DISCOVERY: A Study Examining the Prevalence of Transthyretin Mutations in Subjects Suspected of Having Cardiac Amyloidosis

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Background and Rationale

- Cardiac amyloidosis is caused by extracellular myocardial deposition of either immunoglobulin light-chain (AL) or transthyretin (ATTR) fibrils
- Two forms of ATTR cardiac amyloidosis can cause life-threatening cardiomyopathy:
  - Familial amyloid cardiomyopathy (FAC) – inherited form due to misfolding of mutated ATTR
  - Senile systemic amyloidosis (SSA) – sporadic form caused by deposition of wild-type ATTR
- More than half of over 100 reported ATTR mutations are associated with FAC
- 12 variants of TTR listed in the National Amyloidosis Center reference database[1] as non-amyloid forming and considered not to be associated with FAC
  - G6S is the most common non-pathogenic mutation occurring with similar frequency in healthy subjects and SSA patients[2]
- FAC can be difficult to identify clinically and is likely underdiagnosed
- The DISCOVERY study aims to determine the prevalence of TTR mutations and FAC diagnosis in a cohort of patients with clinical features suggestive of cardiac amyloidosis

[1]NAC Reference Database: http://www.amyloidosismutations.com/mut-attr.php
[2]Sikora et al. Human Genetics (2014)

DISCOVERY Preliminary Results*

Study Design and Eligibility

	Trial Design
Design	A prospective, multi-center, observational study
Primary Objective	Characterize the frequency of TTR mutations in subjects suspected of having cardiac amyloidosis
Secondary Objectives	• Serum biomarkers of cardiac function • Echo parameters • NYHA class • 6-minute walk test (optional) • Fat pad aspirate (optional)
Sample Size	Up to 1000 subjects
Study Sites	Up to 50 centers

Subjects were identified by:

- Retrospective chart review
- ECHO database and ECG parameter search
- Prospectively during visit to the heart failure clinic
- Physician referrals

Key Inclusion criteria:

- Males or females >18 years old
- History of clinical and/or radiologic evidence suggestive of cardiac amyloidosis, including two or more of the following:
  - Heart failure signs and/or symptoms
  - Interventricular septal thickness of >12 mm
  - Left ventricular diastolic dysfunction
  - Low voltage ECG
  - History of carpal tunnel disease

Key Exclusion criteria:

- Known diagnosis of primary (AL) amyloidosis
- Known diagnosis of hereditary cardiomyopathy or cardiomyopathy due to aortic stenosis

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Enrollment and Genotypes

	N (%)
No of patients with samples analyzed	636†
No TTR Mutation (WT)	545 (86)
Non-Pathogenic Mutations^	42 (7)
G6S	39 (6)
T119M	1 (0.2)
R103H#	1 (0.2)
R104H	1 (0.2)
Pathogenic Mutations^	48 (8)
V122I**	44 (7)
V30M	1 (0.2)
T60A	1 (0.2)
G89L	1 (0.2)
D18N	1 (0.2)
Unknown Pathogenicity^	
E72A#	1 (0.2)

†Includes enrollment in US (92%), Spain (5%), Belgium (1%), France (1%) over a 12-month period
^Pathogenicity determined by central laboratory
**4 subjects with homozygous V122I genotype
#Previously unreported TTR mutation
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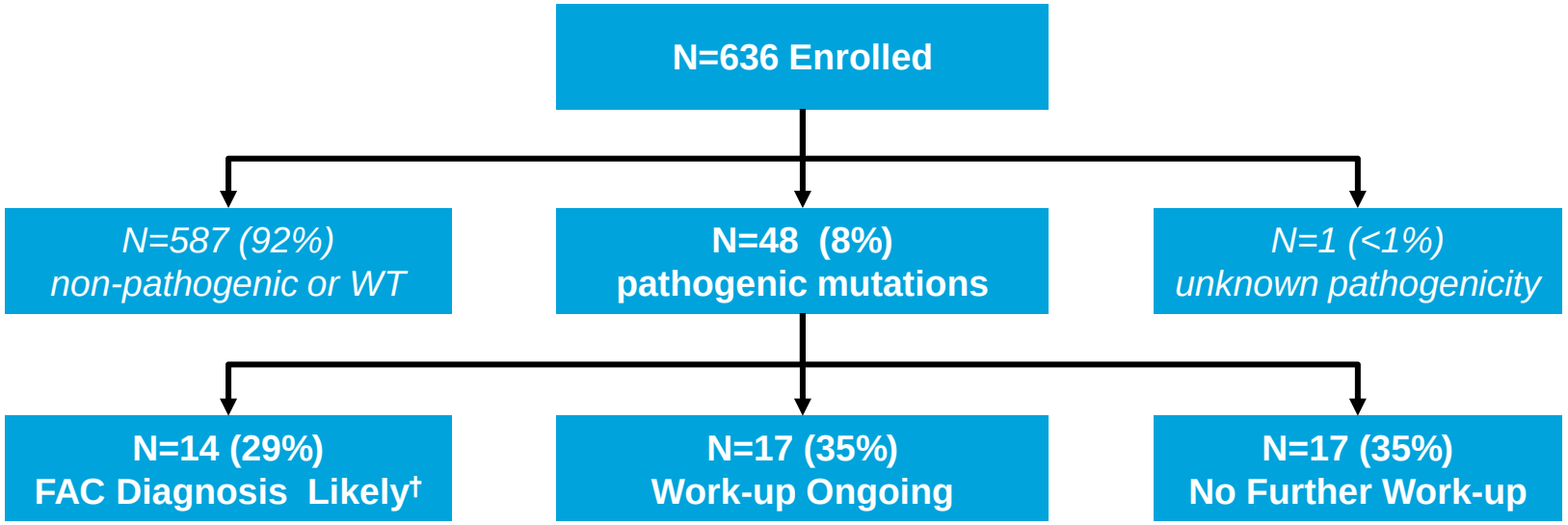
Disposition of Patients



