



# Growth differentiation factor-15 predicts mortality and morbidity after cardiac resynchronisation therapy

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# Background: predicting outcome after CRT

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- Multiple echocardiographic parameters
- But disappointment from PROSPECT<sup>1</sup>
  - American Society of Echocardiography Guidelines 2008: “*dyssynchrony measures should not be used for selection of patients for CRT*”
- Cardiovascular magnetic resonance predicts outcome<sup>2</sup>
  - Scar
  - Dyssynchrony

- 1. ES Cheung *Circulation* 2008;117:2608-2616
- 2. F Leyva *Heart* 2009; 95: 1619-1625

# Role of biomarkers in CRT

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- Baseline BNP did not predict survival in CARE-HF<sup>1</sup>
- Creatinine predicts worse outcome<sup>2,3</sup>
- A pre-implant blood test would be simple and helpful.

- 1. Cleland JG. *JACC* 2008; 52:438-445
- 2. Shalaby A. *PACE* 2008;31:575-9
- 3. Leyva F. *Heart* 2009; 95: 1619-1625

# GDF-15 and cardiovascular disease

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- Transforming growth factor  $\beta$  superfamily
- Stress responsive
- Independently predicts prognosis in
  - STEMI<sup>1</sup>
  - Non-STEMI<sup>2</sup>
  - Idiopathic pulmonary hypertension<sup>3</sup>
  - Heart failure<sup>4</sup> independent of NT-pro-BNP, LVEF and NYHA class
  - Pulmonary embolism
- Rationale for study: no single measure predicts outcome after CRT
- Hypothesis: GDF-15 predicts outcome in patients undergoing CRT

1. Kempf T. Eur Heart J. 2007; 28:2858-65
2. Wollert KC. Circulation. 2007;116:1540-8
3. Nickel N. Am J Respir Crit Care Med. 2008;178:534-41
4. Kempf T. J Am Coll Cardiol. 2007;50:1054-60

# Methods

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- Observational study of patients undergoing CRT-pacing
- Single centre
- Observations (baseline, 6 weeks, 6 monthly there-after)
  - Clinical assessment
    - NYHA class
    - 6 minute walk test
    - Minnesota QoL
  - Echocardiogram
  - Venesection (until 24 months)
  - Cause of death, hospitalisation
- Aims of study:-
  - Derive cut-off for predictor of cardiovascular mortality or heart failure hospitalisation
  - Internal validation
- Followed up - maximum of 5.4 yrs (median 950 days) for events
- GDF-15 measured pre and post (median 360 days) after implantation
- N=158

# Results

|                             | All         | Survivors   | Non-survivors | <i>p</i> * |
|-----------------------------|-------------|-------------|---------------|------------|
| <i>N</i>                    | 158         | 118         | 40            |            |
| Age, (yrs)                  | 68.3 ± 10.6 | 67.5 ± 10.4 | 70.5 ± 11.2   | N          |
| Male gender, n (%)          | 131 (83)    | 93 (79)     | 38 (95)       | 0.0188     |
| NYHA class                  | 3.3 ± 0.4   | 3.2 ± 0.4   | 3.5 ± 0.5     | NS         |
| ICM, n (%)                  | 114 (72)    | 82 (69)     | 32 (80)       | NS         |
| <b>Atrial rhythm, n (%)</b> |             |             |               |            |
| Sinus rhythm                | 122 (77)    | 91 (77)     | 31 (78)       | NS         |
| Atrial fibrillation         | 36 (23)     | 27 (23)     | 9 (23)        | NS         |
| <b>Co-morbidity, n (%)</b>  |             |             |               |            |
| Diabetes mellitus           | 28 (18)     | 19 (16)     | 9(23)         | NS         |
| Hypertension                | 43 (27)     | 34 (29)     | 9 (23)        | N          |
| CABG                        | 34 (22)     | 22 (19)     | 12 (30)       | NS         |

