adjusted HRs of biomarkers for incident cardiovascular events. HRs are per 1-SD increment and are adjusted for age, area, body mass index, systolic blood pressure, diabetes mellitus, smoking, non-HDL cholesterol, HDL-cholesterol, and cardiovascular medication. Shown on the bottom is the HR associated with a continuous score derived from NT-proBNP, C-reactive protein, and troponin I. Apo indicates apolipoprotein; CI, confidence interval.

Epidemiology from community cohorts

Multi-Ethnic Study of Atherosclerosis
" MESA "

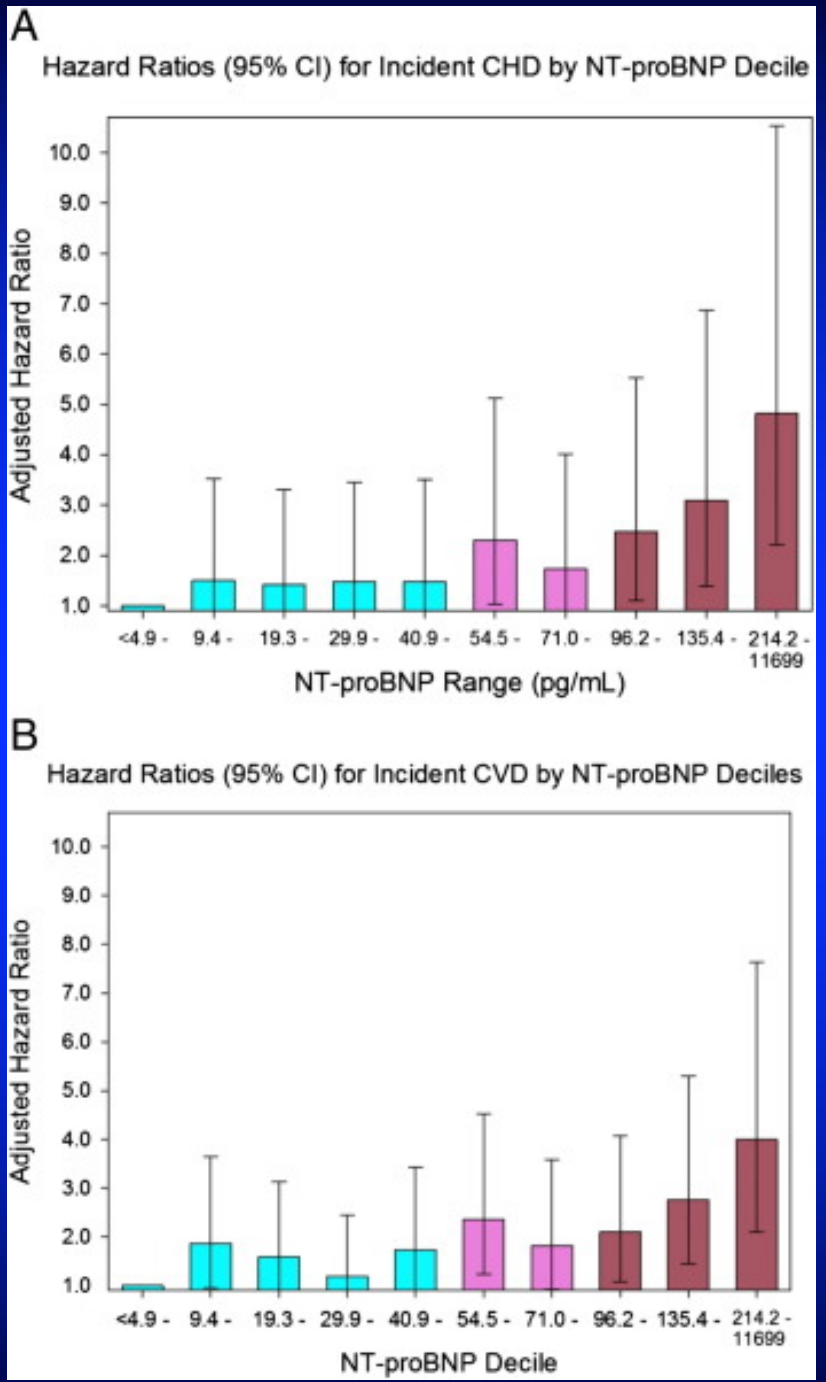


Figure 2. Adjusted HRs for incident CHD (A) and CVD (B) by decile of NT-proBNP. HRs are adjusted for age, sex, race, current smoking (Y/N), family history of heart attack, diabetes, use of antihypertensive therapy, use of statin therapy, body mass index, SBP, ...

Lori B. Daniels, Paul Clopton, Christopher R. deFilippi, Otto A. Sanchez, Hossein Bahrami, Joao A.C. Lima, Russell P. Tracy, David Siscovick, Alain G. Bertoni, Philip Greenland, Mary Cushman, Alan S. Maisel, Michael H. Criqui

Serial measurement of N-terminal pro–B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA)

American Heart Journal, Volume 170, Issue 6, 2015, 1170–1183

http://dx.doi.org/10.1016/j.ahj.2015.09.010

Epidemiology from community cohorts

Multi-Ethnic Study of Atherosclerosis " MESA "

Lori B.Daniels,et al

Serial measurement of N-terminal pro–B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA)

