ESC Late-Breaking Science: Dilated Cardiomyopathy

Clinical phenotypes, gender differences and adverse events associated with truncating variants in the Titin (*TTN*) gene

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on behalf of the
European Genetic Cardiomyopathy Initiative Investigators

Disclosures

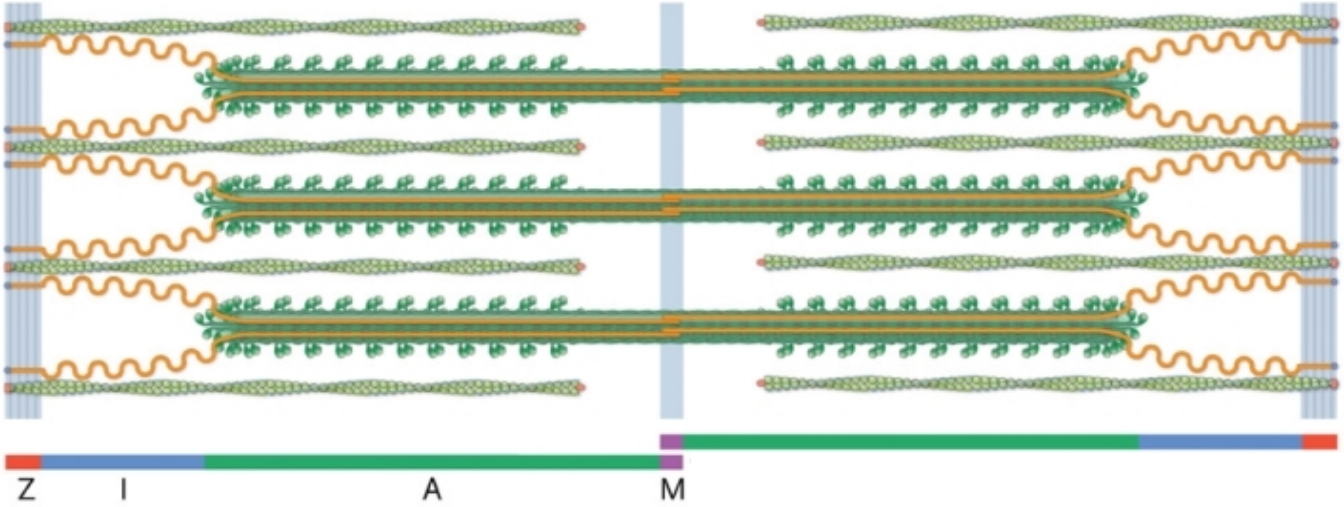
- None to declare.

Dilated Cardiomyopathy (DCM)

- 1/3 of aetiologies of heart failure with estimated prevalence of 1:250
- Morbidity and Mortality
  - Commonest cause for cardiac transplantation (HTx).
- 1 in 4 with idiopathic DCM have a genetic predisposition.
- Truncating variants in the titin gene (*TTNtv*) account for 15-25% of cases of genetic DCM.

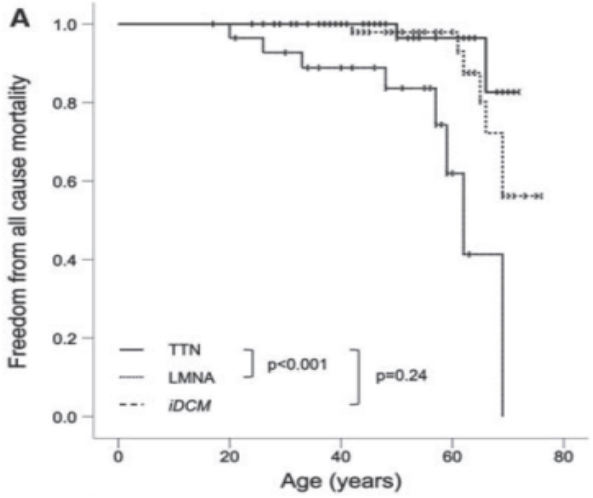
Titin

Herman DS et al. N Engl J Med 2012;366:619-628.



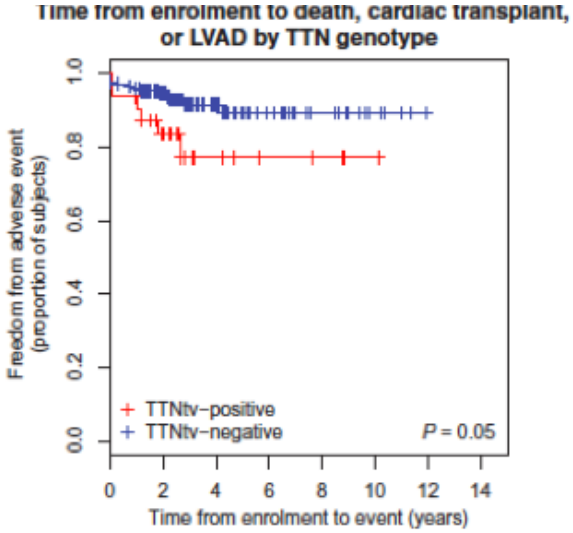
What is known…

Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy



Jansweijer et al. EJHF (2017) 19; 512-521

Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease



Roberts et al. Sci Transl. Med 7 (2015)

Studies are inconsistent with respect to arrhythmia burden, response to optimal medical therapy (OMT), impact of mutation location and overall prognosis.

Aims

- Clinical phenotype of *TTNtv* carriers
- Longitudinal data on clinical phenotype
- Outcomes in mutation carriers
  - Sex differences in clinical phenotypes and outcomes
  - Response to medical therapy

United Kingdom:

1) St. Bartholomew's Hospital, London

Spain:

1) Complejo Hospitalario Universitario A Coruña
2) Hospital Universitario Virgen Arrixaca, Murcia
3) Hospital Universitario Puerta de Hierro, Madrid
4) Hospital Universitario Virgen de la Victoria, Malaga
5) Hospital Universitario Vall d' Hebron, Barcelona
6) Complejo Asistencial Universitario de Salamanca, Salamanca
7) Hospital Universitario 12 de Octubre, Madrid
8) Complejo Hospitalario de Navarra, Navarra
9) Virgen del Rocio University Hospital, Sevilla.

Italy:

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Poland:

1) The Cardinal Stefan Wyszynski Institute of Cardiology, Warsaw.

Denmark:

1) Odense University Hospital, Odense

Australia:

1) Victor Chang Cardiac Institute, Sydney.

European Genetic Cardiomyopathy Initiative Investigators

Methods

- **Multi-centred, longitudinal cohort study**
  - Consecutive probands and relatives with *TTNtv*
  - Baseline visit between 1985-2019

- ***TTNtv* pathogenicity** as per published recommendations

- **Baseline clinical assessment**
  - Symptoms, ECG, Echocardiogram
  - CMR, Holter data

- **Longitudinal follow-up**
  - Routine clinical visits

Primary Endpoint: Adverse Events

- **Composite:**
  - **Arrhythmic end-point:**
    (SCD, Aborted SCD, Appropriate ICD Shock for VT or VF)
  - **Heart failure end-point:**
    (HTx, Destination VAD, ESHF-mortality)
  - Events at or prior to baseline evaluation were not included.

