

Alternative Therapies for ATTR

What your mother never told you

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Curcumin

- Natural polyphenol (diferuloylmethane)
- Inhibits A β aggregation/breaks up A β fibrils
- Blocks toxicity of A β fragments on brain cells
- Competes T4 binding to TTR
- Inhibits steps of ATTR fibril formation

Comment:

- Mouse model of very early amyloid aggregation
- Blood curcumin levels unachievable in humans

Resveratrol

- Stabilizes TTR tetramer conformation
- Promotes aggregation of potentially toxic TTR monomers

Comment:

- Insufficient data in humans
- Effective dose undefined

EGCG

- Stabilizes TTR tetramers
 - Different mechanism than diflunisal
- Inhibits ATTR amyloid fibril formation
- Promotes breakdown of amyloid deposits
 - Early amyloid aggregates
 - Mature/fixed amyloid deposits

EGCG

ATTR

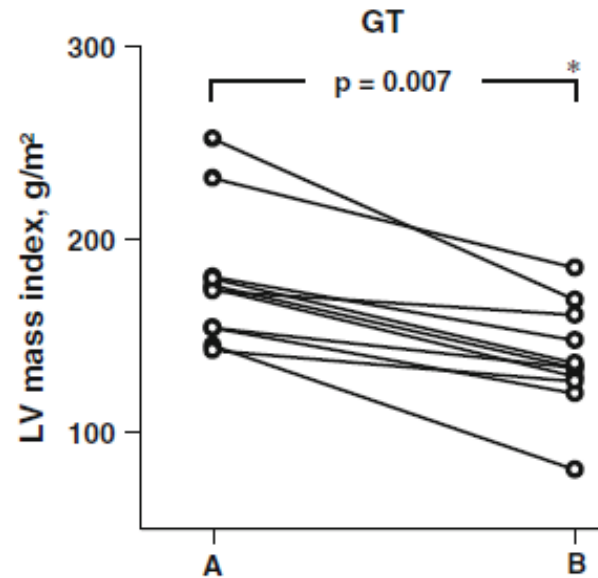
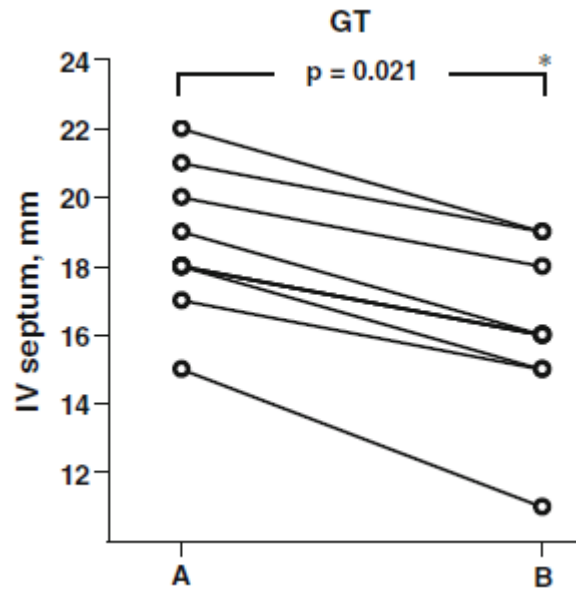
- 14 ATTR cardiomyopathy patients
- EGCG 500-700 mg/day x 12 months
- Findings
 - Echo: no change in LV wall thickness
 - Cardiac MRI: 12.5% decrease LV mass

AL

- 59 patients with AL amyloid cardiomyopathy
- EGCG 600-800 mg/day + AL amyloid treatments
- Findings
 - 11 patients -- > 2 mm septal wall decrease
 - 6 months (range, 3-10)

EGCG

AL Amyloid Cardiomyopathy



Doxycycline/TUDCA

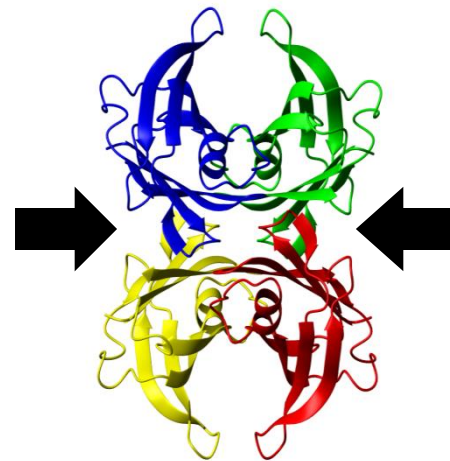
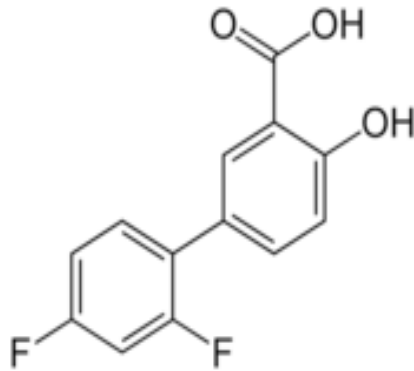
- Doxycycline 100 BID/TUDCA 250 mg TID x 12 m
- 20 Subjects (17 ATTRm, 2 ATTRwt, 1 Domino LT)