American Heart Journal, 2015;170:1170–1183

http://dx.doi.org/10.1016/j.ahj.2015.09.010

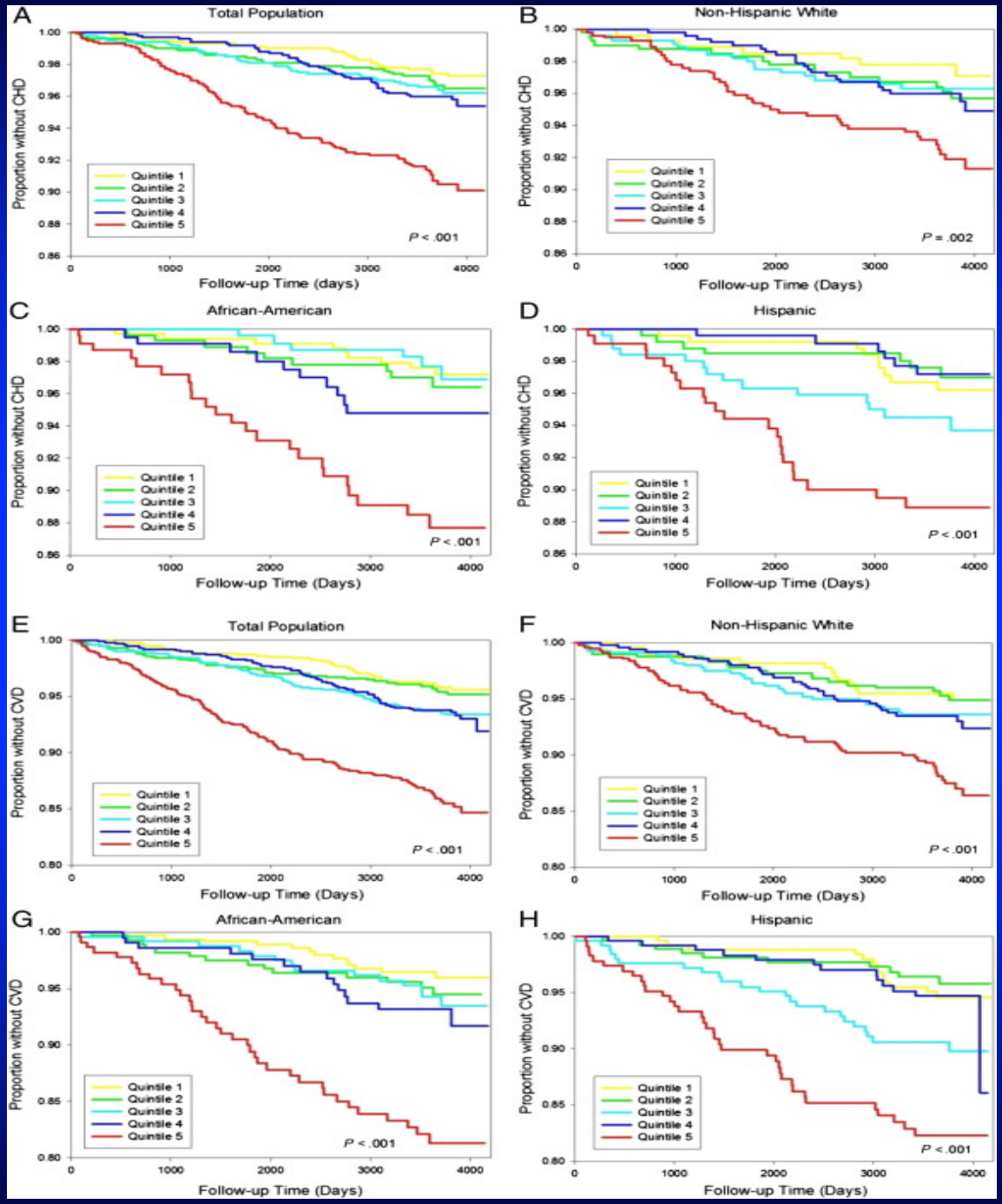


Figure 3. Kaplan-Meier plots based on quintile of NT-proBNP, by ethnicity. The plots show risk of incident CHD and CVD among all participants (A, E), non-Hispanic whites (B, F), African Americans (C, G), and Hispanics (D, H).

Clinical Chemistry 59:12
1802–1810 (2013)

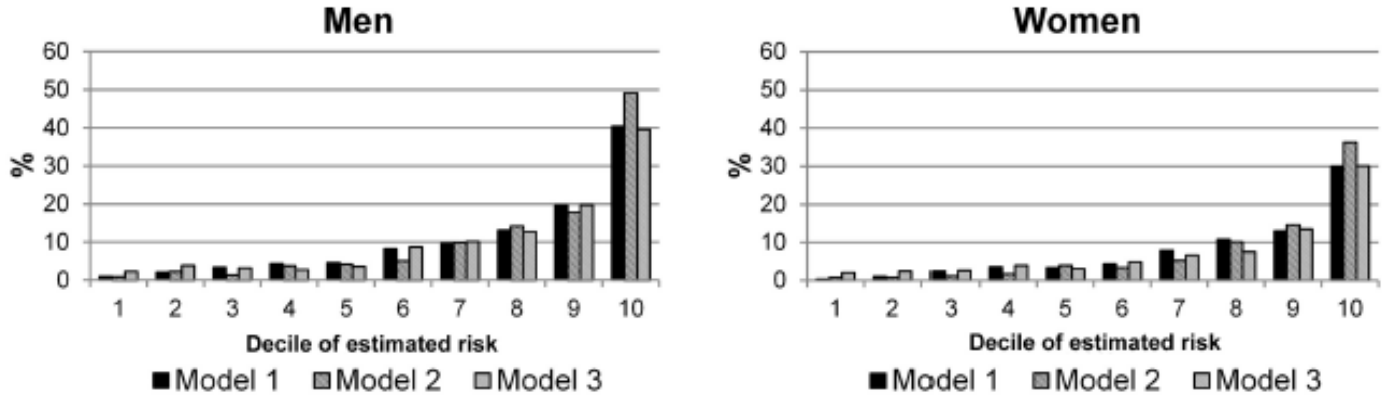
Troponin T and N-Terminal Pro–B-Type Natriuretic Peptide: A Biomarker Approach to Predict Heart Failure Risk—The Atherosclerosis Risk in Communities Study

Vijay Nambi,[1,2,3*] Xiaoxi Liu,[4] Lloyd E. Chambless,[4] James A. de Lemos,[5] Salim S. Virani,[1,2] Sunil Agarwal,[6] Eric Boerwinkle,[7] Ron C. Hoogeveen,[2] David Aguilar,[2] Brad C. Astor,[8] Pothur R. Srinivas,[9] Anita Deswal,[1,2] Thomas H. Mosley,[10] Josef Coresh,[6] Aaron R. Folsom,[11] Gerardo Heiss,[4] and Christie M. Ballantyne[2,3]

METHODS: Using sex-specific models, we added cTnT and NT-proBNP to age and race ("laboratory report" model) and to the ARIC HF model (includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent coronary heart disease, and heart rate) in 9868 participants without prevalent HF; area under the receiver operating characteristic curve (AUC), integrated discrimination improvement, net reclassification improvement (NRI), and model fit were described.

CHRISTCHURCH HEART INSTITUTE
Kaingahou Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH



Models:

Model 1: age, race, systolic blood pressure (SBP), antihypertensive medication use, current smoking, former smoking, diabetes, body mass index (BMI), prevalent coronary heart disease (CHD), heart rate (ARIC HF model)

Model 2: Model 1 + cTnT + NT-proBNP (ARIC HF + biomarker model)

Model 3: age, race, cTnT + NT-proBNP (lab report model)

Note: Troponin modeled as 6 categories and log(NT-proBNP) were used.

Fig. 2. Ten-year risk of HF by decile of estimated risk.

In this figure, we describe, in men and women, the number of individuals in each decile of risk who will have incident HF in 10 years.

RESULTS: Over a mean follow-up of 10.4 years, 970 participants developed incident HF. Adding cTnT and NT-proBNP to the ARIC HF model significantly improved all statistical parameters (AUCs increased by 0.040 and 0.057; the continuous NRIs were 50.7% and 54.7% in women and men, respectively). Interestingly,

Clinical Chemistry 59:12
1802–1810 (2013)

Troponin T and N-Terminal Pro–B-Type Natriuretic Peptide: A Biomarker Approach to Predict Heart Failure Risk—The Atherosclerosis Risk in Communities Study

Table 3. AUC and the goodness-of-fit test statistic.[a]

	AUC		Goodness of model fit: Grønnesby–Borgan test statistic	
	Men	Women	Men	Women
Model 1	0.653 (0.628–0.676)	0.658 (0.634–0.682)	9.33 ($P = 0.41$)	18.32 ($P = 0.03$)
Model 2 (ARIC HF model)	0.779 (0.763–0.800)	0.776 (0.760–0.797)	18.12 ($P = 0.03$)	21.91 ($P = 0.01$)
Model 3 (lab model)	0.789 (0.767–0.812)	0.767 (0.745–0.789)	14.35 ($P = 0.11$)	5.80 ($P = 0.76$)
Model 4 (ARIC HF + biomarkers model)	0.836 (0.821–0.857)	0.817 (0.803–0.837)	14.60 ($P = 0.10$)	18.31 ($P = 0.03$)
Model 2 + cTnT	0.811 (0.797–0.833)	0.804 (0.790–0.825)	15.95 ($P = 0.07$)	20.39 ($P = 0.02$)
Model 2 + NT-proBNP	0.822 (0.805–0.843)	0.804 (0.789–0.826)	7.96 ($P = 0.54$)	19.64 ($P = 0.02$)

[a] Model 1, age + race; model 2, ARIC HF model; model 3, model 1+ cTnT + NT-proBNP (lab model); model 4, model 2 + cTnT + NT-proBNP (ARIC HF + biomarkers model). 95% CI was generated using 1000 bootstraps. ARIC HF model includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent CHD, and heart rate. Biomarkers refer to cTnT and NT-proBNP. Lab model includes age, race, cTnT, and NT-proBNP.