# Results

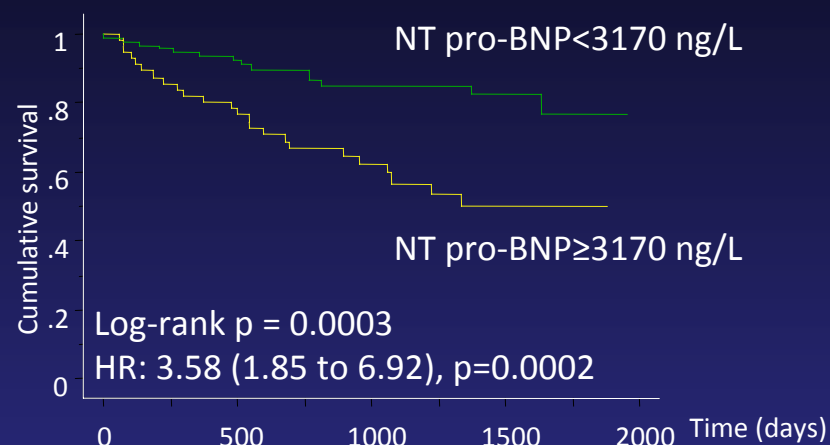
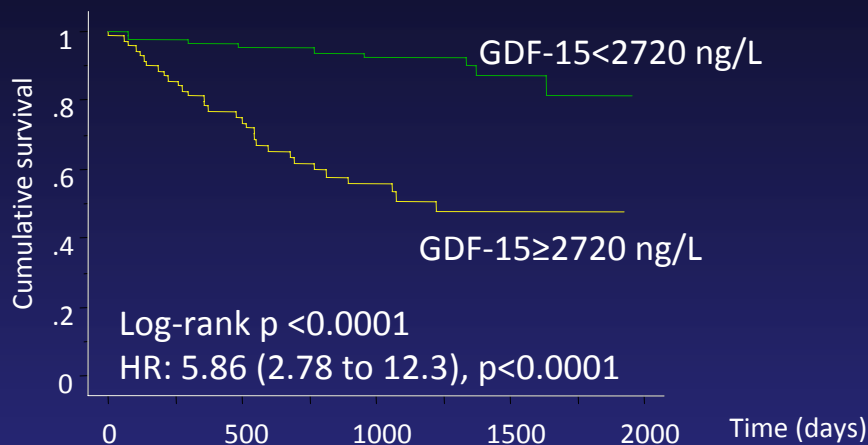
|                                   | All             | Survivors      | Non-survivors  | <i>p</i> *    |
|-----------------------------------|-----------------|----------------|----------------|---------------|
| NT pro-BNP, ng/L                  | 3477 ± 4099     | 2871 ± 3892    | 5262 ± 4221    | <0.0001       |
| GDF-15, ng/L                      | 3839 ± 4082     | 3226 ± 3284    | 5647 ± 5498    | <0.0001       |
| <b>Medication (%) at baseline</b> |                 |                |                |               |
| Loop diuretics                    | 144 (91)        | 108 (92)       | 36 (90)        | NS            |
| ACEI/ARBs                         | 147 (93)        | 112 (95)       | 35 (88)        | NS            |
| Beta-blockers                     | 93 (59)         | 76 (64)        | 17 (43)        | 0.031         |
| Spironolactone                    | 73 (46)         | 55 (47)        | 18 (45)        | NS            |
| <b>ECG and echocardiography</b>   |                 |                |                |               |
| QRS, ms                           | 153.9 ± 28.2    | 152.9 ± 27.6   | 157.0 ± 30.3   | NS            |
| LVEF, %                           | 23.1 ± 9.8      | 24.2 ± 9.7     | 20.2 ± 9.5     | NS            |
| <b>Responders, n (%)</b>          | <b>113 (72)</b> | <b>95 (81)</b> | <b>21 (53)</b> | <b>0.0007</b> |

Responder defined as:

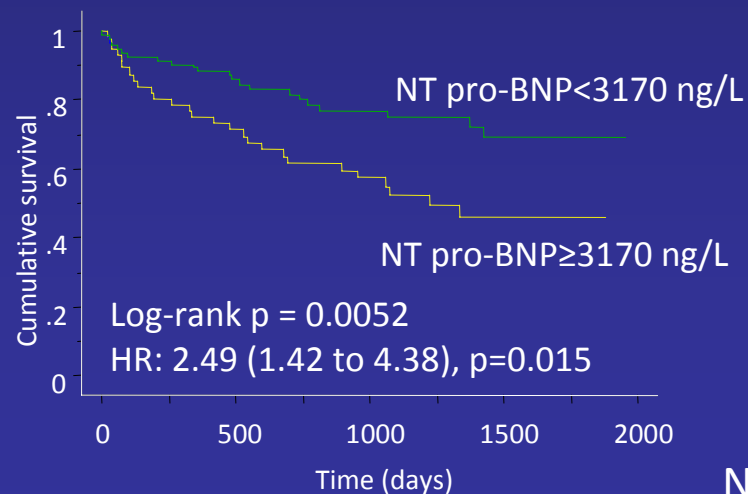
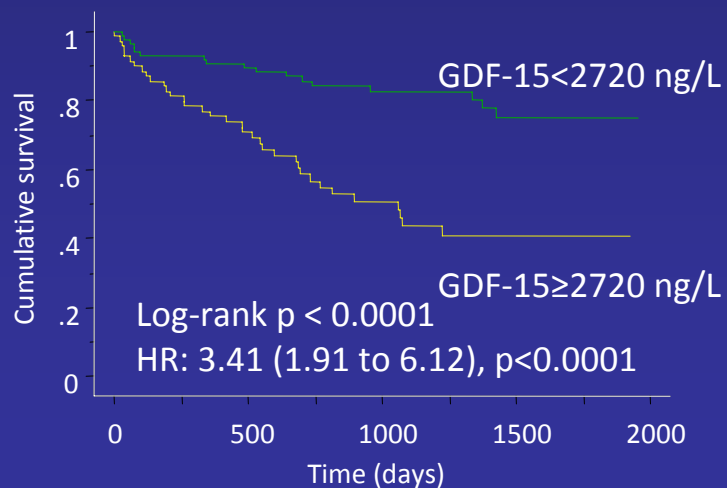
- survival for 1 year without hospitalisations for heart failure
- plus improvement by ≥1 NYHA classes or a 25% in 6-min walking distance

