

## **SUPPLEMENTAL MATERIAL**

### **The utility of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin**

Hanson; Transthyretin as a prognostic indicator in ATTRwt

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## Supplemental Tables

**Supplemental Table 1. ROC analysis before and after the chosen 4-year analysis.**

Variable	3-year analysis		4-year analysis		5-year analysis	
	AUC (95% CI)	<i>p</i> value	AUC (95% CI)	<i>p</i> value	AUC (95% CI)	<i>p</i> value
TTR	0.65 (0.50 – 0.80)	0.06	0.69 (0.53 – 0.85)	0.02	0.68 (0.52 – 0.84)	0.02
LVEF	0.68 (0.52 – 0.84)	0.03	0.64 (0.48 – 0.79)	0.08	0.58 (0.44 – 0.72)	0.30
cTn-I	0.63 (0.48 – 0.78)	0.10	0.60 (0.45 – 0.74)	0.20	0.55 (0.41 – 0.69)	0.50
combined	0.72 (0.56 – 0.89)	0.008	0.77 (0.60 – 0.94)	0.002	0.72 (0.56 – 0.89)	0.006

ROC indicates receiver operatic characteristic; AUC, area under the curve; CI, confidence interval; TTR, transthyretin; LVEF, left ventricular ejection fraction; and cTn-I, cardiac troponin.

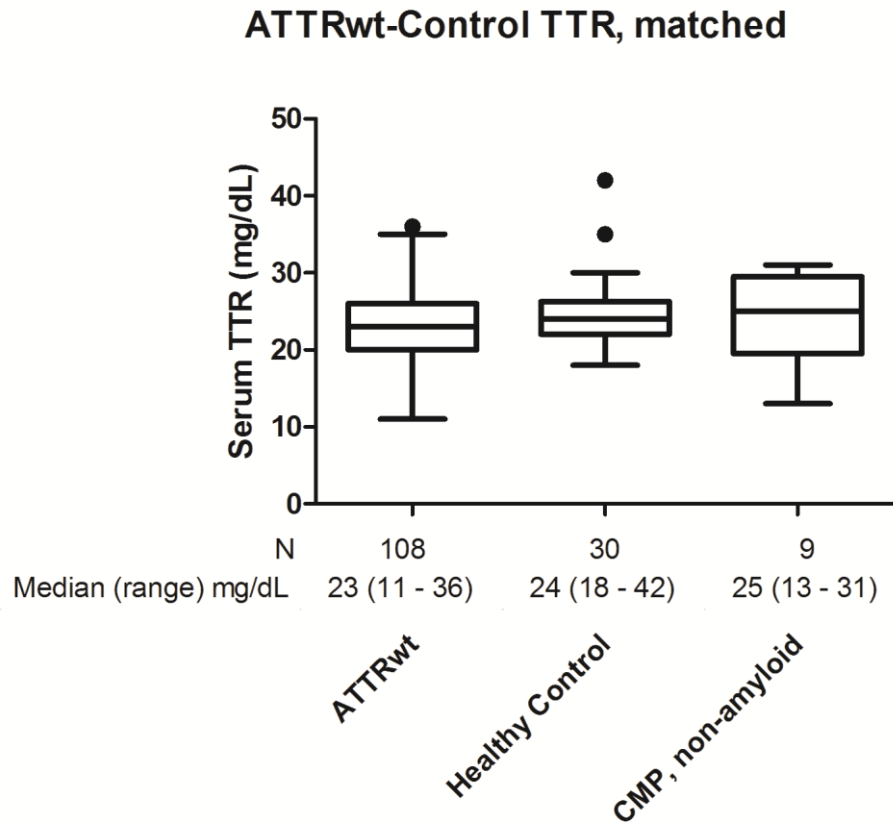
**Supplemental Table 2. Changes in TTR, cTn-I, and LVEF in matched pairs of untreated/diflunisal-treated patients**

		OS predictor variable trends						Matching criteria*			
		TTR (mg/dL)		cTn-I (ng/mL)		LVEF (%)		Age (y)	BMI (kg/m <sup>2</sup> )	Uric acid (mg/dL)	BNP (pg/mL)
		Baseline	Δ 1-year	Baseline	Δ 1-year	Baseline	Δ 1-year	Baseline			
Pair 1	untreated	20	-2	0.039	0.018	60	0	75.4	26	7.7	321
	treated	20	10	0.033	-0.005	70	-7	78.7	30	6.0	499
Pair 2	untreated	22	-2	0.083	0.017	56	-1	73.2	25	6.1	147
	treated	23	9	0.088	-0.022	29	8	76.7	24	6.4	167
Pair 3	untreated	28	-6	0.104	0.068	20	13	73.0	27	6.8	395
	treated	24	6	0.169	-0.038	55	8	71.3	24	4.7	238
Pair 4	untreated	28	-1	0.055	0.037	49	3	62.6	31	8.6	569
	treated	26	7	0.057	-0.005	61	1	67.7	32	9.4	119
Pair 5	untreated	25	-2	0.068	0.006	53	2	76.5	26	5.6	769
	treated	26	4	0.028	0	60	-5	77.8	26	6.4	323

\*Matching criteria included (in order of importance): TTR  $\pm$  4 mg/dL, age  $\pm$  5.1 y, BMI  $\pm$  4 kg/m<sup>2</sup>, Uric acid  $\pm$  2.1, cTn-I  $\pm$  0.06. All patients were within normal c-reactive protein (CRP) ranges. BNP values are listed as an additional cardiac biomarker reference for health status.