Broadening and improving cardiovascular risk assessment with natriuretic peptides measurement: individual-participant meta-analysis of 40 prospective cohorts.

The Natriuretic Peptides Studies Collaboration

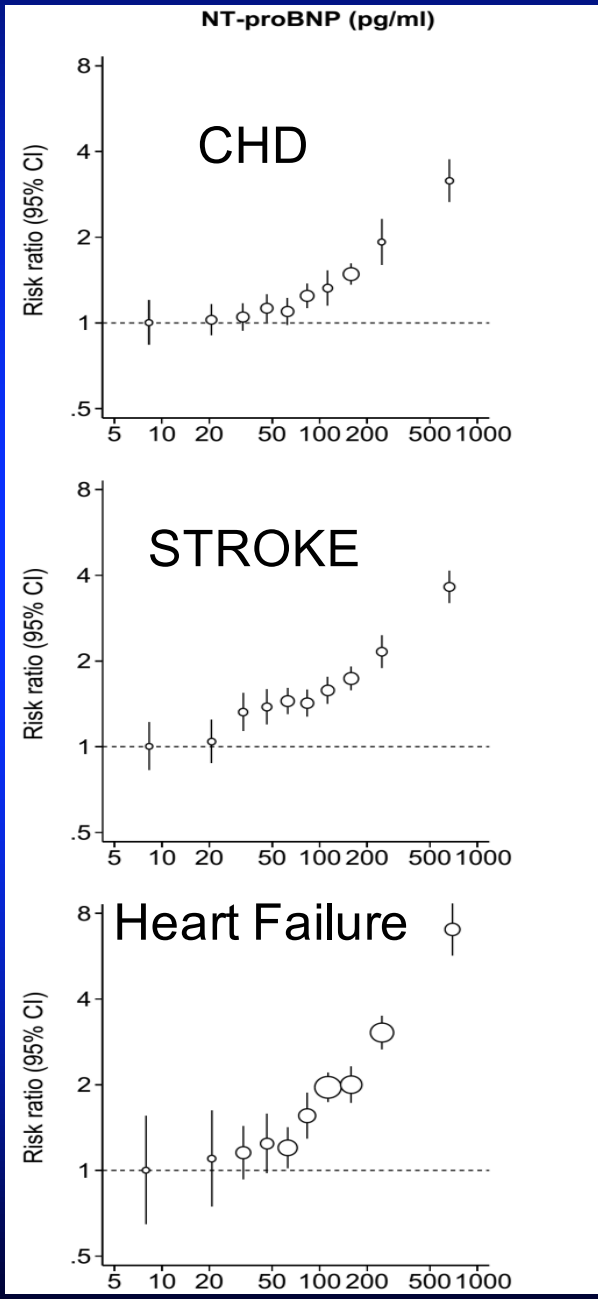
Data from 40 prospective cohorts involving 95,617 participants without a history of CVD at baseline. Follow up median 7.8 years.

Risk ratios = adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol and HDL-C and, where appropriate, stratified by sex.

Total of:-

- 4,716 CHD outcomes (from 34 cohorts)
- 3,760 stroke outcomes (from 29 cohorts)
- 2,008 heart failure outcomes (from 14 cohorts).

***Interpretation*: In people without baseline CVD, adding NT-proBNP assessment to conventional risk factors could improve accuracy of CHD and stroke risk prediction as well as broaden CVD prediction to include first-onset heart failure.**



IS THERE ANY TRIAL EVIDENCE SUPPORTING EFFICACY OF MARKER-GUIDED RISK STRATIFICATION TO TRIGGER TREATMENT ?

CHRISTCHURCH HEART INSTITUTE
Rangahau Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

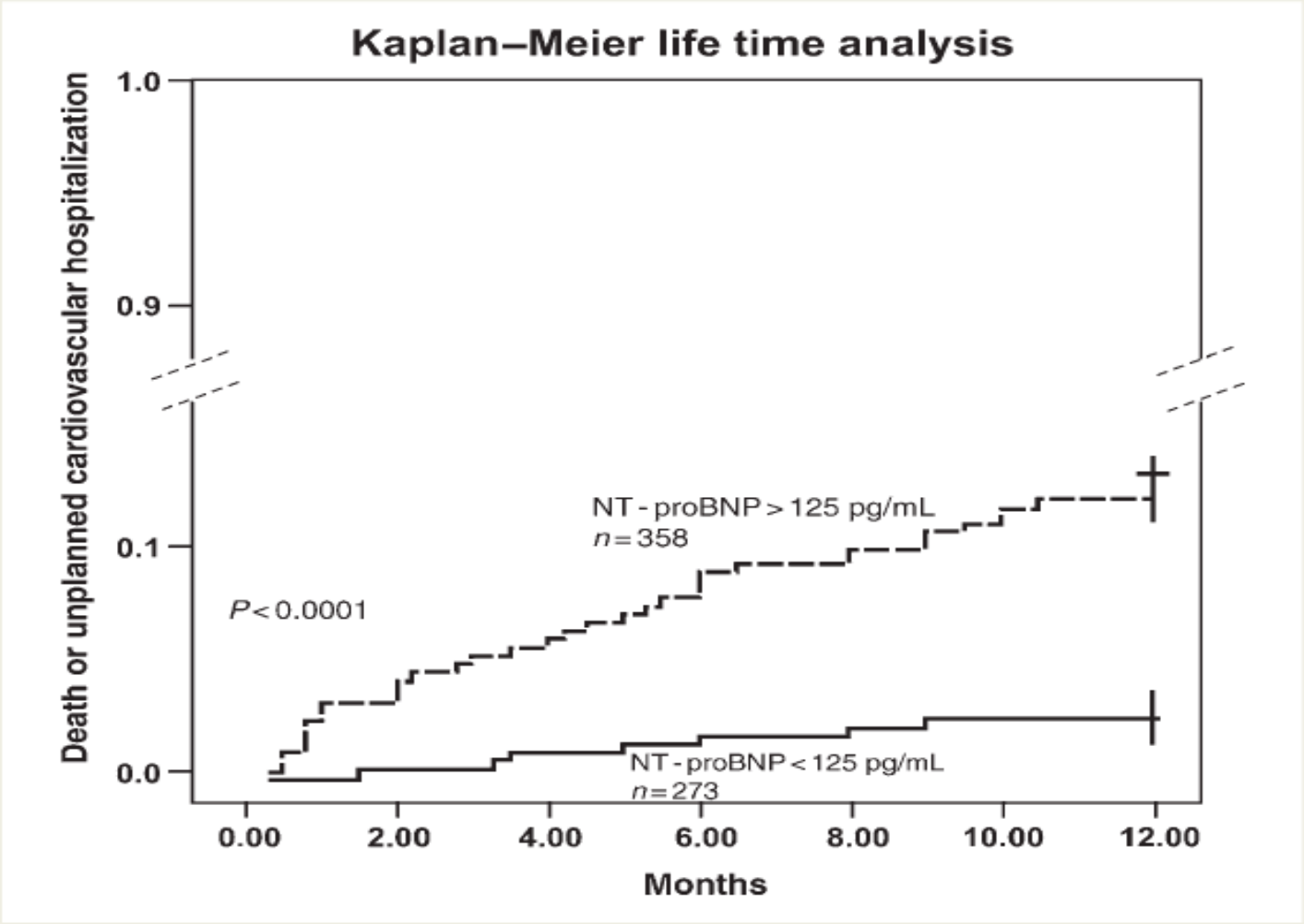


Figure 1 Kaplan–Meier curves of all-cause mortality or unplanned cardiovascular hospitalization in 631 diabetic patients according to plasma-levels of NT-proBNP at baseline. Solid line: patients with NT-proBNP levels below cut-off (<125 pg/mL). Dashed line: patients with NT-proBNP levels above cut-off (>125 pg/mL). Log-rank test for overall difference, $P < 0.0001$.

PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease)

A Prospective Randomized Controlled Trial

Martin Huelsmann, MD,* Stephanie Neuhold, MD,*† Michael Resl, MD,‡ Guido Strunk, PHD,§‖ Helmut Brath, MD,¶ Claudia Francesconi, MD,# Christopher Adlbrecht, MD,* Rudolf Prager, MD,** Anton Luger, MD,‡ Richard Pacher, MD,* Martin Clodi, MD‡

Vienna, Austria; and Dortmund, Germany

JACC 2013; 62:1365-72.

Inclusion Criteria

Type 2 DM ≥ 6/12
Age ≥ 18years
NT-proBNP >125pg/ml

INTERVENTION

Maximized RAAS / Beta blockade
Versus
Usual Care

Exclusion Criteria

-Hx of Cardiac Disease
-ECG changes incl Afib, ST-T wave abnormalities,BBB
-Abnormal Echo (with exception of diastolic dysfunction) ie low EF, wall motion abnormalities, significant valve dysfunction

- Expectancy < 1 year
- Chronic Infections
- Cortisone Rx
- Renal replacement Rx
- Childbearing age sans reliable contraception

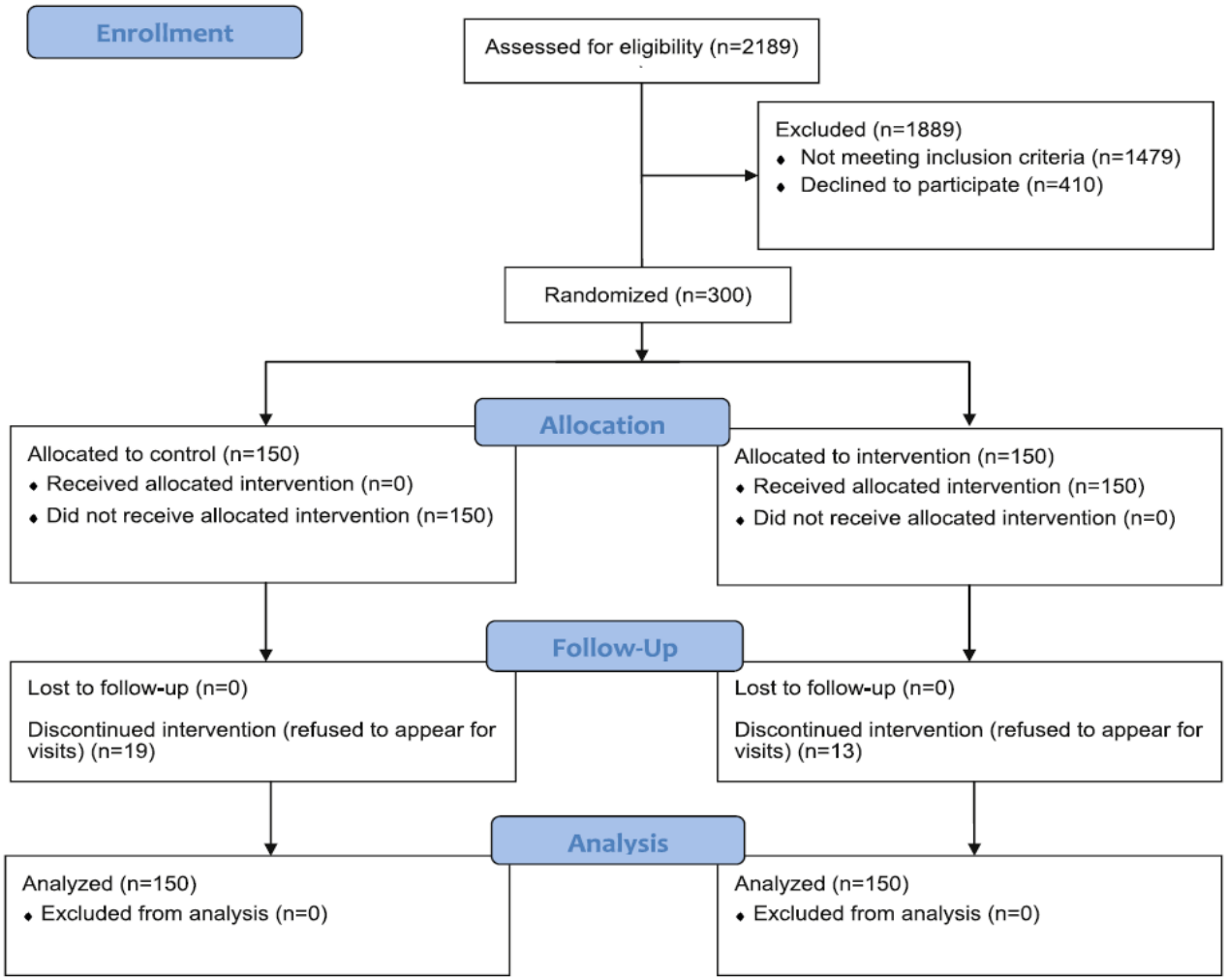


Figure 1 **Flow Diagram**

Enrollment, randomization, and follow-up of study participants.

Table 2 Baseline Characteristics and Follow-Up Values

	Control Baseline (n = 150)	Intensified Baseline (n = 150)	p Value	Control 12 Months (n = 131)	Intensified 12 Months (n = 137)	p Value
Blood pressure systolic, mm Hg	151 ± 22	151 ± 23	0.10	144 ± 22*	145 ± 22*	0.83
Heart rate, beats/min	72 ± 11	72 ± 12	0.78	72 ± 12	68 ± 11*	0.004
RAS antagonist, %	79	77	0.78	78	95*	0.0001
RAS % target dose	55 ± 40	57 ± 42	0.59	74 ± 31*	92 ± 30*	0.0001
Beta-blocker, %	45	54	0.13	44	85*	0.0001
Beta-blocker % target dose	24 ± 32	32 ± 35	0.05	54 ± 29*	80 ± 31*	0.0001
Statins	71 (47.3%)	72 (48.0%)	0.10	61 (40.7%)	70 (46.7%)	0.17
Aspirin	62 (41.3%)	63 (42.0%)	1.0	51 (34.0%)	63 (42.0%)	0.098
Oral antidiabetic drugs	68 (45.3%)	71 (47.3%)	0.62	61 (40.7%)	67 (44.7%)	0.62
Insulin	45 (30.0%)	42 (28.0%)	0.73	44 (29.3%)	35 (23.3%)	0.12
Triglycerides, mg/dl	154 ± 76	152 ± 70	0.83	146 ± 85	151 ± 85	0.63
LDL cholesterol, mg/dl	96 ± 33	94 ± 29	0.34	94 ± 32	89 ± 29*	0.21
eGFR, ml/min	81.5 ± 18.2	82.9 ± 18.2	0.51	82.2 ± 18.7	77 ± 17.6*	0.14
HbA_{1c}, %	6.9 ± 1	7.1 ± 1.1	0.27	7.1 ± 1.2*	7.1 ± 1	0.78
NT-proBNP, pg/ml	266 (181–402)	235 (169–343)	0.18	264 (167–394)	248 (169–433)	0.65

Values are mean ± SD, %, n (%), or median (interquartile range). *$p < 0.05$ baseline versus 12 months within a group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

eGFR = estimated glomerular filtration rate; NT-proBNP: N-terminal pro–B-type natriuretic peptide; RAS = renin-angiotensin system.