Secondary Endpoint: Response to OMT

LV Reverse Remodeling (LVRR):

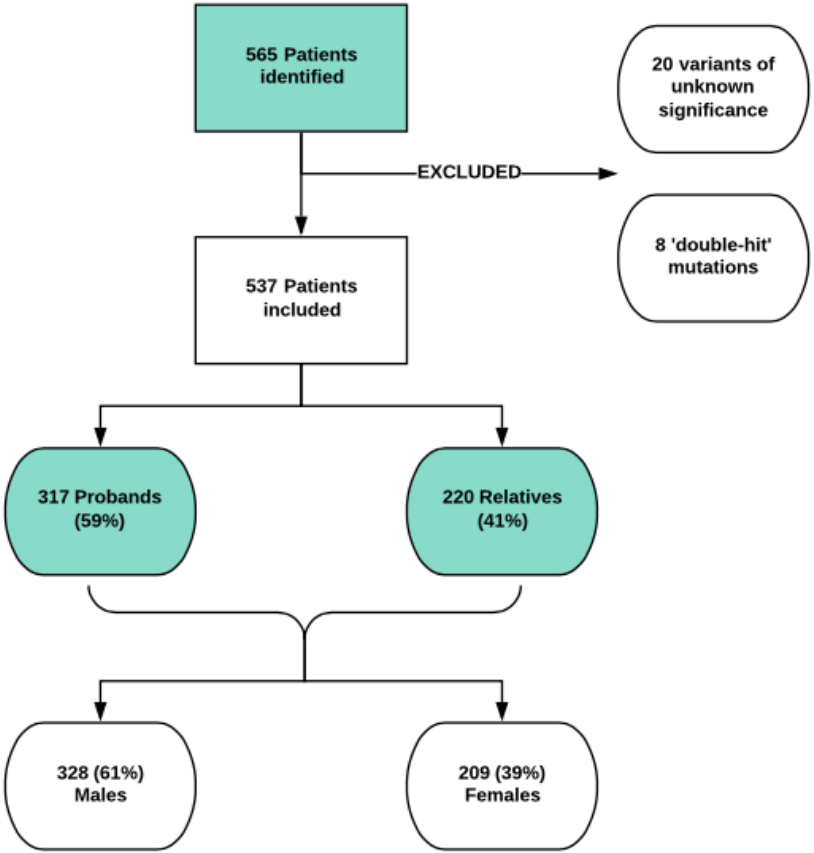
– LV normalization (LVEF improvement to ≥50%)

or

– Absolute LVEF increase by ≥10% from baseline.