# GDF-15 and NT pro-BNP and outcome

## Cardiovascular mortality

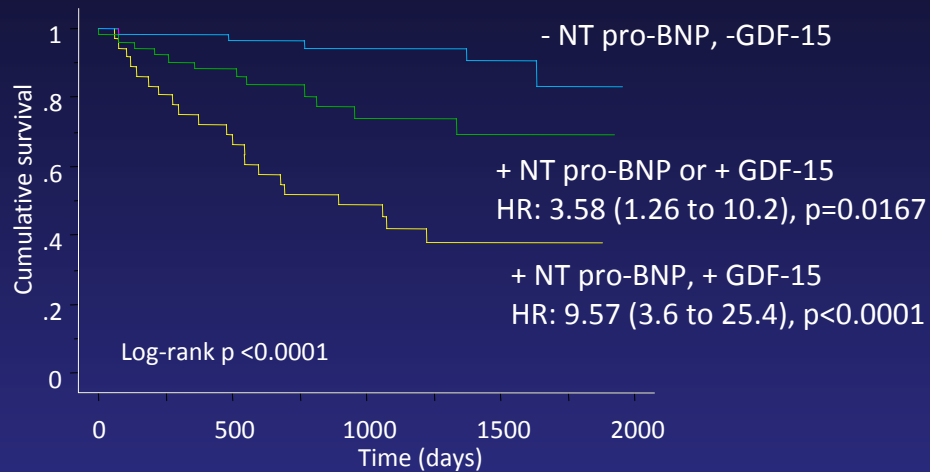


## Cardiovascular mortality or hospitalisation for HF

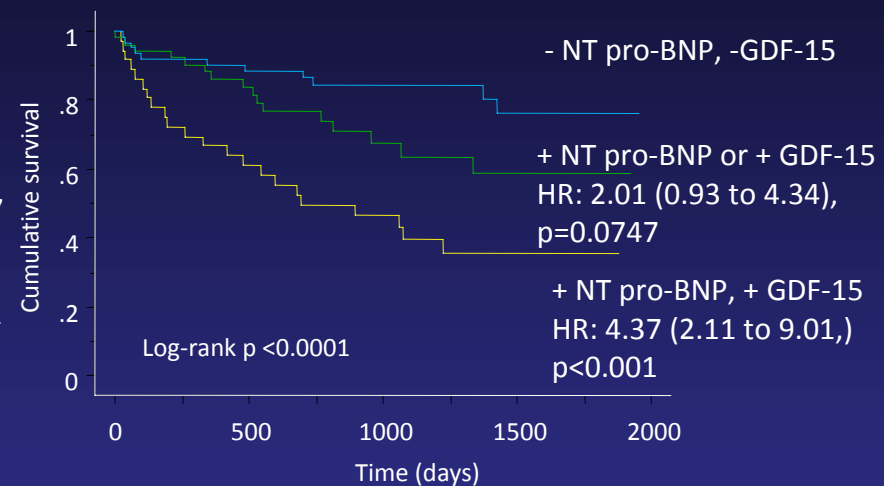


# Combined GDF-15 and NT pro-BNP and outcome

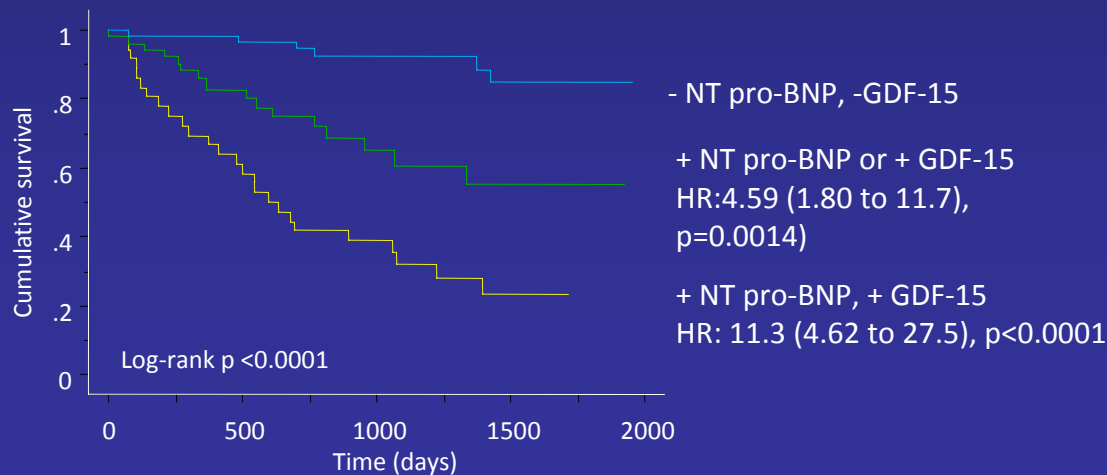
## Cardiovascular mortality



## Cardiovascular mortality or hospitalisation for HF



## Total mortality



# Predictors of cardiovascular mortality

|                     | Univariate                 |             | Multi-variable |                              |                  |
|---------------------|----------------------------|-------------|----------------|------------------------------|------------------|
|                     | HR (95% CL)                | LR $\chi^2$ | <i>p</i>       | HR (95% CL)                  | <i>p</i>         |
| Age                 | 1.03 (1.00 to 1.06)        | 2.48        | 0.0914         |                              |                  |
| Female gender       | 0.24 (0.06 to 0.99)        | 3.9         | 0.0483         |                              |                  |
| Ischemic etiology   | 1.56 (0.72 to 3.40)        | 1.28        | 0.2580         |                              |                  |
| <b>NYHA class</b>   | <b>2.79 (1.49 to 5.23)</b> | <b>10.4</b> | <b>0.0013</b>  | <b>[1.67 (0.92 to 3.12)]</b> | <b>0.0902]**</b> |
| Creatinine          | 1.01 (1.00 to 1.02)        | 4.15        | 0.1167         |                              |                  |
| <b>NT pro-BNP *</b> | <b>2.79 (1.55 to 5.26)</b> | <b>12.4</b> | <b>0.0004</b>  | <b>2.16 (1.17 to 4.17)</b>   | <b>0.0137</b>    |
| <b>GDF-15</b>       | <b>5.31 (2.31 to 11.9)</b> | <b>14.6</b> | <b>0.0001</b>  | <b>3.83 (1.46 to 9.51)</b>   | <b>0.0069</b>    |