PONTIAC TRIAL

CHRISTCHURCH HEART INSTITUTE

UNIVERSITY of OTAGO NEW ZEALAND CHRISTCHURCH

PONTIAC TRIAL

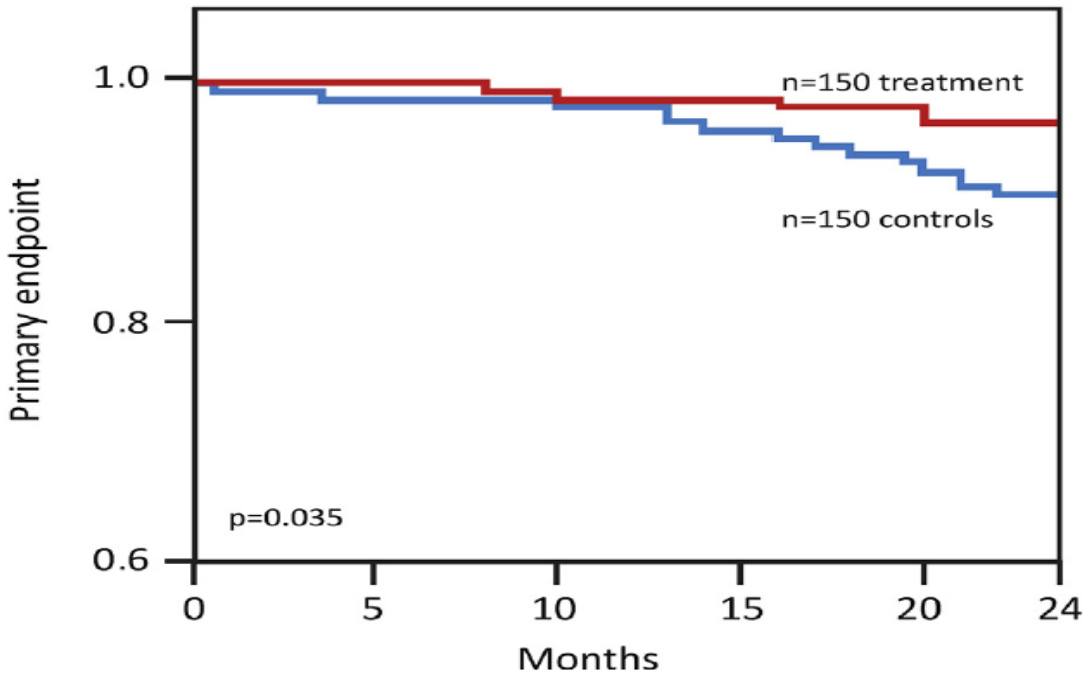


Figure 2 Kaplan-Meier Curves of the Primary Endpoint Hospitalization or Death Due to Cardiac Disease According to Treatment Strategy

Red line = intensified group. **Blue line** = control group. Log-rank test for overall difference, p = 0.035.

Table 3 Reasons for Hospitalizations

Hospitalization Due to	All	Control	Intensified	p Value
Any reason	135 (45%)	77 (51%)	58 (39%)	0.02
Cardiovascular event	25 (8%)	18 (12%)	7 (5%)	0.02
Cardiac event	19 (6%)	14 (9%)	5 (3%)	0.03
Heart failure	8 (3%)	7 (5%)	1 (1%)	0.003

Research

Original Investigation

Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

The STOP-HF Randomized Trial

Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O'Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabhagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD

JAMA. 2013;310(1):66-74.

JAMA. 2013;310(1):66-74.

Inclusion Criteria

- Over 40 years

AND 1 or more of:-

-Hypertension (Rx ≥ 1/12)
-Hypercholesterolemia (TC>5.0 mmol/L and/ or LDL > 3.0 mmol/L or on anti-lipid Rx
-Obesity (BMI>30)
-Vascular Disease incl coronary artery disease, Cerebrovasc disease and PVD
-Diabetes
-Arrhythmia requiring Rx
-Mod to severe valve disease

Exclusion Criteria

-Refusal to consent
-Established LV systolic dysfunction
-Evidence or Hx of symptomatic HF
- Survival < study period

STOP-HF

CHRISTCHURCH HEART INSTITUTE
Rangahau Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

The Intervention

Consecutive consenting patients fulfilling Incl and not Excl criteria recruited by Study Nurse and randomized 1:1 to :-

CONTROL

Per Primary Care :-

- Advice on lifestyle modifications
- Risk Factor intervention as determined
- ≥ 1 Annual review
- No knowledge of BNP result - repeated annually by Nurse and referred if BNP moved to > 50pg/ml

