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Promising Therapies On The Horizon For Treatment Of ATTR Amyloidosis

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Relevant Disclosures

- Consulting / honoraria – Pfizer, Akcea, Alnylam, Amgen
- Research support – Pfizer, Akcea, Alnylam, Takeda
- Off-label use – Diflunisal, Doxycycline, TUDCA/Ursodiol

The NEW ENGLAND JOURNAL of MEDICINE

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Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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The NEW ENGLAND JOURNAL of MEDICINE

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Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

ORIGINAL ARTICLE

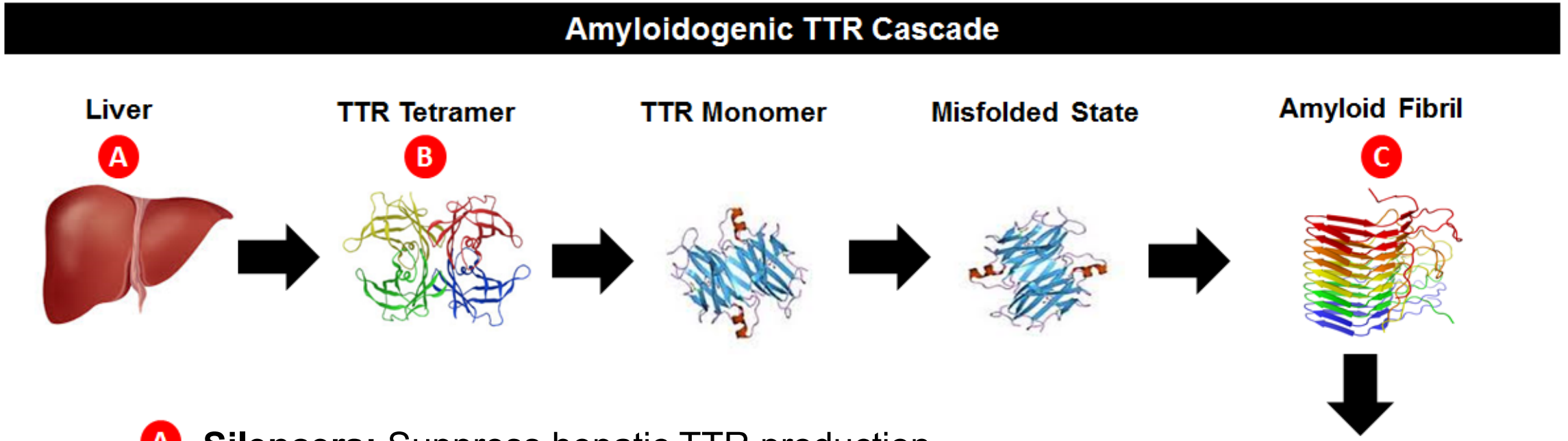
Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

Objectives

- Discuss the use of TTR **‘Silencers’** for the treatment of ATTR amyloidosis
- Discuss the use of TTR **‘Stabilizers’** for the treatment of ATTR amyloidosis
- Discuss the use of ATTR **‘Degraders’** for the treatment of ATTR amyloidosis
- Will not be discussing issues related to conventional cardiovascular management of ATTR amyloidosis patients