| Log combined index  | 7.03 (2.91 + 17.5)         | 19.1        | <0.00001       |                              |                  |
| QRS duration        | 1.00 (0.99 to 1.01)        | 0.25        | 0.6181         |                              |                  |
| Atrial fibrillation | 0.99 (0.47 to 2.08)        | 0.00        | 0.9752         |                              |                  |
| <b>LVEF</b>         | <b>0.96 (0.93 to 0.99)</b> | <b>5.51</b> | <b>0.0189</b>  | <b>[0.98 (0.94 to 1.01)]</b> | <b>0.2728]**</b> |
| <b>Medication</b>   |                            |             |                |                              |                  |
| Diuretic            | 0.73 (0.22 to 2.38)        | 0.28        | 0.6146         |                              |                  |
| ACE-I or ARA        | 1.34 (0.47 to 3.76)        | 0.3         | 0.5848         |                              |                  |
| Beta-blocker        | 1.77 (0.94 to 3.35)        | 3.17        | 0.0751         |                              |                  |
| Spironolactone      | 0.98 (0.52 to 1.83)        | 0.01        | 0.9368         |                              |                  |

LVEF and NYHA class failed to enter the final model

# Model development – predicting cardiovascular mortality

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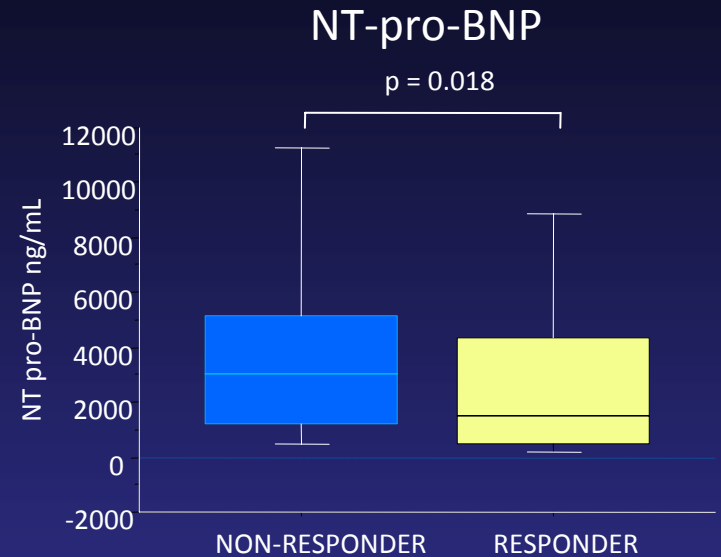
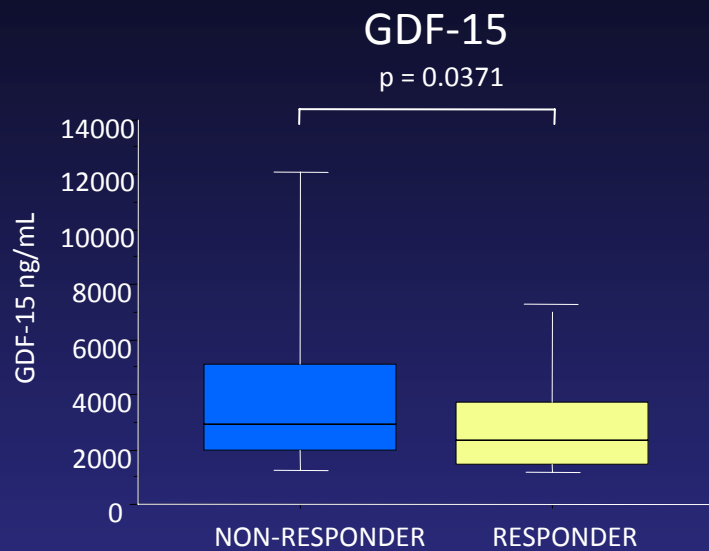
- 4 candidate variables chosen
  - Log GDF-15
  - Log NT pro-BNP
  - NYHA class
  - LVEF
- Final model components
  - Log GDF-15
  - Log NT pro-BNP
- Cox proportional hazards model validated with bootstrapping 500 times
- Combined biomarker index:-
  - $[0.7533 \times \text{NT pro-BNP (pg/ml)}] + [(1.3257 \times \text{GDF-15 (ng/ml)}]$
  - Bias corrected slope 0.85