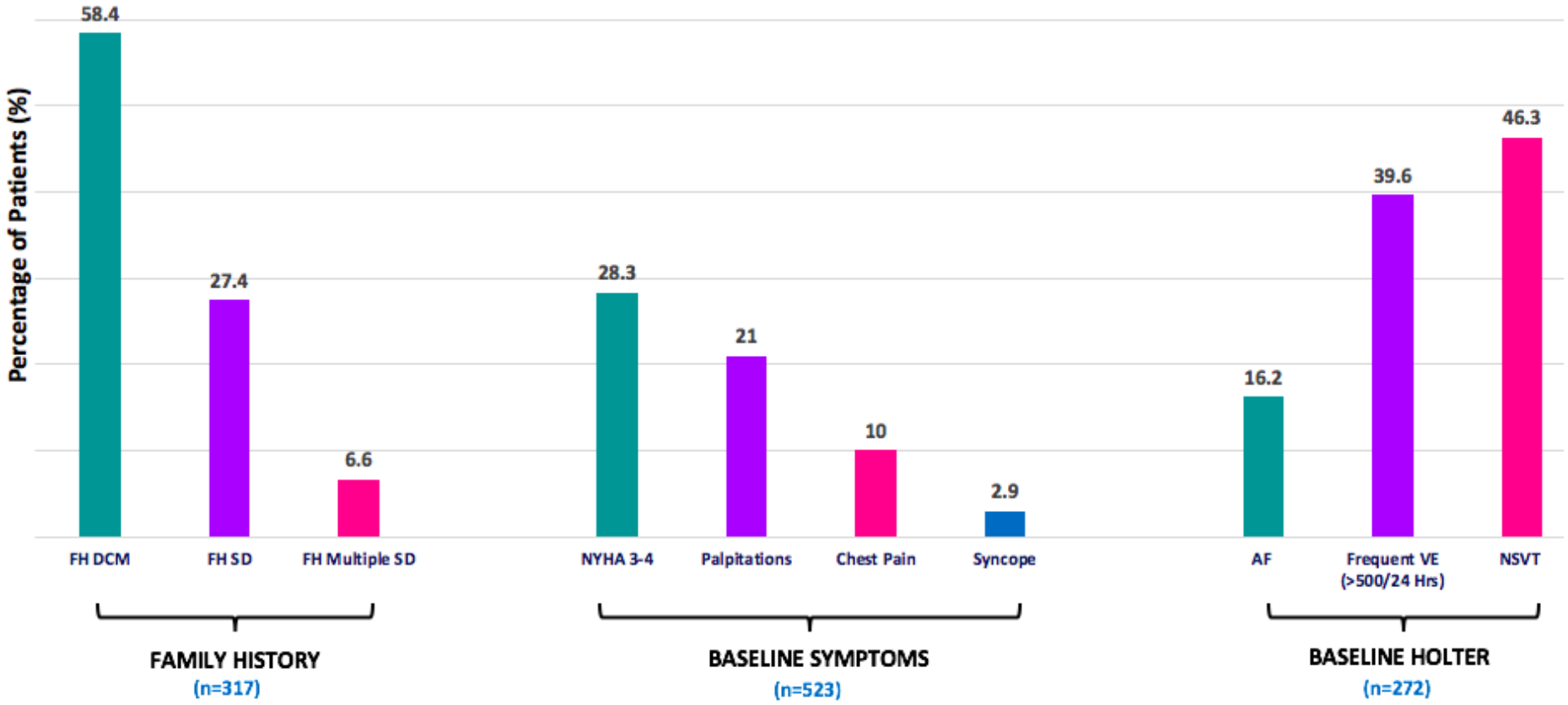
Results

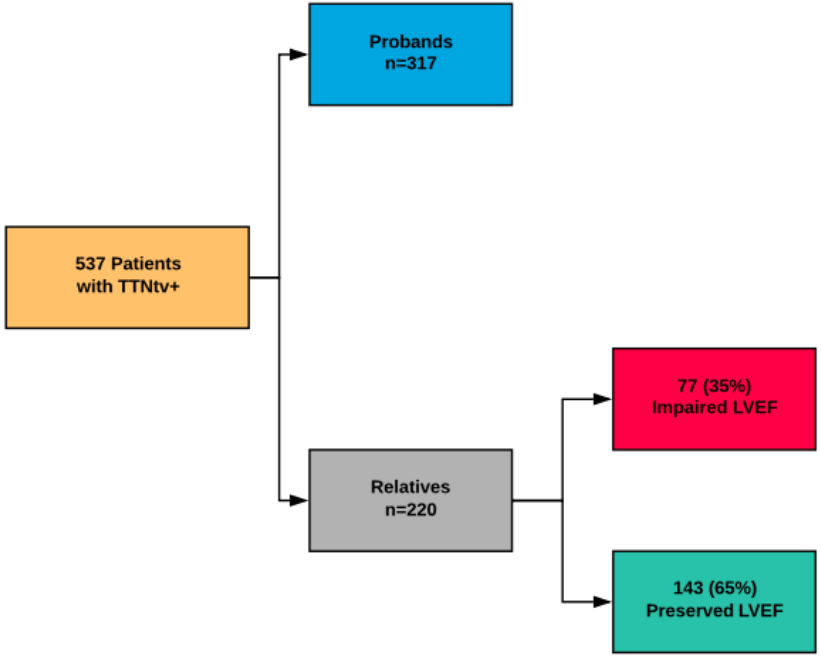
Median family size 1; IQR 1-2

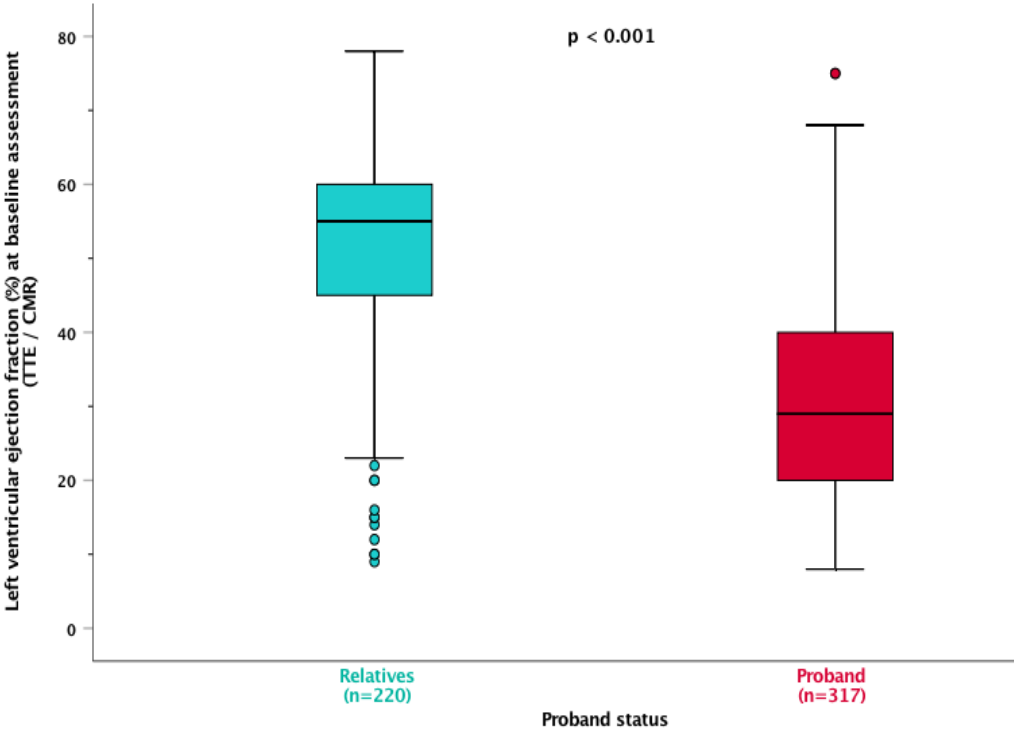


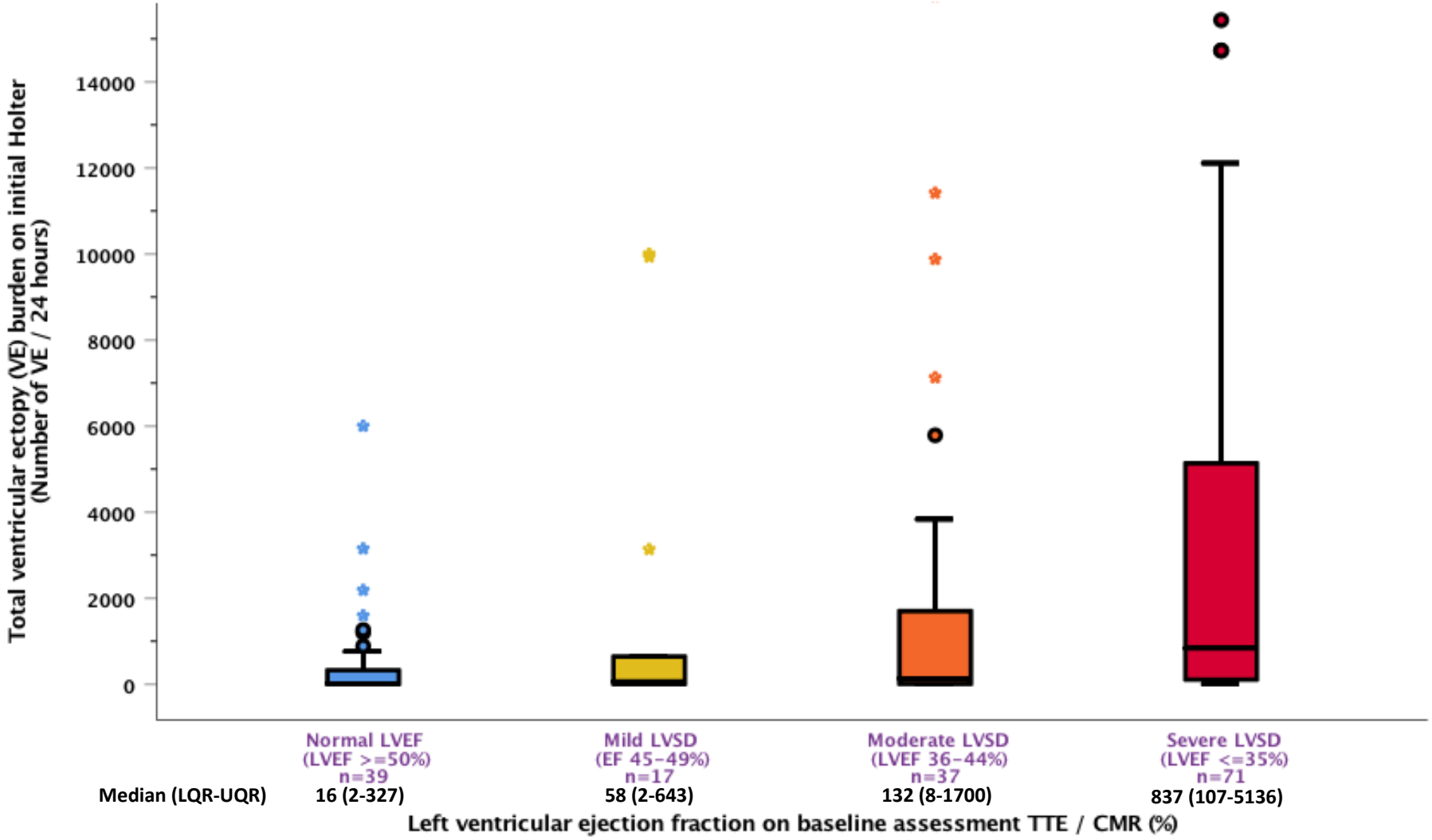
Baseline characteristics

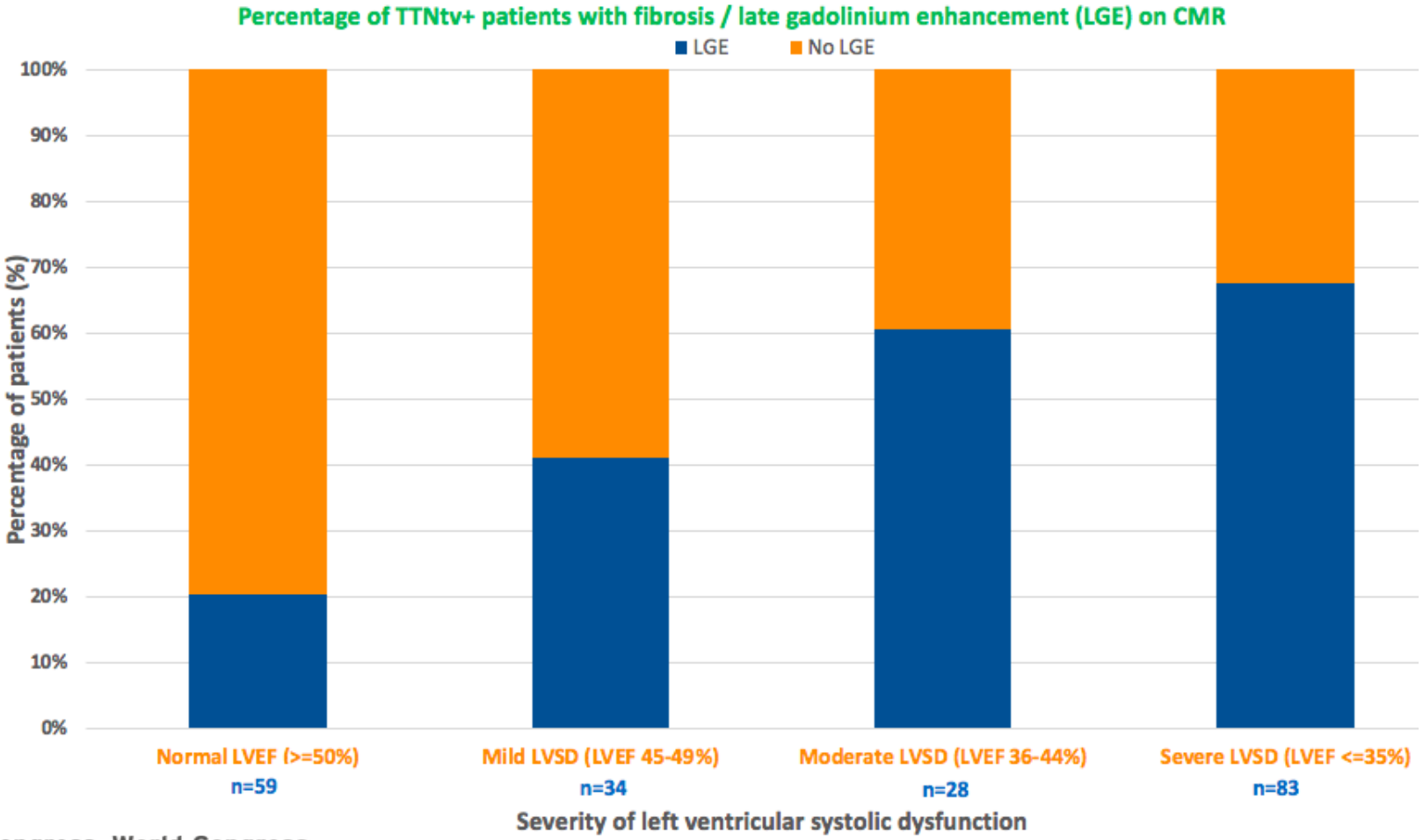
Bar chart demonstrating the percentage of TTNtv+ patients with various characteristics at baseline evaluation