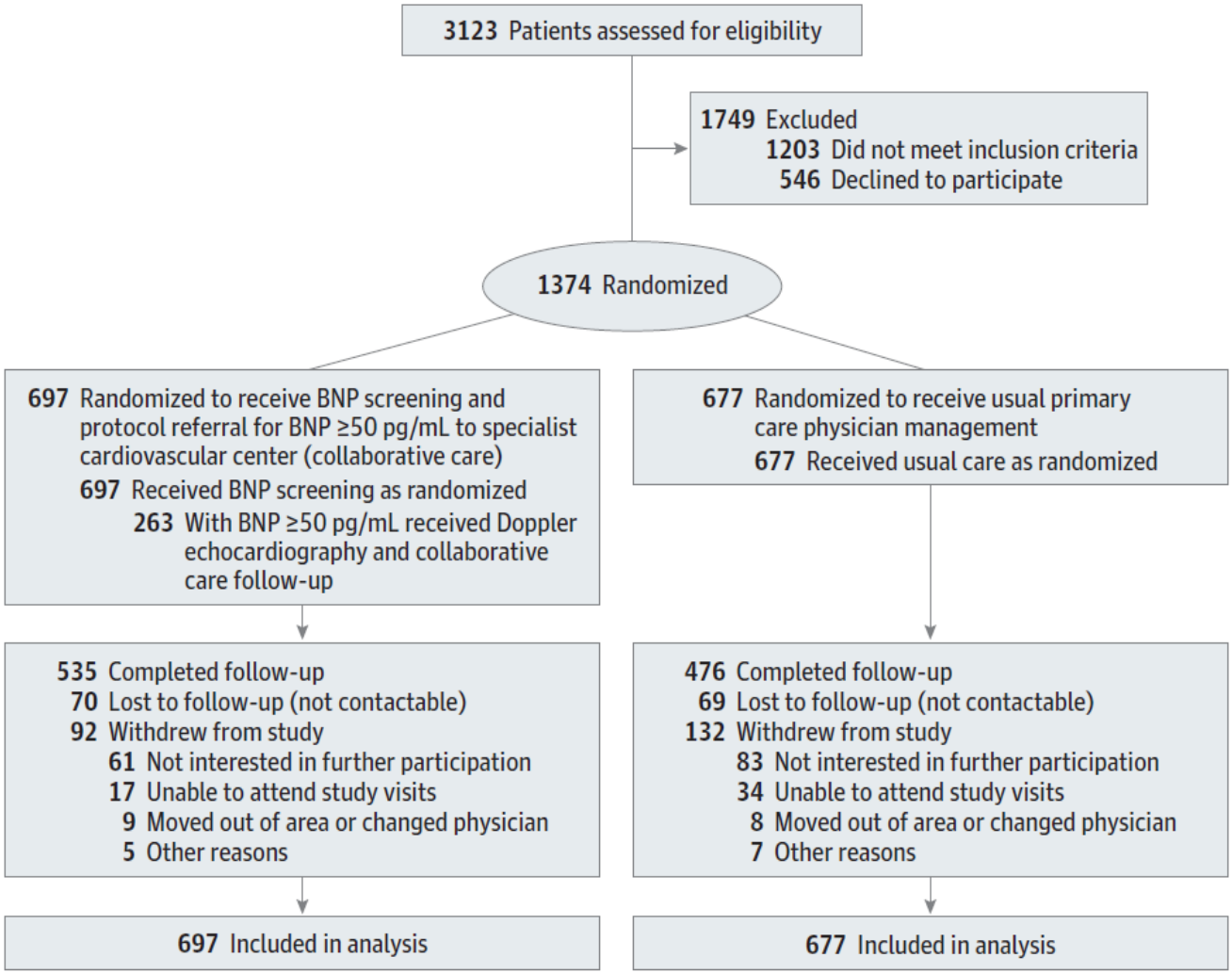
INTERVENTION

- BNP results to Primary Care
- BNP < 50pg/ml managed as control (albeit with disclosure of BNP values to patients and their primary care physicians)
- BNP>50pg/ml =referred to Cardiovascular Service
- **Doppler Echo and review by Cardiologist -> decided on any further Dx or Rx**
- **Multi-dimensional Rx -optimal risk factor management**
  - coaching by specialist nurse, lifestyle, adherence to meds
  - collaborative care, ≥ 1annual specialist review, incl repeat echo, repeat BNP and other Dx's as appropriate …all conveyed to Primary Care giver.

FINAL:- At trial termination ALL CONTROL and INTERVENTION underwent blinded Echo and Clinical Assessment.

STOP-HF

Figure 1. Participant Flow



JAMA. 2013;310(1):66-74.

BNP indicates brain-type natriuretic peptide.

JAMA. 2013;310(1):66-74.