# Predicting outcome after CRT

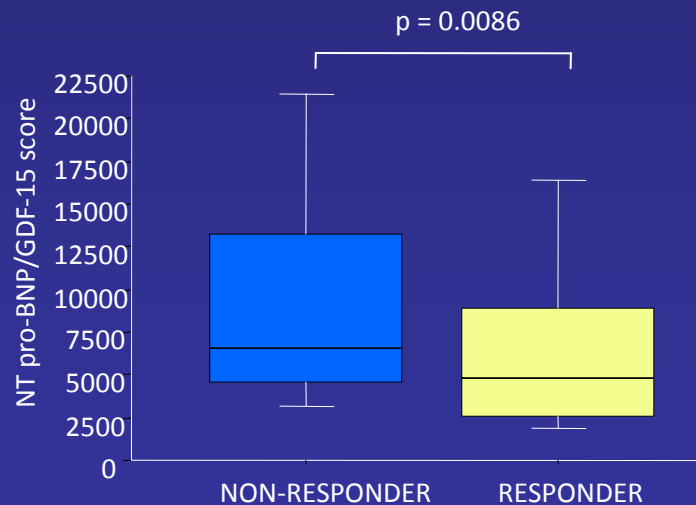
|  | <b>GDF-15<br/>&gt; 2720 ng/l</b> | <b>NT-pro-BNP<br/>&gt; 3170 ng/L</b> | <b>Combined<br/>biomarker index<br/>of GDF-15 and<br/>NT-pro-BNP</b> |
|--|----------------------------------|--------------------------------------|--|
| Cardiovascular mortality HR,<br>(CI)                           | 5.31<br>(2.31 - 11.9)            | 2.79<br>(1.55 – 5.26)                | 9.57<br>(3.6 -25.4)  |
| Mortality HR,<br>(CI)  | 5.59<br>(2.69 – 11.4)            | 4.3<br>(2.43 – 7.97)                 | 11.3<br>(4.62 – 11.7)  |
| Cardiovascular mortality or HF<br>hospitalisations<br>HR, (CI) | 3.41<br>(1.91 – 6.12)            | 2.42<br>(1.42 – 4.38)                | 4.37<br>(2.11 – 9.01)  |