537 Patients
with TTNtv+
Probands
n=317
Relatives
n=220
77 (35%)
Impaired LVEF
143 (65%)
Preserved LVEF

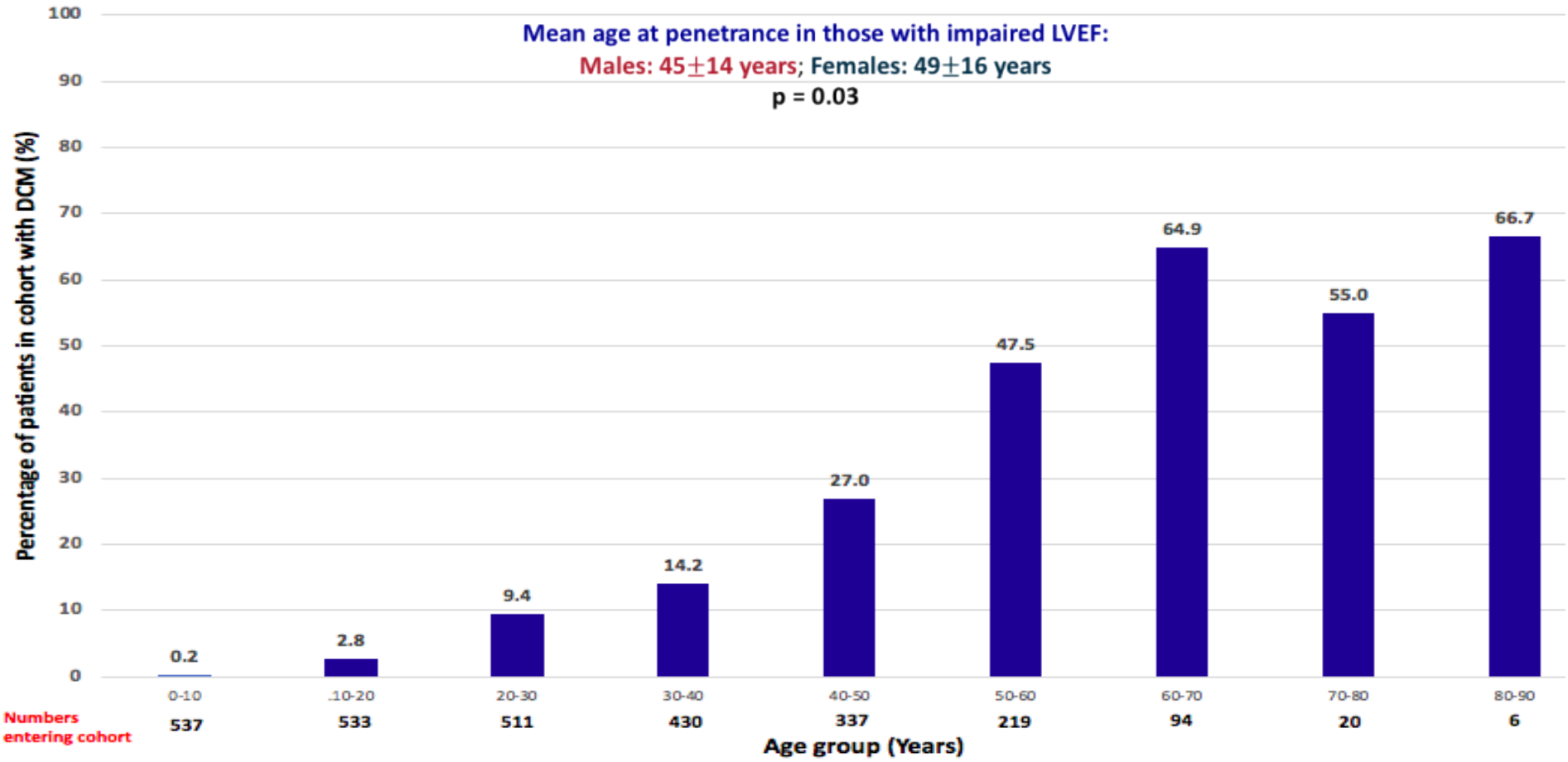

p < 0.001
Left ventricular ejection fraction (%) at baseline assessment
(TTE / CMR)
80
60
40
20
0
Relatives
(n=220)
Proband
(n=317)
Proband status


Total ventricular ectopy (VE) burden on initial Holter
(Number of VE / 24 hours)
14000
12000
10000
8000
6000
4000
2000
0
Normal LVEF
(LVEF >=50%)
n=39
Mild LVSD
(EF 45-49%)
n=17
Moderate LVSD
(LVEF 36-44%)
n=37
Severe LVSD
(LVEF <=35%)
n=71
Median (LQR-UQR)
16 (2-327)
58 (2-643)
132 (8-1700)
837 (107-5136)
Left ventricular ejection fraction on baseline assessment TTE / CMR (%)

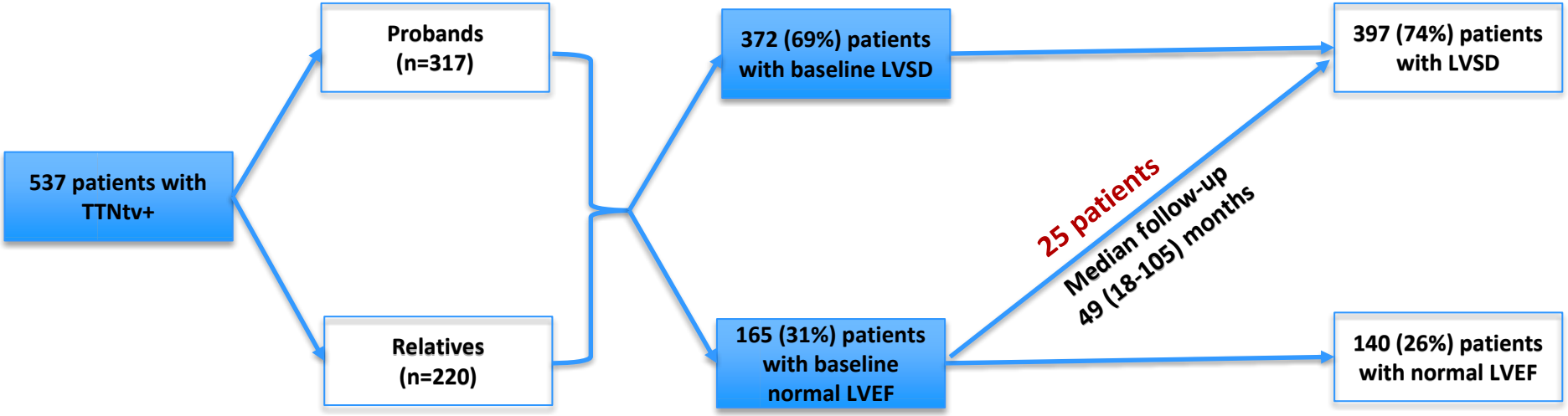

Percentage of TTNtv+ patients with fibrosis / late gadolinium enhancement (LGE) on CMR
LGE
No LGE
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of patients (%)
Normal LVEF (>=50%)
n=59
Mild LVSD (LVEF 45-49%)
n=34
Moderate LVSD (LVEF 36-44%)
n=28
Severe LVSD (LVEF <=35%)
n=83
Severity of left ventricular systolic dysfunction