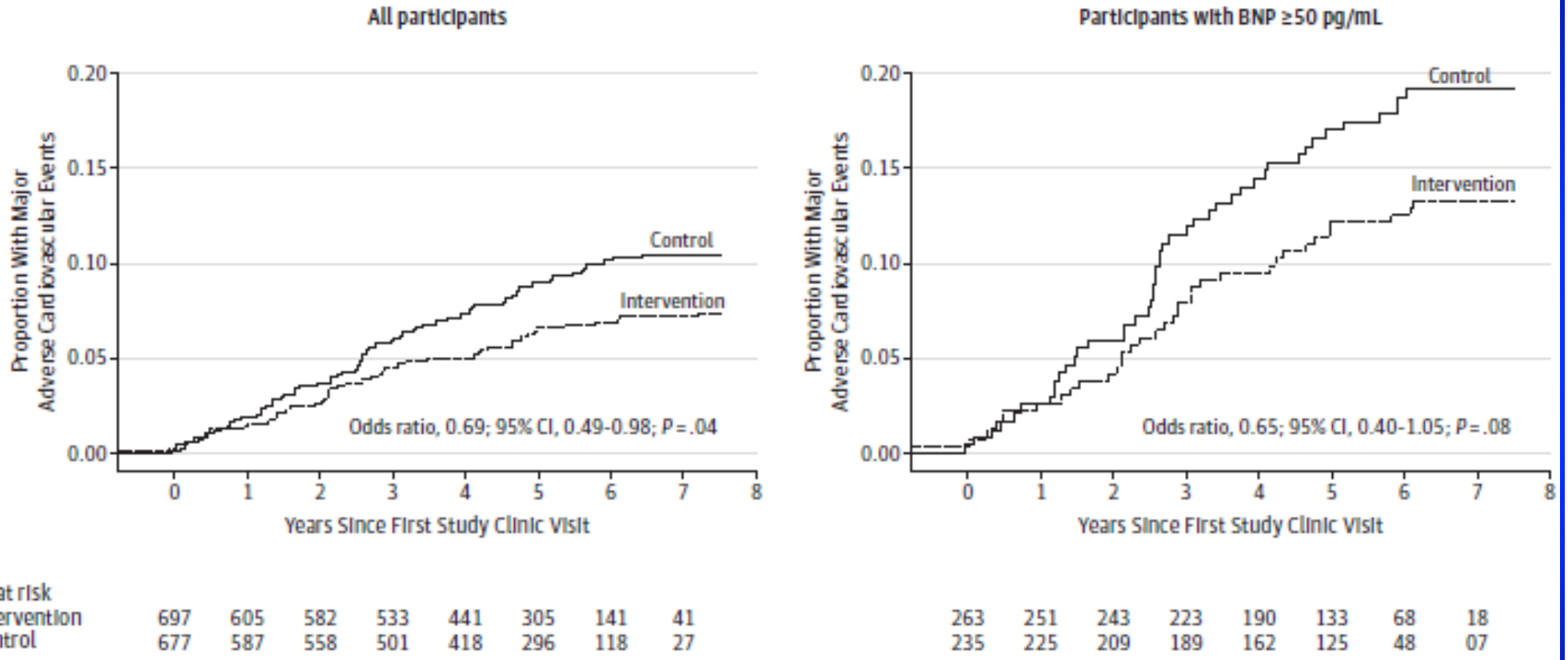
Table 2. End-Point Prevalence Analysis

End-Point Events	No. (%) of Participants		Unadjusted Multiple Imputation, OR (95% CI)	*P* Value	Adjusted Multiple Imputation, OR (95% CI)	*P* Value
	Control	Intervention				
All patients	n=677	n=697				
Heart failure or LVD	59 (8.7)	37 (5.3)	0.55 (0.37-0.82)	.003	0.57 (0.38-0.86)	.007
Heart failure or LVSD	33 (4.9)	23 (3.3)	0.63 (0.38-1.04)	.07	0.65 (0.38-1.09)	.10
Asymptomatic LVSD	19 (2.8)	16 (2.3)	0.73 (0.38-1.40)	.34	0.70 (0.37-1.31)	.26
Asymptomatic LVDD	26 (3.8)	14 (2.0)	0.51 (0.28-0.92)	.03	0.58 (0.32-1.06)	.08
Asymptomatic LVD	45 (6.6)	30 (4.3)	0.57 (0.37-0.88)	.01	0.60 (0.39-0.93)	.02
Arrhythmia	29 (4.3)	21 (3.0)	0.72 (0.43-1.23)	.23	0.77 (0.45-1.32)	.35
Heart failure	14 (2.1)	7 (1.0)	0.48 (0.20-1.20)	.12	0.52 (0.21-1.32)	.17
Myocardial infarction	11 (1.6)	8 (1.1)	0.71 (0.30-1.72)	.45	0.71 (0.29-1.74)	.46
Pulmonary embolism/deep vein thrombosis	10 (1.5)	4 (0.6)	0.51 (0.18-1.44)	.21	0.47 (0.16-1.40)	.18
Stroke/transient ischemic attack	28 (4.1)	13 (1.9)	0.48 (0.26-0.91)	.02	0.51 (0.27-0.96)	.04
Major adverse cardiovascular events[a]	71 (10.5)	51 (7.3)	0.69 (0.49-0.98)	.04	0.72 (0.50-1.03)	.08
Participants with BNP ≥50 pg/mL	n=235	n=263				
Heart failure or LVD	44 (18.7)	25 (9.5)	0.44 (0.26-0.73)	.002	0.46 (0.27-0.79)	.005
Heart failure or LVSD	29 (12.3)	17 (6.5)	0.46 (0.24-0.90)	.03	0.48 (0.24-0.97)	.04
Asymptomatic LVSD	17 (7.2)	12 (4.6)	0.52 (0.24-1.14)	.11	0.51 (0.24-1.06)	.07
Asymptomatic LVDD	15 (6.4)	8 (3.0)	0.48 (0.21-1.07)	.08	0.58 (0.26-1.30)	.19
Asymptomatic LVD	32 (13.6)	20 (7.6)	0.47 (0.27-0.83)	.01	0.50 (0.28-0.90)	.02
Arrhythmia	23 (9.8)	18 (6.8)	0.69 (0.36-1.31)	.26	0.71 (0.37-1.36)	.30
Heart failure	12 (5.1)	5 (1.9)	0.43 (0.15-1.19)	.11	0.47 (0.16-1.33)	.15
Myocardial infarction	6 (2.6)	2 (0.8)	0.31 (0.06-1.65)	.17	0.29 (0.05-1.53)	.15
Pulmonary embolism/deep vein thrombosis	5 (2.1)	2 (0.8)	0.30 (0.06-1.50)	.14	0.30 (0.05-1.62)	.16
Stroke/transient ischemic attack	14 (6)	9 (3.4)	0.57 (0.25-1.31)	.19	0.67 (0.28-1.57)	.36
Major adverse cardiovascular events[a]	45 (19.1)	35 (13.3)	0.65 (0.40-1.05)	.08	0.68 (0.41-1.11]	.13

Abbreviations: BNP, brain-type natriuretic peptide; LVD, left ventricular dysfunction; LVDD, left ventricular diastolic dysfunction; LVSD, left ventricular systolic dysfunction; OR, odds ratio.

[a] Major adverse cardiovascular events included arrhythmia, heart failure, myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.

Figure 2. Kaplan-Meier Analysis of Major Adverse Cardiovascular Events in the Full Study Sample and in Participants With BNP ≥50 pg/mL



No. at risk								
Intervention	697	605	582	533	441	305	141	41
Control	677	587	558	501	418	296	118	27

263	251	243	223	190	133	68	18
235	225	209	189	162	125	48	07

BNP indicates brain-type natriuretic peptide. Major adverse cardiovascular events included arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure. In the full sample, 51 (7.3%) of 697 patients were admitted for major adverse cardiovascular events in the intervention group and 71 (10.5%) of 677 were admitted in the control group. In participants with BNP ≥50 pg/mL, 35 (13.3%) of 263 were admitted for major adverse cardiovascular events in the intervention group and 45 (19.1%) of 235 were admitted in the control group.

Table 3. Event Rate Analysis

Events	No. of Events		No. of Person-Years		Events per 1000 Person-Years		Unadjusted Multiple Imputation, IRR (95% CI)	*P* Value	Adjusted Multiple Imputation, IRR (95% CI)	*P* Value
	Control	Intervention	Control	Intervention	Control	Intervention				
All patients										
Arrhythmia	45	29	2898.26	2917.16	15.5	9.9	0.69 (0.43-1.12)	.13	0.74 (0.45-1.21)	.19
Heart failure	18	8	2898.26	2917.16	6.2	2.7	0.47 (0.20-1.09)	.09	0.52 (0.22-1.23)	.13
Myocardial infarction	11	8	2898.26	2917.16	3.8	2.7	0.73 (0.31-1.75)	.31	0.73 (0.30-1.75)	.31
Pulmonary embolism/deep vein thrombosis	11	4	2898.26	2917.16	3.8	1.4	0.50 (0.18-1.39)	.17	0.48 (0.17-1.36)	.15
Stroke/transient ischemic attack	32	16	2898.26	2917.16	11	5.5	0.53 (0.29-0.96)	.05	0.58 (0.32-1.06)	.09
Major adverse cardiovascular events[a]	117	65	2898.26	2917.16	40.4	22.3	0.60 (0.45-0.81)	.002	0.64 (0.48-0.86)	.006
Participants with BNP ≥50 pg/mL										
Arrhythmia	38	25	1051.17	1150.29	36.2	21.7	0.63 (0.38-1.06)	.09	0.62 (0.37-1.04)	.08
Heart failure	16	5	1051.17	1150.29	15.2	4.3	0.35 (0.13-0.98)	.06	0.38 (0.14-1.05)	.07
Myocardial infarction	6	2	1051.17	1150.29	5.7	1.7	0.32 (0.06-1.68)	.16	0.29 (0.06-1.48)	.13
Pulmonary embolism/deep vein thrombosis	5	2	1051.17	1150.29	4.8	1.7	0.31 (0.06-1.55)	.14	0.34 (0.06-1.83)	.18
Stroke/transient ischemic attack	17	12	1051.17	1150.29	16.2	10.4	0.64 (0.31-1.34)	.2	0.78 (0.37-1.63)	.32
Major adverse cardiovascular events[a]	82	46	1051.17	1150.29	78	40	0.54 (0.37-0.77)	.002	0.56 (0.39-0.81)	.004

Abbreviations: BNP, brain-type natriuretic peptide; IRR, incidence rate ratio.

[a] Major adverse cardiovascular events included arrhythmia, heart failure, myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.

JAMA. 2013;310(1):66-74.

eTable 3. Prescribed Drugs at Baseline and Follow-up

	Baseline		Follow up		Chi-square p-values	
Medication class	**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

JAMA. 2013;310(1):66-74.

European Journal of Heart Failure (2015) **17**, 672–679
doi:10.1002/ejhf.286

Cost-effectiveness of natriuretic peptide-based screening and collaborative care: a report from the STOP-HF (St Vincent's Screening TO Prevent Heart Failure) study

Mark T. Ledwidge[1,2], Eoin O'Connell[1], Joseph Gallagher[1,2], Lesley Tilson[3], Stephanie James[1], Victor Voon[1,2], Margaret Bermingham[4], Elaine Tallon[1], Chris Watson[2], Rory O'Hanlon[1], Michael Barry[3], and Kenneth McDonald[1,2]*

[1]St Vincent's University Hospital, Chronic Cardiovascular Disease Management Unit, Dublin, Ireland; [2]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland; [3]St James Hospital, National Centre for Pharmacoeconomics, Dublin, Ireland; and [4]School of Pharmacy, University College, Cork, Ireland

Received 14 November 2014; revised 27 March 2015; accepted 31 March 2015

Aims Prevention of cardiovascular disease and heart failure (HF) in a cost-effective manner is a public health goal. This work aims to assess the cost-effectiveness of the St Vincent's Screening TO Prevent Heart Failure (STOP-HF) intervention.

