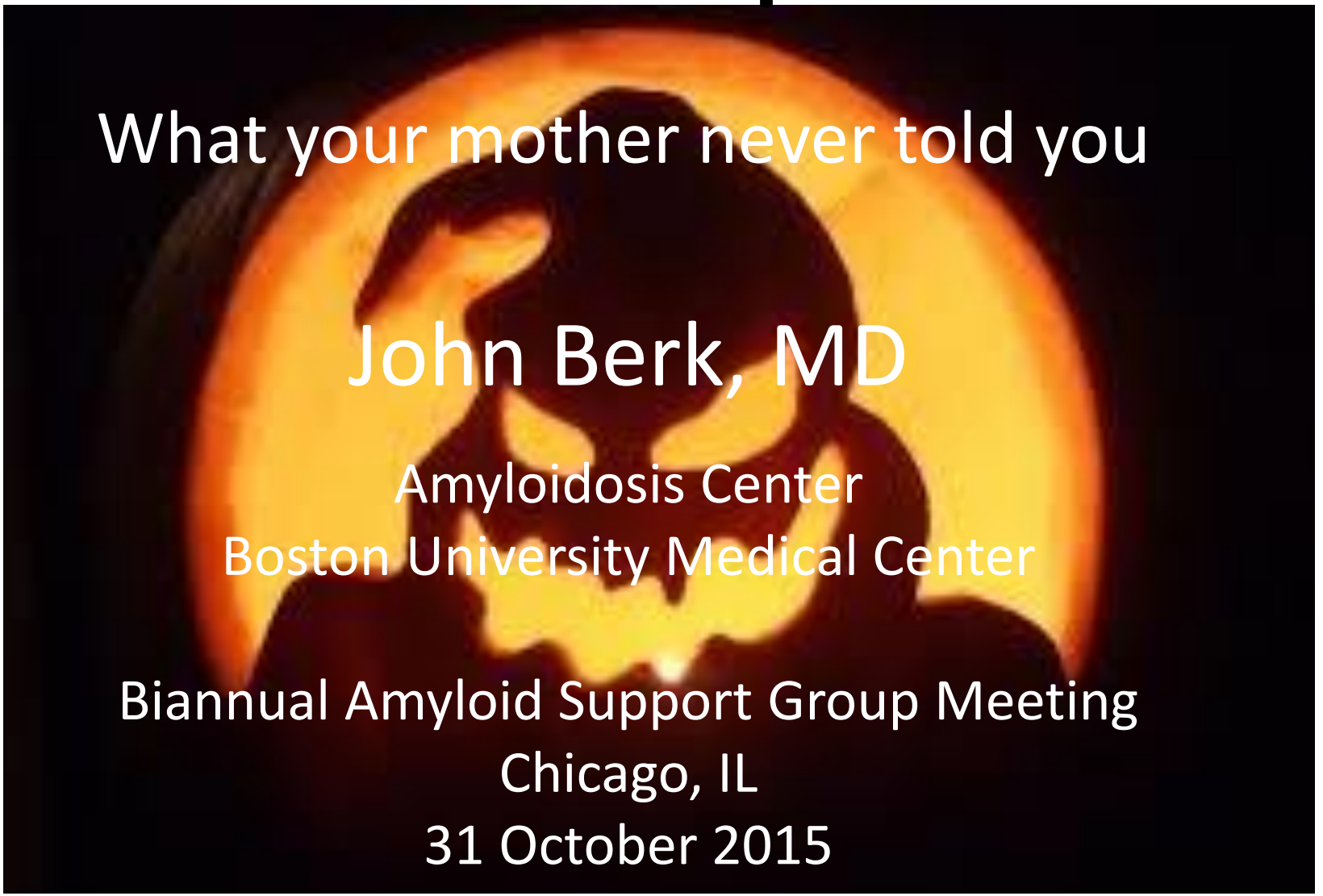
Alternative Therapies for ATTR



What your mother never told you

John Berk, MD

Amyloidosis Center
Boston University Medical Center

Biannual Amyloid Support Group Meeting
Chicago, IL
31 October 2015

Curcumin

- Natural polyphenol (diferuloylmethane)
- Inhibits Aβ aggregation/breaks up Aβ fibrils
- Blocks toxicity of Aβ 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

Ferreira N et al. 2013; 1832(1):39

Resveratrol

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

Comment:

- Insufficient data in humans
- Effective dose undefined

Bourgault S et al. Biochem Biophys Res Comm. 2011; 410(4):707

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

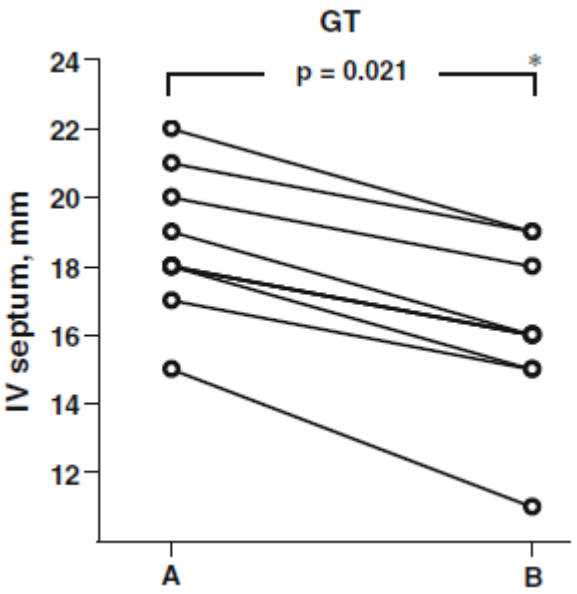
AL

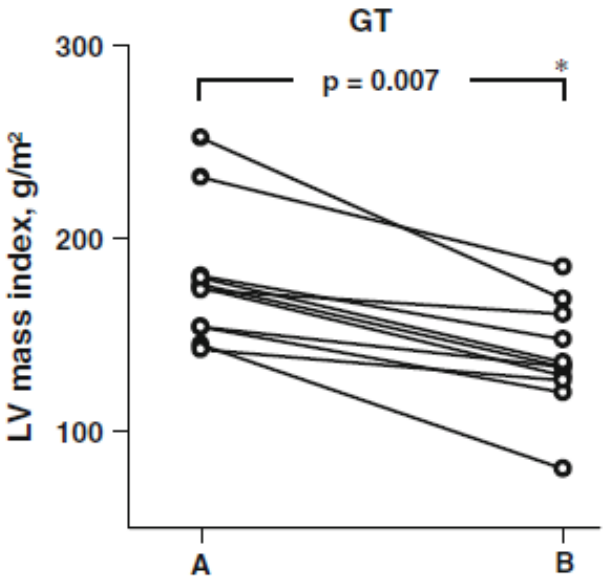
- 59 patients with AL amyloid cardiomyopathy
- ECGC 600-800 mg/day + **AL amyloid treatments**
- Findings
    - 11 patients -- > 2 mm septal wall decrease
    - 6 months (range, 3-10)

Kristen AV et al. Clin Res Cardiol 2012; 101(10):805
Mereles D et al. Clin Res Cardiol 2010; 99:483

EGCG

AL Amyloid Cardiomyopathy





Mereles D et al. Clin Res Cardiol 2010; 99:483

Doxycycline/TUDCA

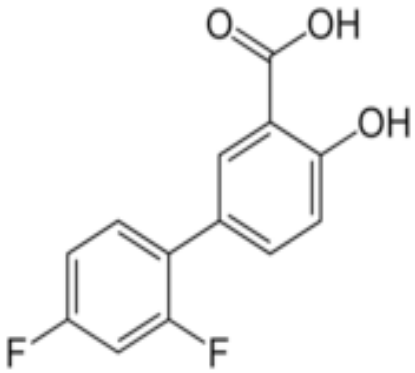
- Doxycycline 100 BID/TUDCA 250 mg TID x 12 m
- 20 Subjects (17 ATTRm, 2 ATTRwt, 1 Domino LT)

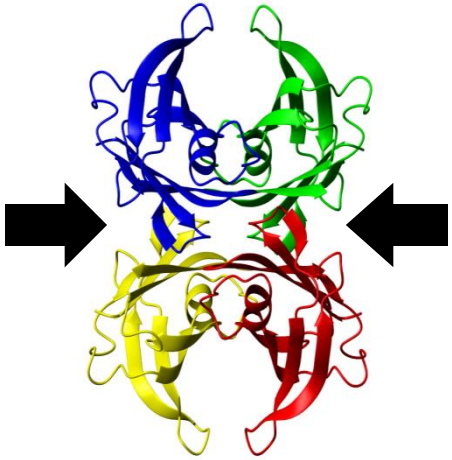
Months	N	Nerves	Heart
6	10		
12	7	Subst. stability	No progress
Discontinue	2		
Lost	1		