Months	N	Nerves	Heart
6	10		
12	7	Subst. stability	No progress
Discontinue	2		
Lost	1		



Diflunisal IND 68092

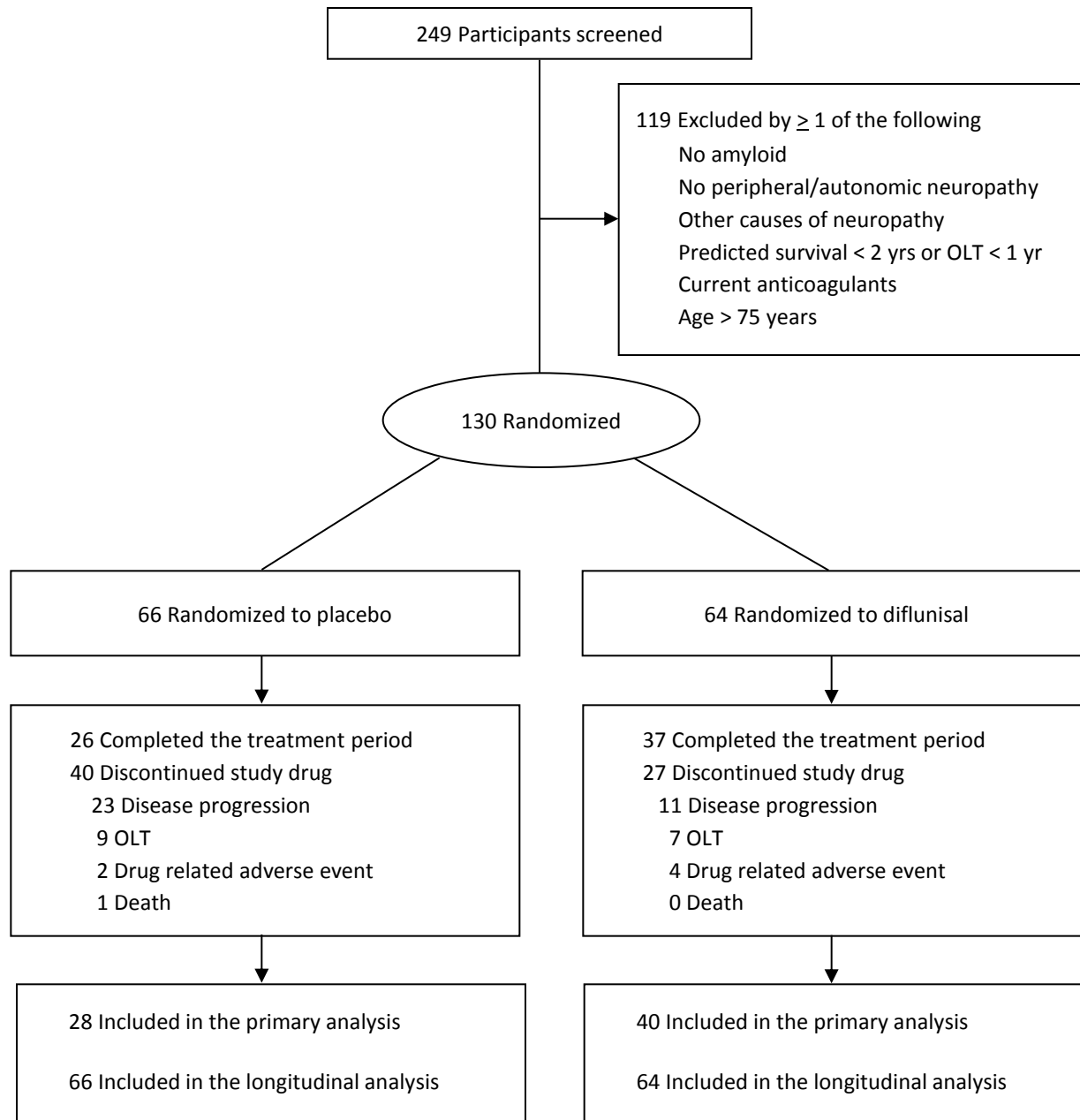
- 2',4'-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity





Study design

- Multi-center, international, RCT
- Primary endpoint:
 - Neurologic Impairment Score + 7 (NIS+7)
- Secondary endpoints:
 - Kumamoto neurologic scale
 - Modified body mass index (mBMI)
 - Quality of Life Questionnaire (SF-36)





Conclusions

- Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
- Effective across gender, mutations, and severity of disease at entry
- Provides a rare example of repurposing old drugs for new indications