P < 0.001

# Relationship of baseline biomarkers and response to CRT



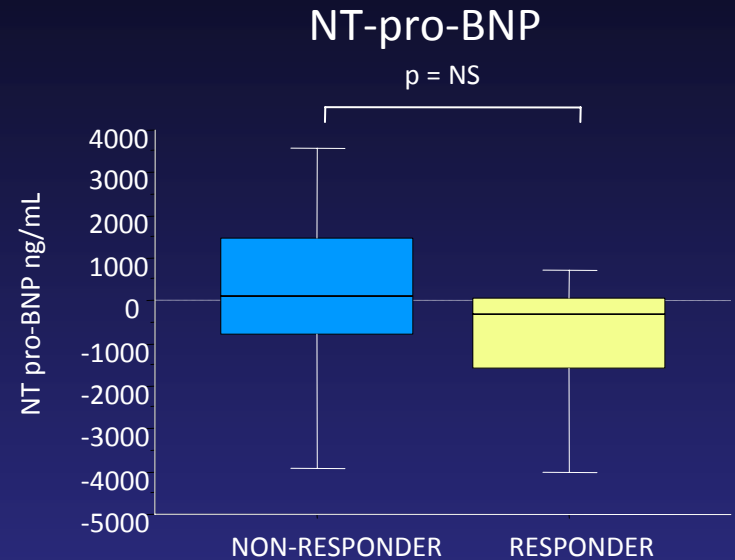
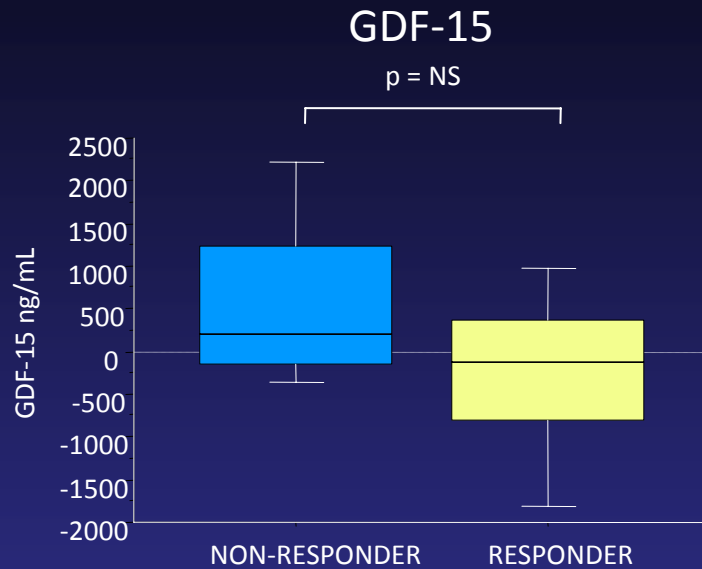
## GDF-15 and NT-pro-BNP



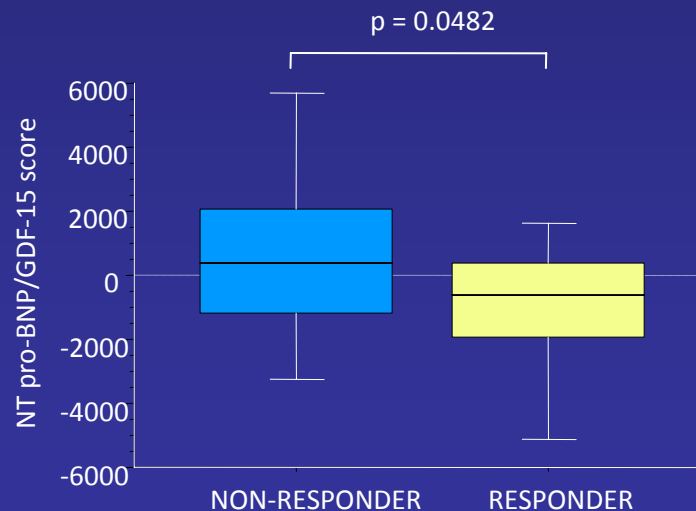
Responder defined as:

- survival for 1 year without hospitalisations for heart failure
- plus improvement by  $\geq 1$  NYHA classes or a 25% in 6-min walking distance

# Changes from baseline of GDF-15 and NT-pro-BNP in relation to response to CRT



## GDF-15 and NT-pro-BNP



Responder defined as:

- survival for 1 year without hospitalisations for heart failure
- plus improvement by  $\geq 1$  NYHA classes or a 25% in 6-min walking distance

# Conclusions

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- Pre-implant GDF-15
  - superior to NT pro-BNP in predicting mortality and morbidity
  - Role in stratifying risk
  - independent of NT pro-BNP, QRS duration, LVEF
  - Measured alone, does not predict response
- Combined measurement of GDF-15 and NT pro-BNP enhances predictive value
- Future research could examine the role of biomarkers in patient selection
  
- Limitations:
  - Time course of reduction in GDF-15 unknown
  - Temporal variability of plasma levels GDF-15 unknown
  - Patients undergoing CRT-D were excluded.
  - Predictive model needs external validation
  
- Acknowledgements
  - The patients of Good Hope Hospital. The CCU, cath lab, cardiac physiologists and laboratory staff. Mr Nick Irwin, Janet Brashaw-Smith, Lisa Ball, Jane Tipping. Research support from Medtronic and St Jude Medical