Penetrance

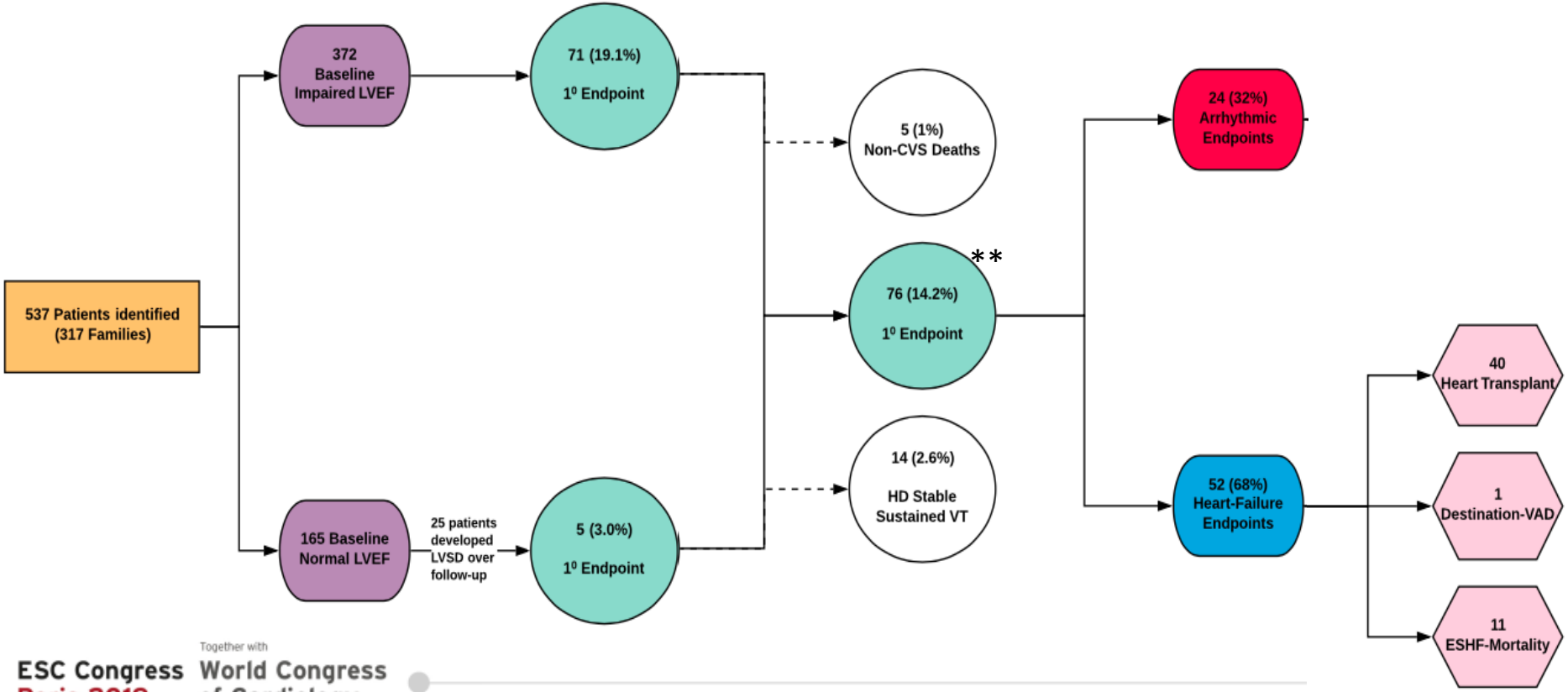
Bar chart demonstrating age-related penetrance of DCM in TTNtv for the overall cohort (n=537)