- 8 positive by fat pad aspirate
- 6 positive by endomyocardial biopsy^

- 10 with negative fat pad aspirate

- 12 (25%) Decline of further work-up
  - 3 with negative fat pad aspirates
- 2 (4%) Declining health
- 3 (6%) Other (asymptomatic, cognitive issues, HIV history)

- 36% (8 out of 22) of evaluable fat pad aspirates positive for amyloid
- 75% (6 out of 8) of endomyocardial biopsies positive for amyloid

†Final diagnosis determined by investigator. Some histopathology performed outside of DISCOVERY study.
^Includes 1 patient with negative fat pad aspirate and 5 patients without evaluable fat pad aspirate
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Demographics and Qualifying Entry Criteria

	Pathogenic Mutation N=48	Non-Pathogenic Mutation N=42	WT TTR N=545
Median Age, years (Range)	70 (40–91)	66 (51–89)	65 (21–94)
Male, n (%)	31 (65)	30 (71)	349 (64)
Race, n (%)			
Black	42 (88)	9 (21)	352 (65)
White	4 (8)	31 (74)	158 (29)
Asian	–	–	7 (1)
Other	2 (4)	2 (5)	28 (5)
Heart Failure Sign and Symptoms, n (%)	37 (77)	34 (81)	431 (79)
Left Ventricular Diastolic Dysfunction, n (%)	33 (69)	21 (50)	384 (71)
IVS Thickness >12 mm, n (%)	41 (85)	32 (76)	377 (69)
Low Voltage ECG, n (%)	7 (15)	3 (7)	36 (7)
History of Carpal Tunnel Syndrome, n (%)	7 (15)	8 (19)	52 (10)

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Clinical Characteristics of Patients with Pathogenic Mutations

	Work-Up Ongoing *or* No Further Work-Up		Likely FAC Diagnosis†	
	N (%)	Median (range)	N (%)	Median (range)
Age, years	34	69 (40–91)	14	72 (52–78)
NYHA Class	30		13	
I	9 (30)		0	
II	10 (33)		2 (15)	
III	11 (37)		9 (69)	
IV	0		2 (15)	
TTR Genotypes				
V122I	33 (97)		11 (77)	
T60A	0		1 (8)	
V30M	0		1 (8)	
D18N	0		1 (8)	
G89L	1 (3)		-	
6-MWD [meters]	22	336 (75–510)	8	290 (62–367)
Cardiac Biomarkers				
NT-proBNP [pg/mL]	25	1593 (50–21236)	11	4658 (1873–20860)
Echocardiogram				
IVS Thickness [mm]	20	16 (11–22)	10	18 (14–21)
Ejection Fraction [%]	19	54 (23–75)	10	39 (28–55)
Cardiac Output [L/min]	19	3.3 (1.8–6.4)	10	2.7 (1.5–4.5)
LV Mass [gram]	20	295 (168–482)	9	319 (278-389)
Peak Longitudinal Strain [%]	19	-13.1 (-20.1 to -6.5)	10	-8.8 (-12 to -7)

Majority of patients with likely FAC diagnosis are >60 years (13/14) and have IVS thickness ≥17 mm (9/10) and have NYHA Class III heart failure (9/13)

†Final diagnosis determined by investigator
*Data transfer 6Oct2015

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Summary

- Rapid enrollment suggests substantial interest by cardiologists to investigate the prevalence of ATTR in their heart failure patients
- Genetic screening detects pathogenic TTR genotypes in 8% of patients with clinical suspicion for cardiac amyloidosis
  - Most common mutation observed is V122I in African Americans
- 29% of patients in this study with pathogenic TTR genotypes have likely FAC diagnosis
  - Further work-up ongoing in an additional 35% of patients with pathogenic genotypes
  - Age >60 years and IVS thickness ≥17 mm were seen in majority of patients with FAC diagnosis
- Future strategies to improve FAC diagnosis are needed
  - 25% of patients with a pathogenic mutation declined further work-up and potential diagnosis
  - Fat pad aspirate has low sensitivity; negative results warrant further work-up to further evaluate a potential diagnosis
- Genetic screening for TTR mutations and work-up for TTR cardiac amyloidosis is warranted in patients with cardiomyopathy and clinical suspicion of cardiac amyloidosis

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Acknowledgements

Patients Participating in DISCOVERY Study

DISCOVERY Investigators and Site Staff

Thank You

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