Methods and results This is a substudy of 1054 participants with cardiovascular risk factors [median age 65.8 years, interquartile range (IQR) 57.8:72.4, with 4.3 years, IQR 3.4:5.2, follow-up]. Annual natriuretic peptide-based screening was performed, with collaborative cardiovascular care between specialist physicians and general practitioners provided to patients with BNP levels >50 pg/mL. Analysis of cost per case prevented and cost-effectiveness per quality-adjusted life year (QALY) gained was performed. The primary clinical endpoint of LV dysfunction (LVD) with or without HF was reduced in intervention patients [odds ratio (OR) 0.60; 95% confidence interval (CI) 0.38–0.94; $P = 0.026$]. There were 157 deaths and/or emergency hospitalizations for major adverse cardiac events (MACE) in the control group vs. 102 in the intervention group (OR 0.68; 95% CI 0.49–0.93; $P = 0.01$). The cost per case of LVD/HF prevented was €9683 (sensitivity range −€843 to €20 210), whereas the cost per MACE prevented was €3471 (sensitivity range −€302 to €7245). Cardiovascular hospitalization savings offset increased outpatient and primary care costs. The cost per QALY gain was €1104 and the intervention has an 88% probability of being cost-effective at a willingness to pay threshold of €30 000.

OLMSTEDT - "STOP HF"

Biomarkers in Community

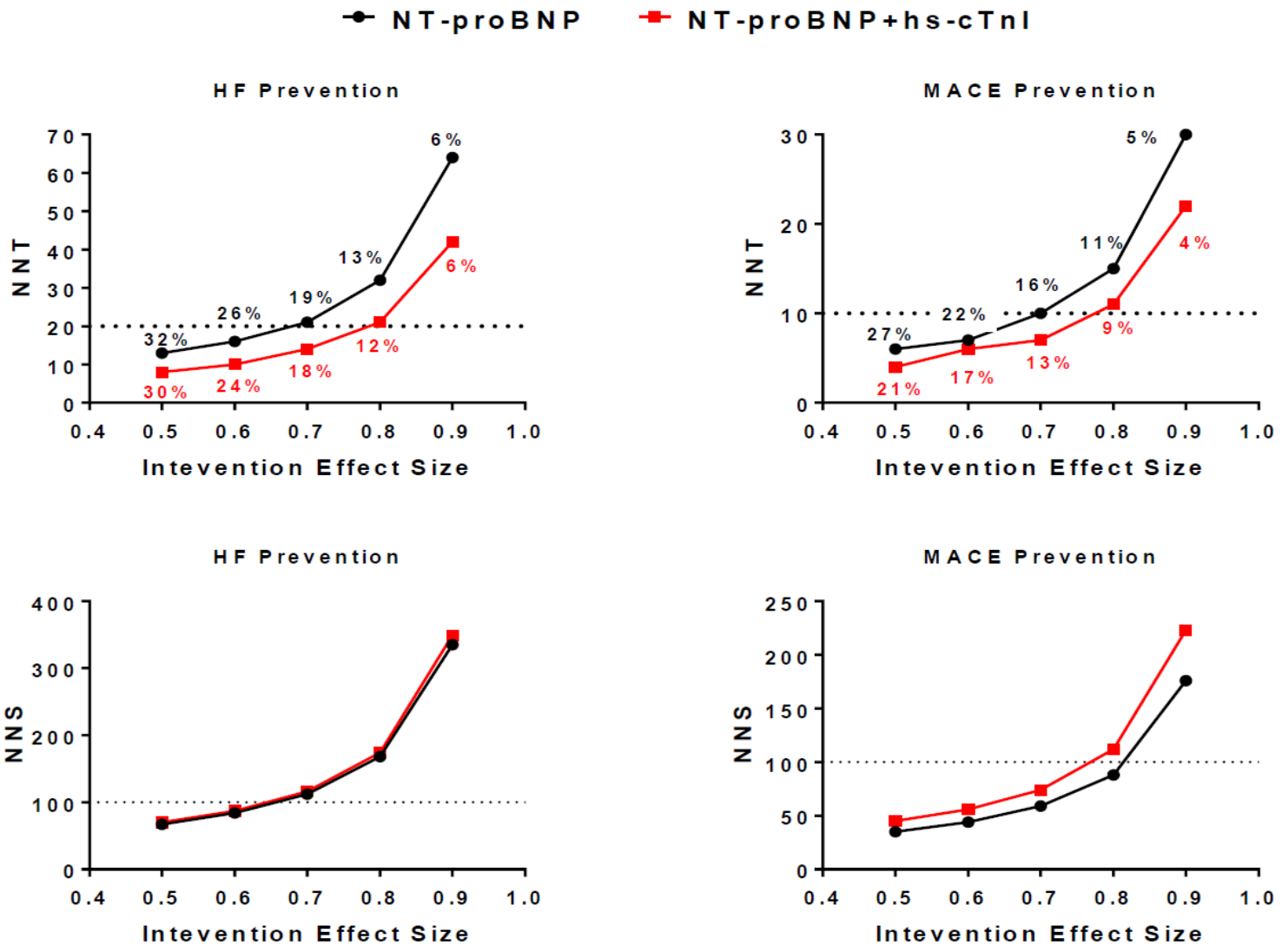
NNS and NNT for MACE and HF

An NT-proBNPguided preventative intervention with an intervention effect size (4-year hazard ratio for intervention in biomarker positive cohort) of ≤ 0.7 would reduce the global burden of HF by ≥ 20% and MACE by ≥ 15%. Per this simulation, the NNS to prevent one HF event or MACE in four years would be ≤ 100 with a NNT to prevent one HF event of ≤ 20 and one MACE of ≤ 10.

CHRISTCHURCH HEART INSTITUTE
Rangahau Manawa o Otautahi

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH

Figure 3


NT-proBNP
NT-proBNP+hs-cTnI
HF Prevention
NNT
70
60
50
40
30
20
10
0
32%
26%
19%
13%
6%
30%
24%
18%
12%
6%
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Intevention Effect Size
MACE Prevention
NNT
30
20
10
0
27%
22%
16%
11%
5%
21%
17%
13%
9%
4%
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Intevention Effect Size
HF Prevention
NNS
400
300
200
100
0
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Intevention Effect Size
MACE Prevention
NNS
250
200
150
100
50
0
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Intevention Effect Size

NZ Proposal : Early N Terminal pro BNP Triggered Treatment to Reduce Adverse Cardiovascular Events (" ENTTRANCE")

Foundation Work:-

1. Consolidate NZ national team:- epidemiology, cardiology, general medicine, primary care, clinical trialists.
2. Interrogate "PREDICT" Primary Care decision support/data base to update contemporary risk -> event relationships.
3. Assay NT-proBNP and hs TnT/TnI in over 8,000 community dwelling NZ'ers with documented follow-up
4. Assess additional risk stratification offered by adding NT-proBNP /hsTn to conventional profiling.
5. Define population in equipoise re intervention.
6. Design adequately- powered trial of intensified intervention following modified STOP-HF design.
7. Engagement with stakeholders.
8. Engagement with Maori .

Randomized Controlled Trials

1. Primary prevention informed by 1-8 above.
2. Secondary prevention (1 year post ACS) informed by CDCS data.

CHRISTCHURCH HEART INSTITUTE

THANK YOU FOR YOUR ATTENTION

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND
CHRISTCHURCH