Therapeutic Targets of the Amyloidogenic TTR Cascade



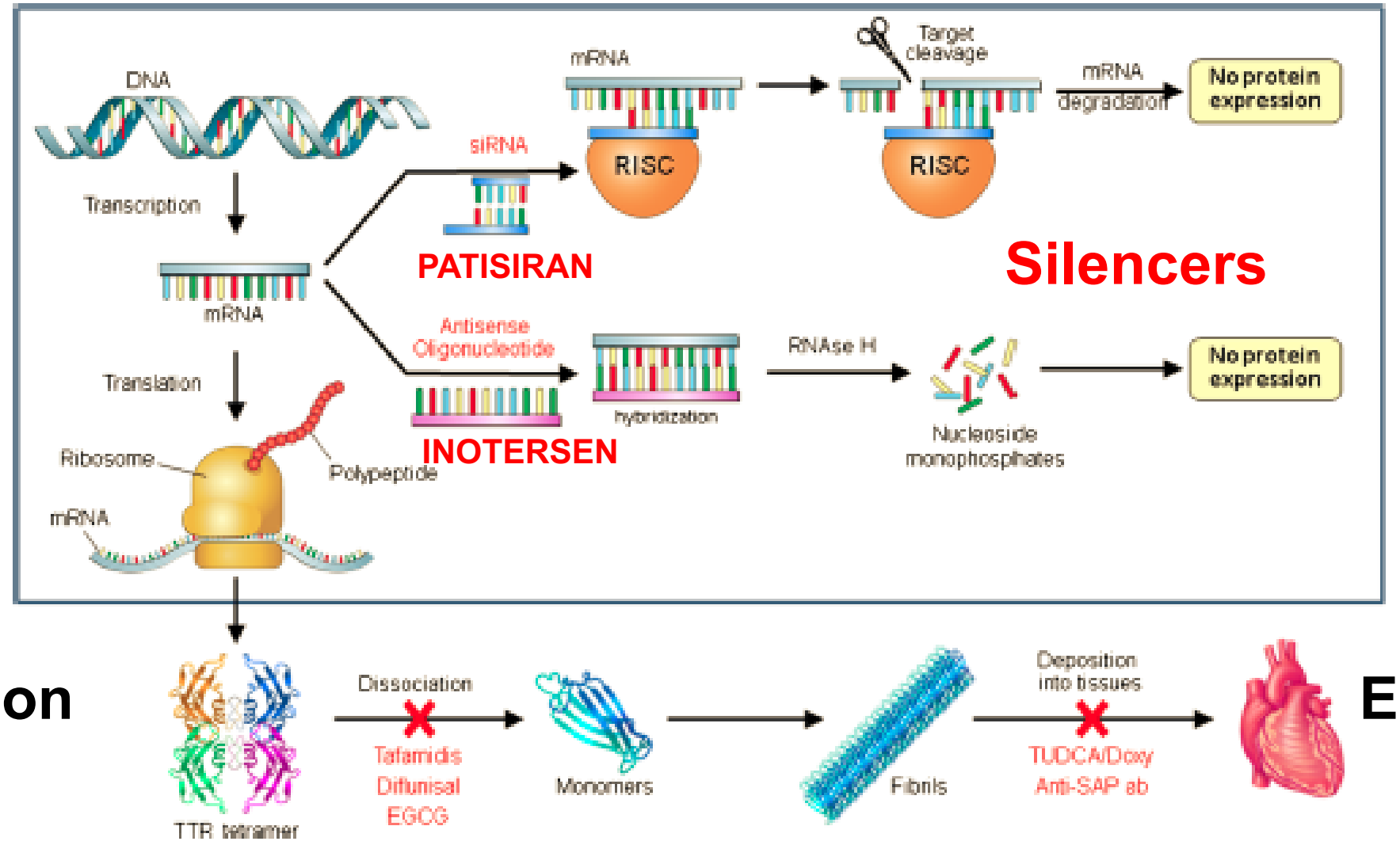
- A **Silencers:** Suppress hepatic TTR production
- B **Stabilizers:** Stabilize circulating TTR from dissociation
- C **Degraders:** Breakdown amyloid fibril tissue deposits

Castano et al. Heart Fail Rev 2015;20:163

TTR Silencers

- Suppress hepatic production of transthyretin
- Two agents have recently shown benefit in phase III clinical trials, both for mutant ATTR polyneuropathy
  - **Inotersen** - antisense oligonucleotide
  - **Patisiran** - small interfering RNA