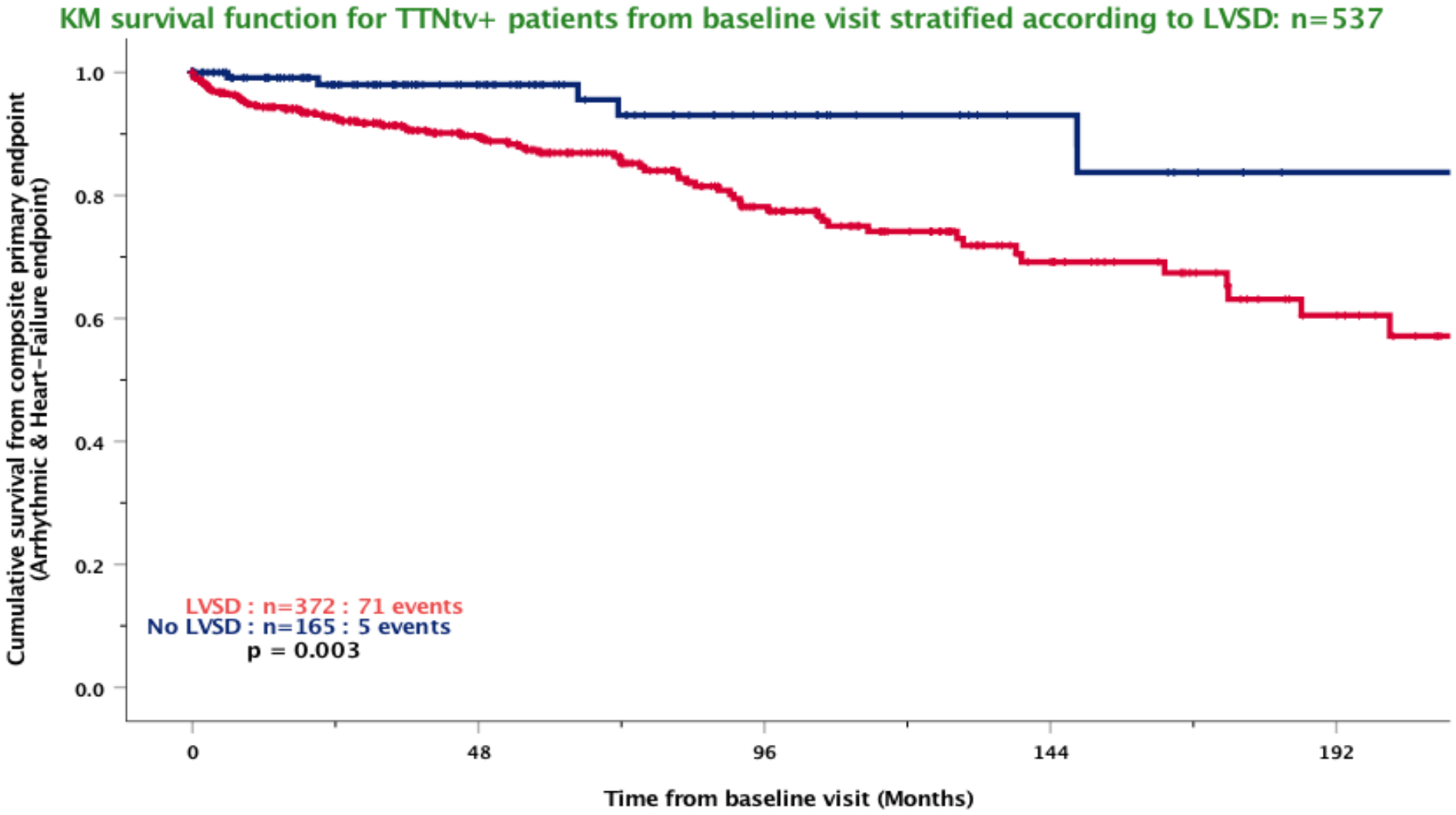
Baseline Diagnosis & Follow-Up

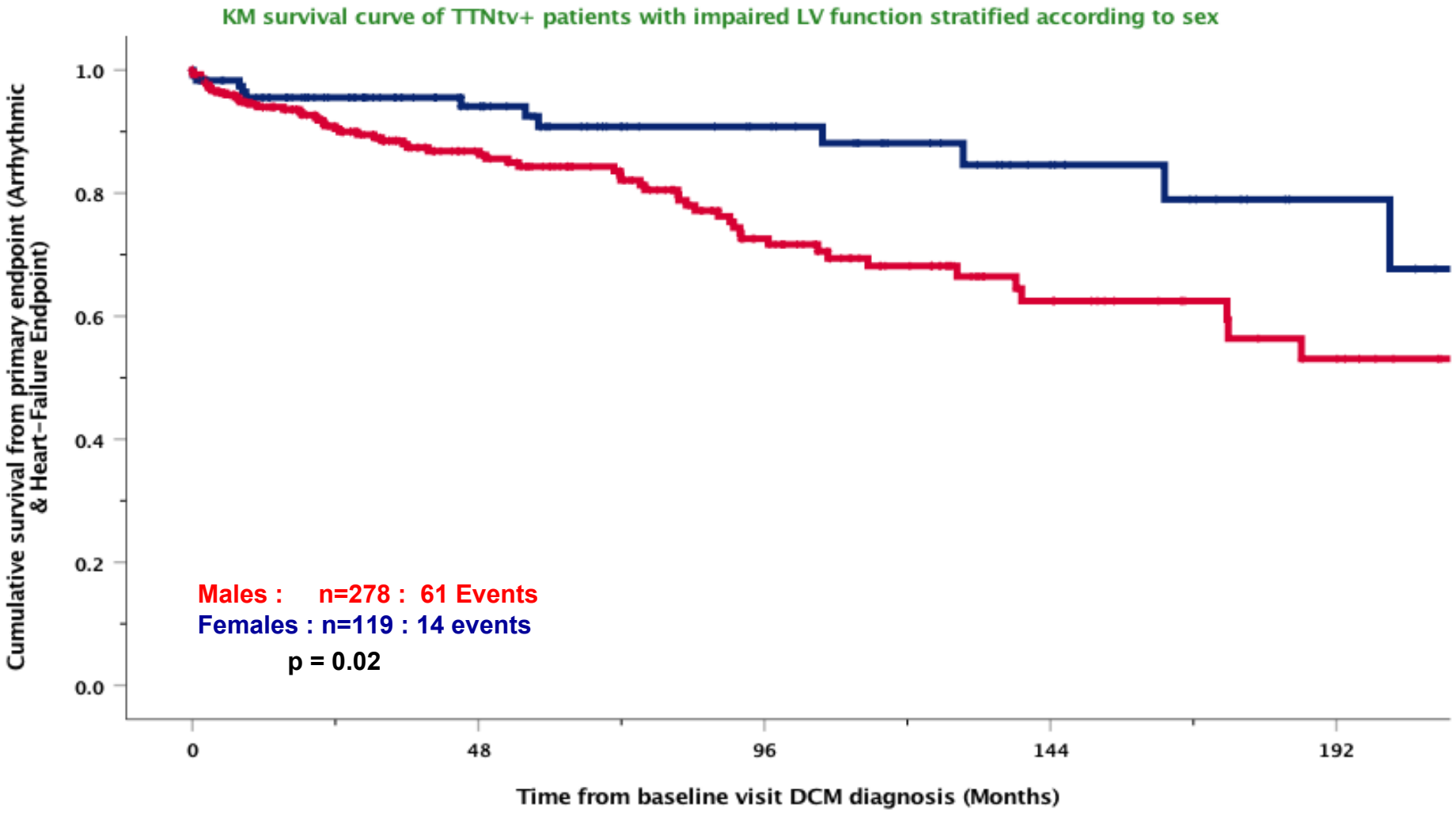


Outcomes



**16 (3%) patients had multiple endpoint events


KM survival function for TTNtv+ patients from baseline visit stratified according to LVSD: n=537
Cumulative survival from composite primary endpoint (Arrhythmic & Heart-Failure endpoint)
1.0
0.8
0.6
0.4
0.2
0.0
LVSD : n=372 : 71 events
No LVSD : n=165 : 5 events
p = 0.003
0
48
96
144
192
Time from baseline visit (Months)

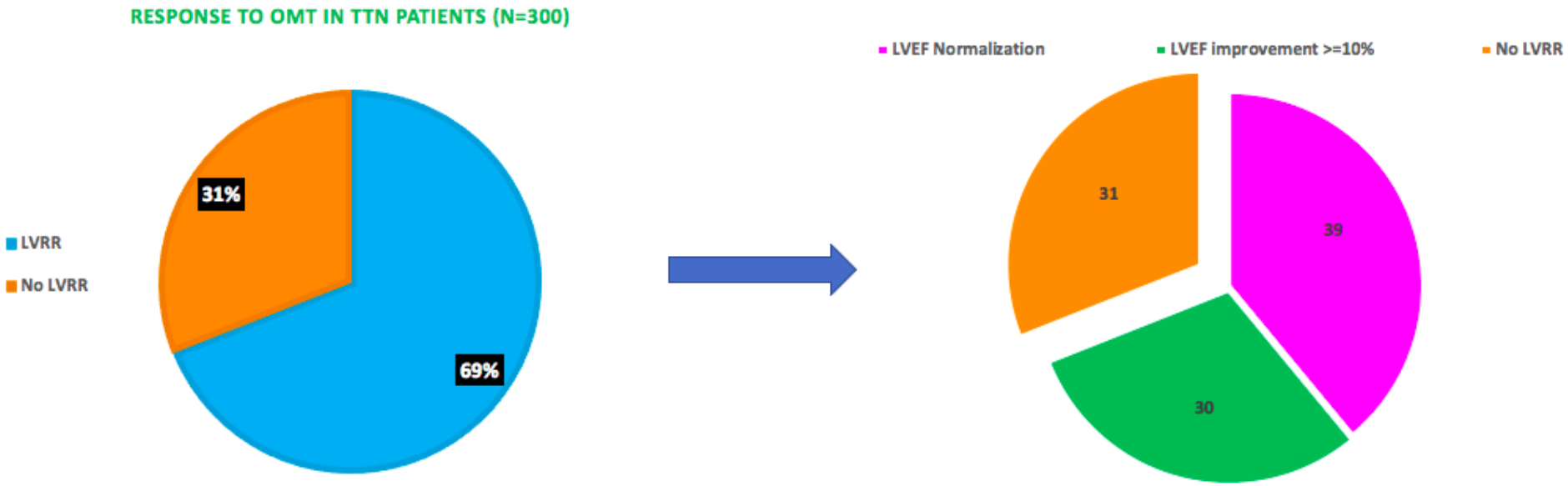

KM survival curve of TTNtv+ patients with impaired LV function stratified according to sex
Cumulative survival from primary endpoint (Arrhythmic & Heart-Failure Endpoint)
1.0
0.8
0.6
0.4
0.2
0.0
Males : n=278 : 61 Events
Females : n=119 : 14 events
p = 0.02
0
48
96
144
192
Time from baseline visit DCM diagnosis (Months)