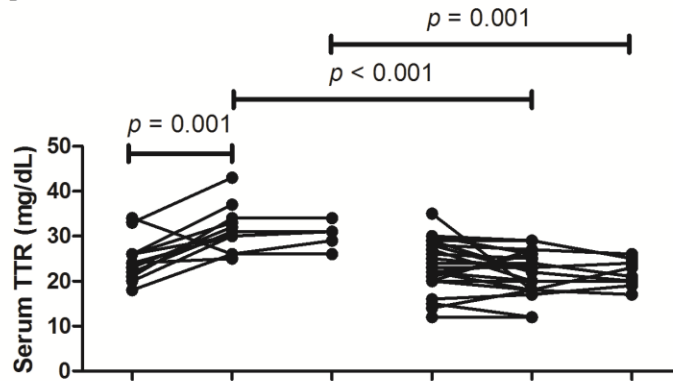
TTR indicates transthyretin; cTn-I, cardiac troponin I, LVEF, left ventricular ejection fraction; OS, overall survival; BMI, body mass index; BNP, b-type natriuretic peptide.

## Supplemental Figures and Figure Legends

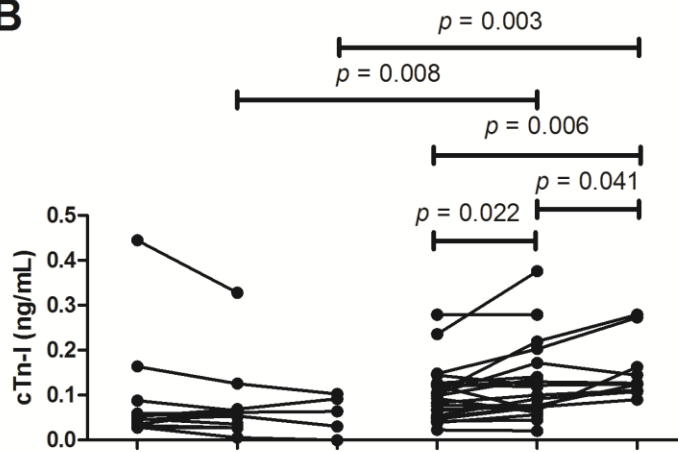


**Supplemental Figure 1. Baseline serum transthyretin (TTR) concentration in wild-type transthyretin amyloidosis (ATTRwt) compared to matched, healthy controls and matched non-amyloid cardiomyopathy (CMP) controls.** Depicted in Tukey box plots, baseline TTR values in the ATTRwt group, selected for Caucasian males over age 60 years ( $n = 108$ ), were not different from matched, healthy controls ( $n = 30$ ;  $p = 0.109$ ) nor matched non-amyloid CMP controls ( $n = 9$ ;  $p = 0.484$ ) using an unpaired two-sided t-test with Welch's correction. Number of cases (N) and median (range) values corresponding to each group are shown below the plot.

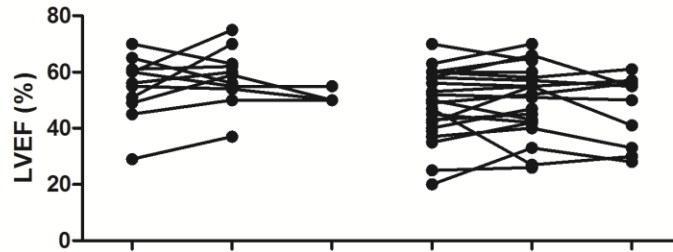
**A**



**B**



**C**



	Diflunisal-treated			Untreated		
	Initial Visit	1-year Follow-up	2-year Follow-up	Initial Visit	1-year Follow-up	2-year Follow-up
N	12	12	5	23	23	10
TTR, median (range), mg/dL	24 (18 - 34)	30 (25 - 43)	31 (26 - 34)	23 (12 - 35)	22 (12 - 29)	20 (17 - 26)
cTn-I, median (range), ng/mL	0.050 (0.028 - 0.445)	0.057 (0.006 - 0.328)	0.064 (0.0 - 0.103)	0.099 (0.023 - 0.279)	0.096 (0.021 - 0.376)	0.126 (0.090 - 0.279)
LVEF, median (range), %	58 (29 - 70)	57 (37 - 75)	50 (50 - 55)	50 (20 - 70)	53 (26 - 70)	52 (28 - 61)

**Supplemental Figure 2. Longitudinal study of prognostic parameters of overall survival in diflunisal-treated and untreated wild-type transthyretin amyloidosis (ATTRwt)** Individual values were obtained at baseline, 1-year and 2-year evaluations for serum transthyretin (TTR) (A), cardiac troponin (cTn-I) (B), and left ventricular ejection fraction (LVEF) (C). In each panel, diflunisal-treated cases are plotted on the LEFT and untreated cases on the RIGHT. The number (N) and median (range) values for each variable are shown in a table beneath the graphs.