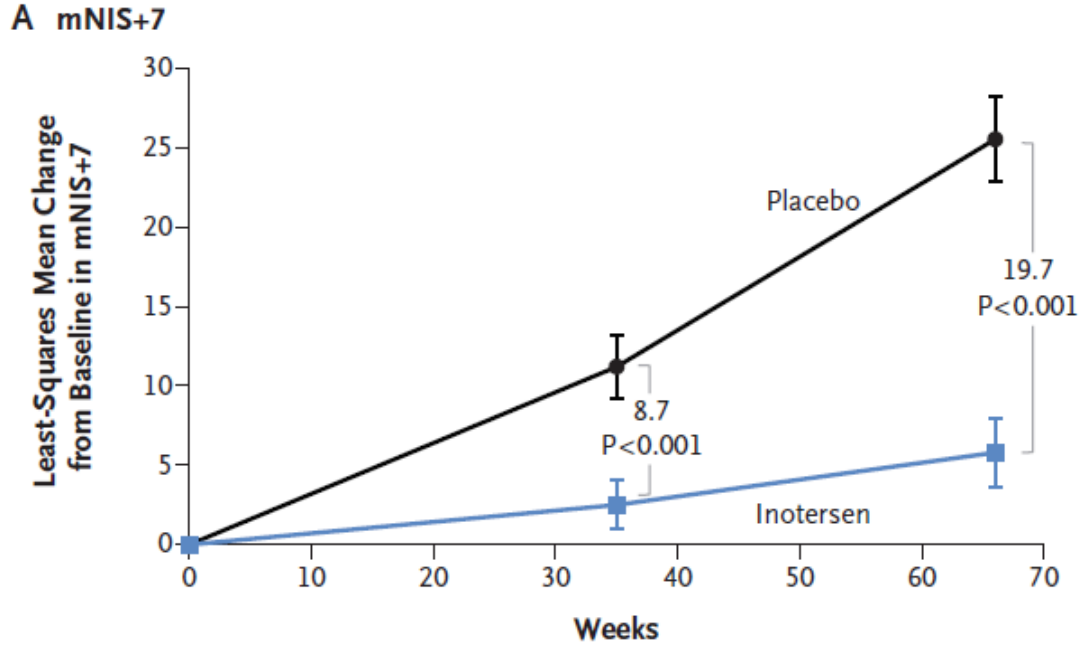
ATTR Pharmacologic Therapies



Vranian et al. Curr Cardiol Rep 2015;17:100

Inotersen

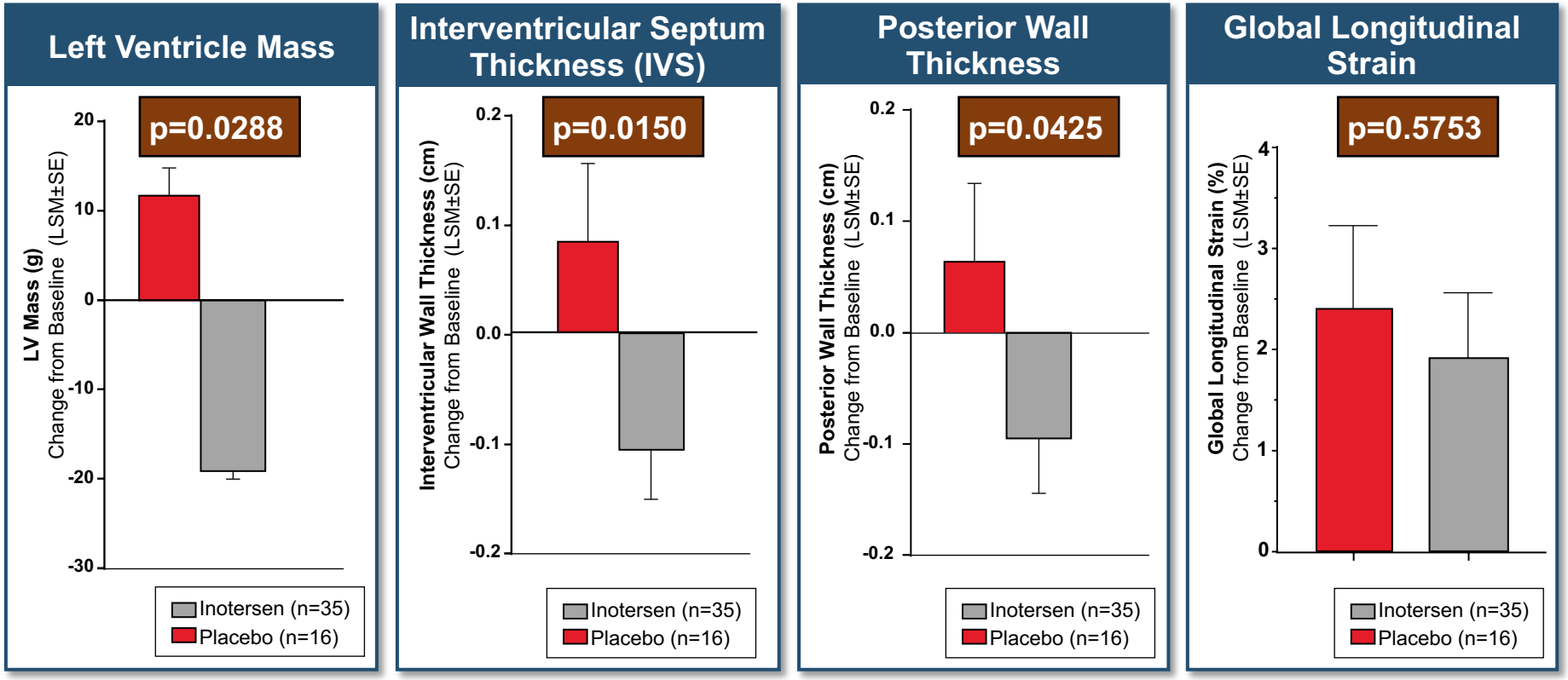
- Weekly subcutaneous dosing
- NEURO-TTR RCT (N=172) enrolled ambulatory patients with mATTR polyneuropathy, Inotersen vs placebo, 17 month FU
- Significantly ↓ neuropathy progression, 36% improved
- Safety
  - 3 pts had plts ↓ <25, 1 ICH death
  - 3 pts had glomerulonephritis
  - Plt, renal monitoring improved safety
- Approved by Heath Canada Oct 2018
  - Plts >100, eGFR >45, vitamin A suppl