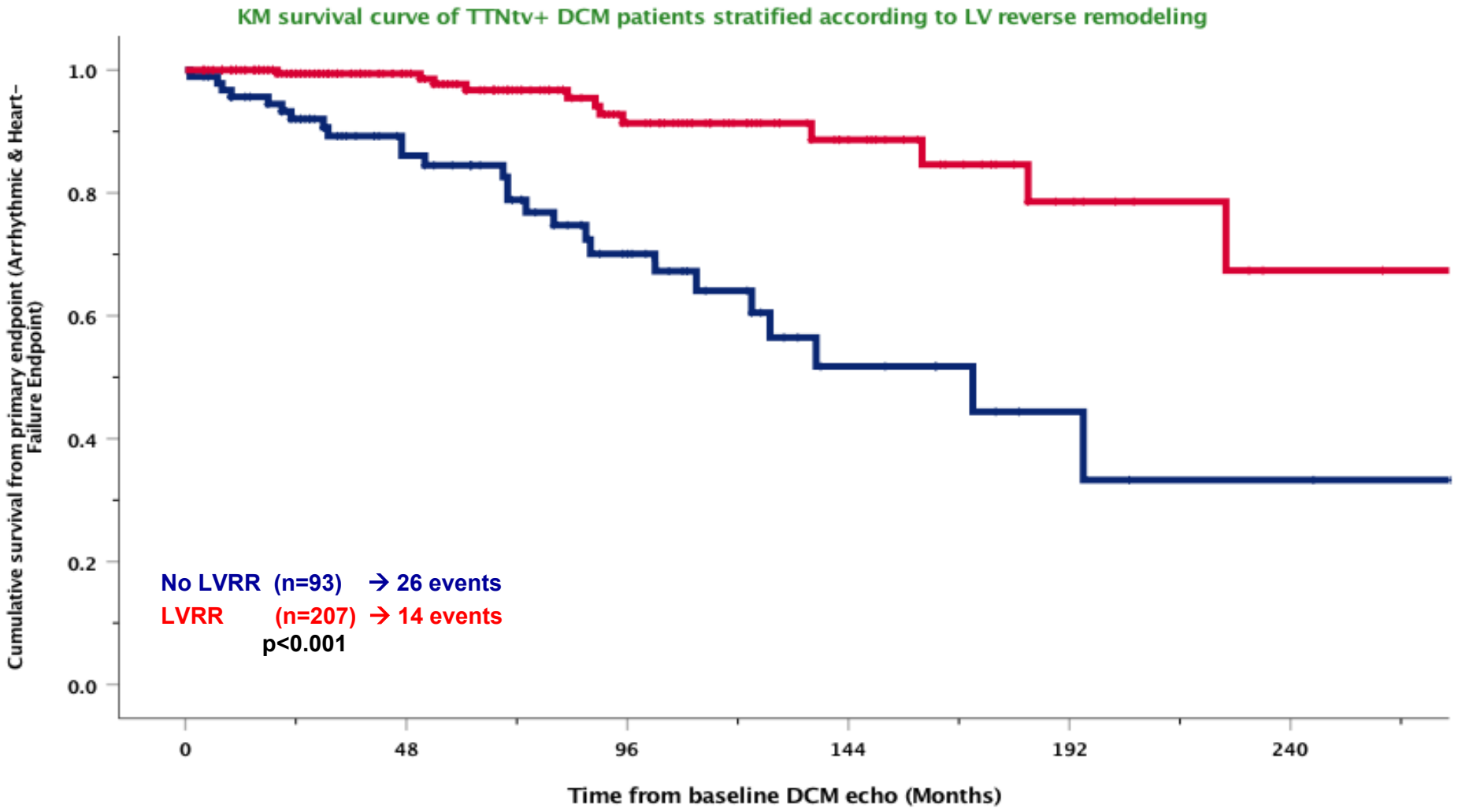
Secondary Endpoint

- **OMT in patients with impaired LVEF <50%:**
  - **95% on ACEi / ARB**
  - **93% on ß-blockers**
  - **69% on mineralocorticoid antagonist**

  - 15% switched to ARNI
  - 14% on ivabradine
  - 1% on ISDN / Hydralazine combination
  - 62% required oral loop diuretics.

Response to Medical Therapy




KM survival curve of TTNtv+ DCM patients stratified according to LV reverse remodeling
Cumulative survival from primary endpoint (Arrhythmic & Heart-Failure Endpoint)
1.0
0.8
0.6
0.4
0.2
0.0
No LVRR (n=93) → 26 events
LVRR (n=207) → 14 events
p<0.001
0
48
96
144
192
240
Time from baseline DCM echo (Months)

Conclusions

- Arrhythmogenic (AF, NSVT, Sustained VT)
  - Penetrance approximately 50% by age 60 - later than *LMNA, FLNC*
- Almost 15% have adverse events over follow-up – majority HF events
  - Majority arrhythmic endpoints occur in Severe LVSD
- Response to OMT is reasonably good but LVSD may recur and predispose to risk
- Males have more adverse phenotypes and events over follow-up

Authors

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Sources of Funding

This work was supported by grants from the following institutions:

1) University College London Hospitals / University College London receive a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme, London, UK (Perry Elliott).

2) Instituto de Salud Carlos III (ISCIII) [PI15/01551, PI17/01941, AC16/0014, IFI17/00003], CIBERCV (CB16/11/00403), ERA-CVD Joint Transnational Call 2016 (Genprovic) and Spanish Society of Cardiology (2014 to P.G.-P. and 2018 to A.R.-C.). Grants from ISCIII and the Spanish Ministry of Economy and Competitiveness are supported by the Plan Estatal de I+D+I 2013-2016 – European Regional Development Fund (FEDER) "A way of making Europe". Madrid, Spain (Maria Alejandra Restrepo-Cordoba; Pablo Garcia-Pavia).

3) DETECTIN-HF project (ERA-CVD framework), Warsaw, Poland ZB and GT (Grażyna Truszkowska; Zofia Bilinska).

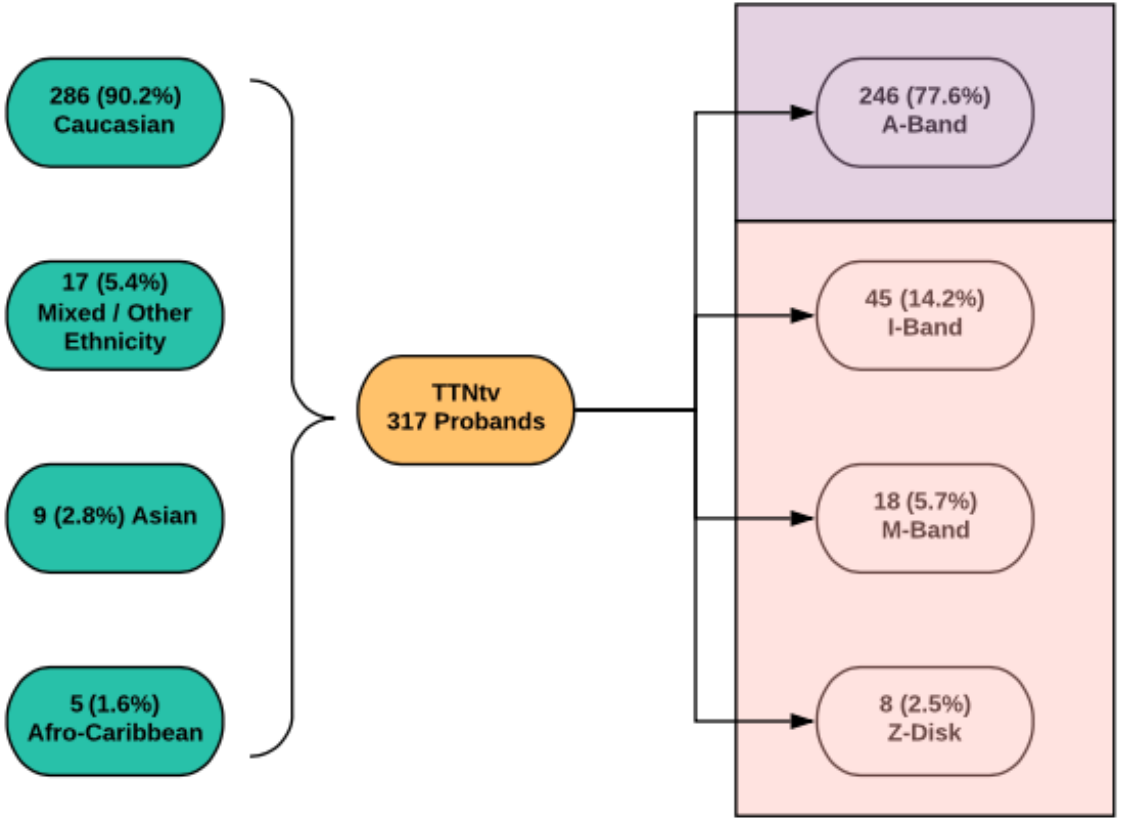
4) Wellcome Trust Collaborative Award in Sciences, London, UK (201543/Z/16/Z) (Perry M. Elliott; Mathias Gautel).