Obici L et al. Amyloid 2012; 19S (1): 34-6

Diflunisal IND 68092

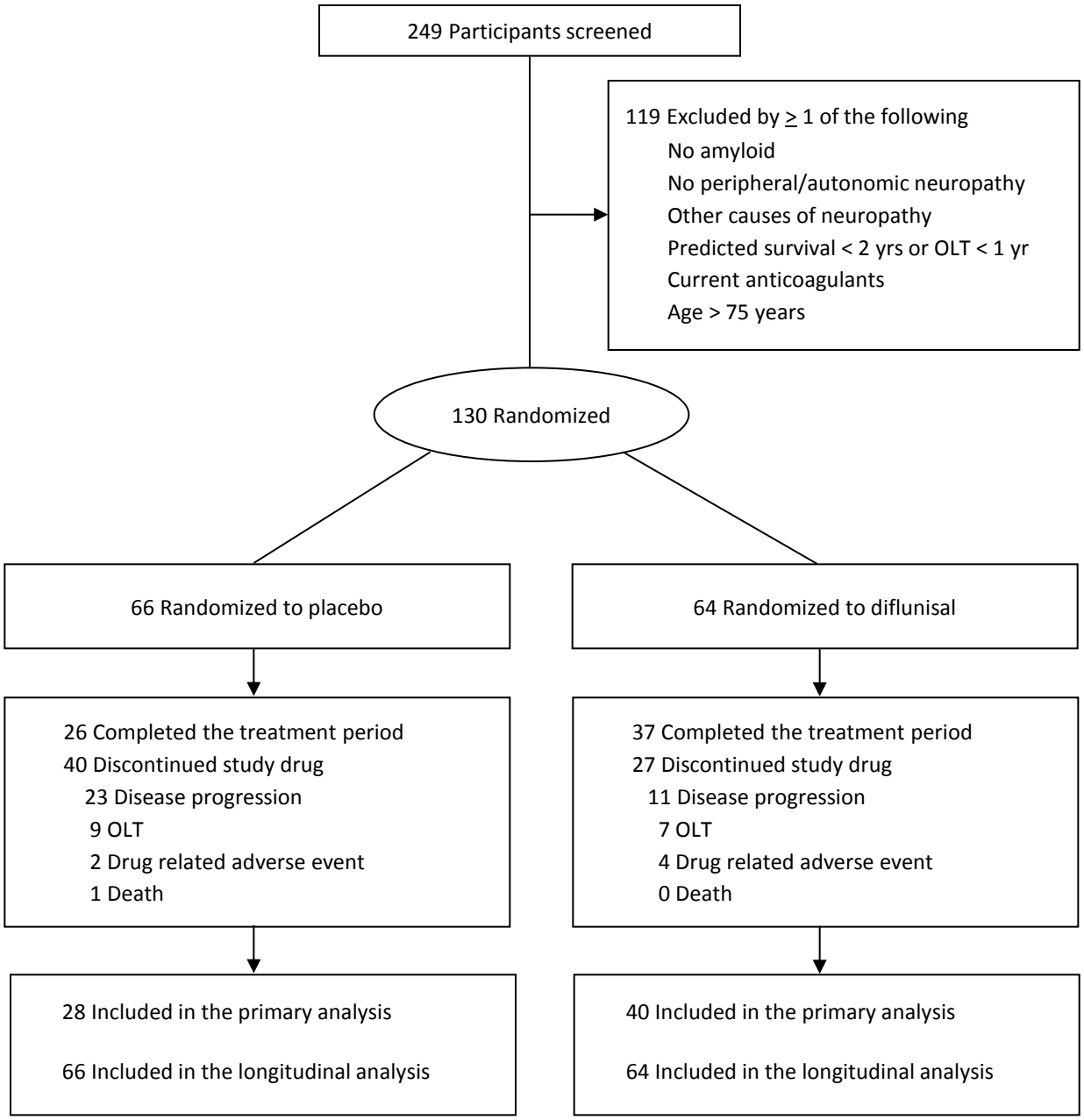
- 2’,4’-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity





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)


249 Participants screened
119 Excluded by ≥ 1 of the following
No amyloid
No peripheral/autonomic neuropathy
Other causes of neuropathy
Predicted survival < 2 yrs or OLT < 1 yr
Current anticoagulants
Age > 75 years
130 Randomized
66 Randomized to placebo
64 Randomized to diflunisal
26 Completed the treatment period
40 Discontinued study drug
23 Disease progression
9 OLT
2 Drug related adverse event
1 Death
37 Completed the treatment period
27 Discontinued study drug
11 Disease progression
7 OLT
4 Drug related adverse event
0 Death
28 Included in the primary analysis
66 Included in the longitudinal analysis
40 Included in the primary analysis
64 Included in the longitudinal analysis

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