Acknowledgements:

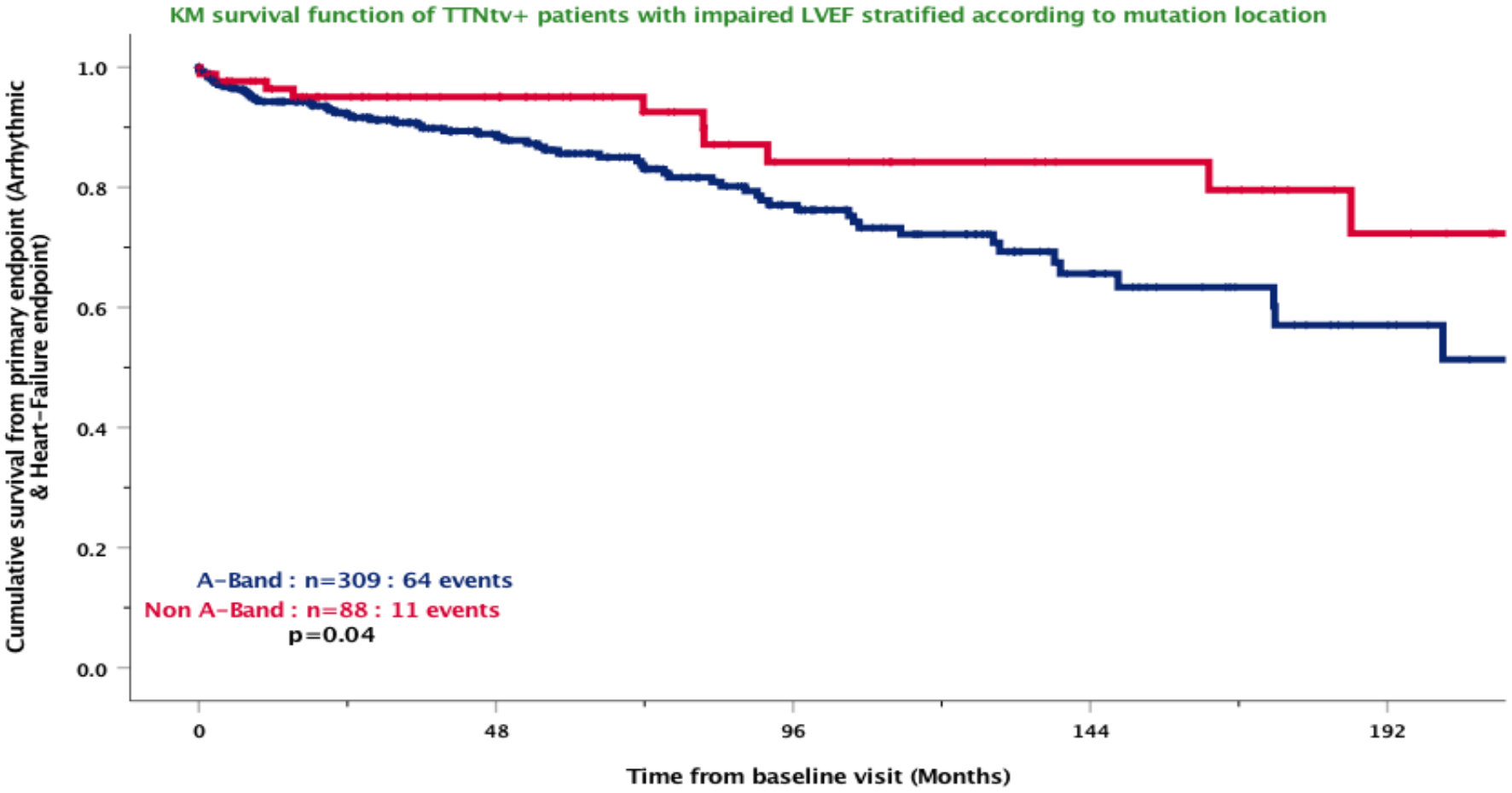
Several centres are members of the European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-Heart) – Barts Heart Centre, St. Bartholomew's Hospital, London; University Hospital Puerta de Hierro Majadahonda, Madrid, Spain; University Hospital Virgen Arrixaca, Murcia, Spain.

Thank You

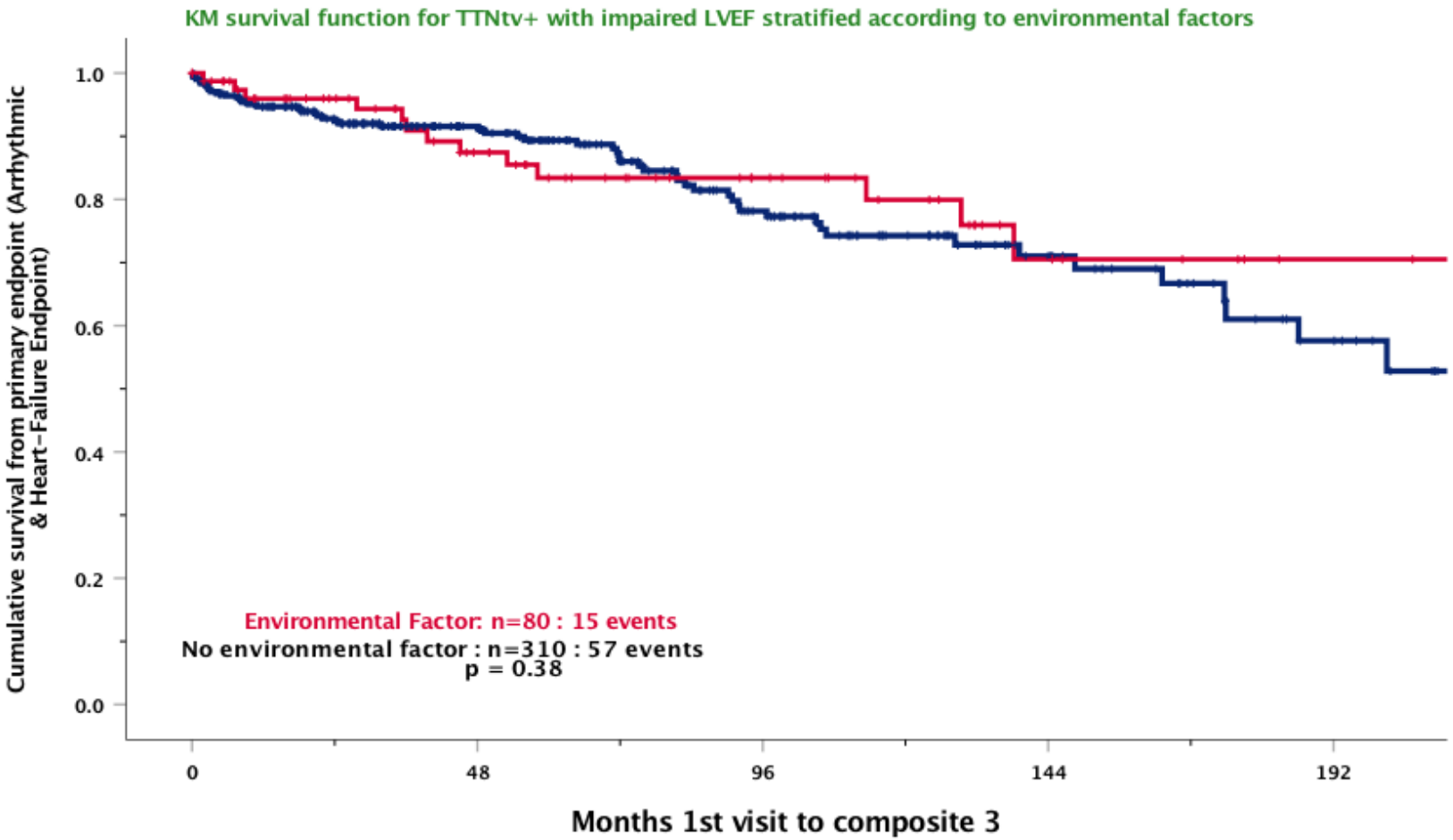
TTN Band


286 (90.2%)
Caucasian
17 (5.4%)
Mixed / Other
Ethnicity
9 (2.8%) Asian
5 (1.6%)
Afro-Caribbean
TTNtv
317 Probands
246 (77.6%)
A-Band
45 (14.2%)
I-Band
18 (5.7%)
M-Band
8 (2.5%)
Z-Disk

A-Band vs Non A-Band TTNtv in DCM / HNDC



Transient Responders

- Patients in whom LVEF continued to decrease by ≥5% whilst on OMT and in those in whom EF drops ≥ 5% after LVRR.
- 60/88 (68%) were transient responders

Role of Environmental Factors?