Benson et al. NEJM 2018;379(1):22

Inotersen - Improved Cardiac Endpoints

- Neuro-TTR study sub-analysis of pts with cardiac involvement

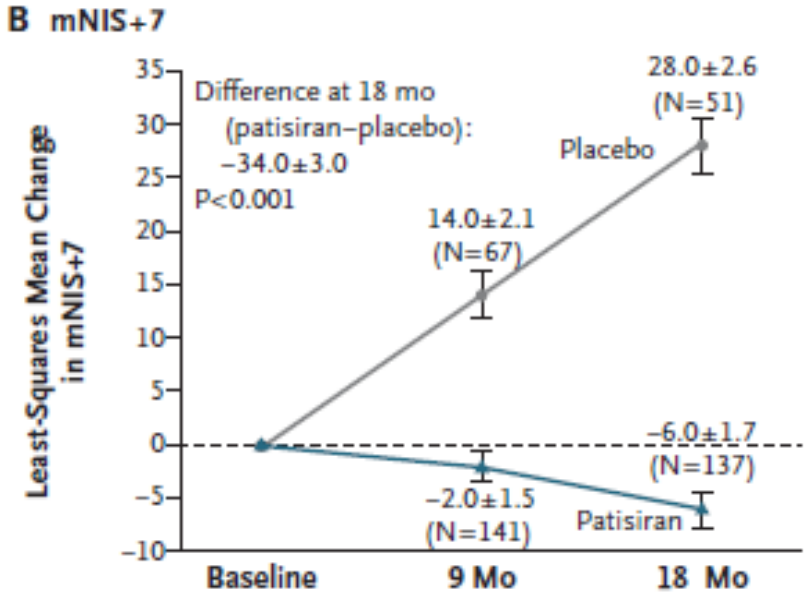


- Single-center open-label investigator-sponsored trial of ATTR CA patients receiving Inotersen
  - 6MWD improved by 13.7 m after 3 years (N=13)

Benson et al. NEJM 2018;379(1):22
Dasgupta et al. ACC 2019

Patisiran

- Intravenous dosing every 3 weeks
- APOLLO RCT (N=225) enrolled ambulatory patients with mATTR polyneuropathy, Patisiran vs placebo, 18 months FU
- Significantly ↓ neuropathy progression, 56% improved
- Safety
  - Similar adverse event rates between groups
  - 19% infusion rxn (9% placebo), none serious
  - Vitamin A supplementation
- Under Health Canada review

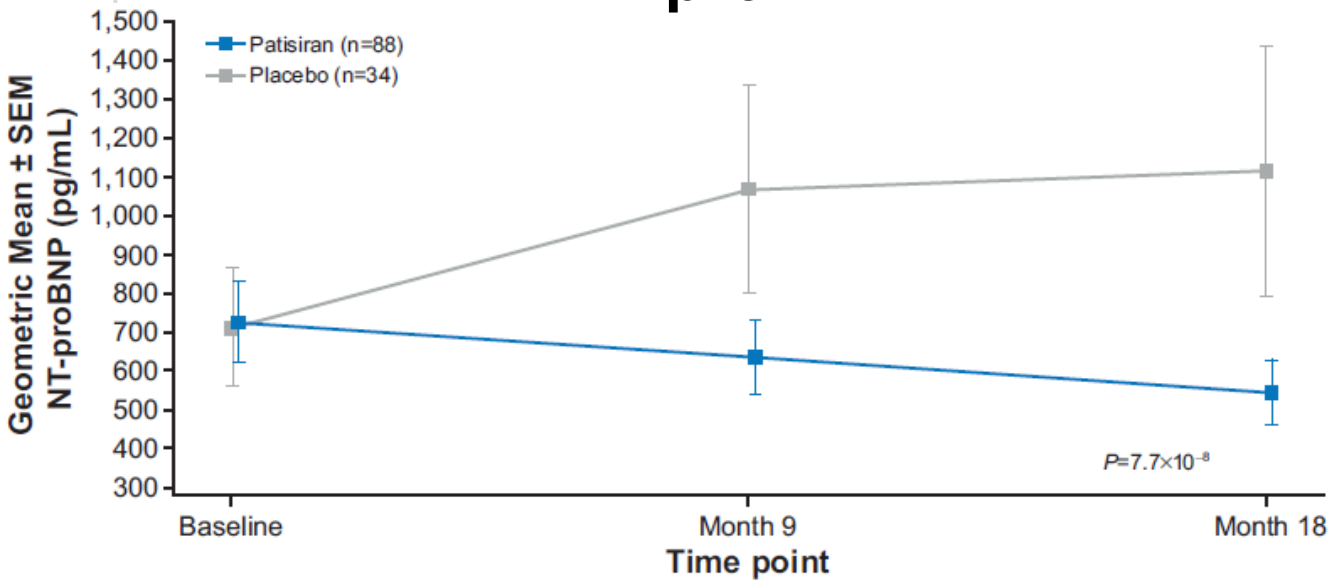


Adams et al. NEJM 2018;379(1):11

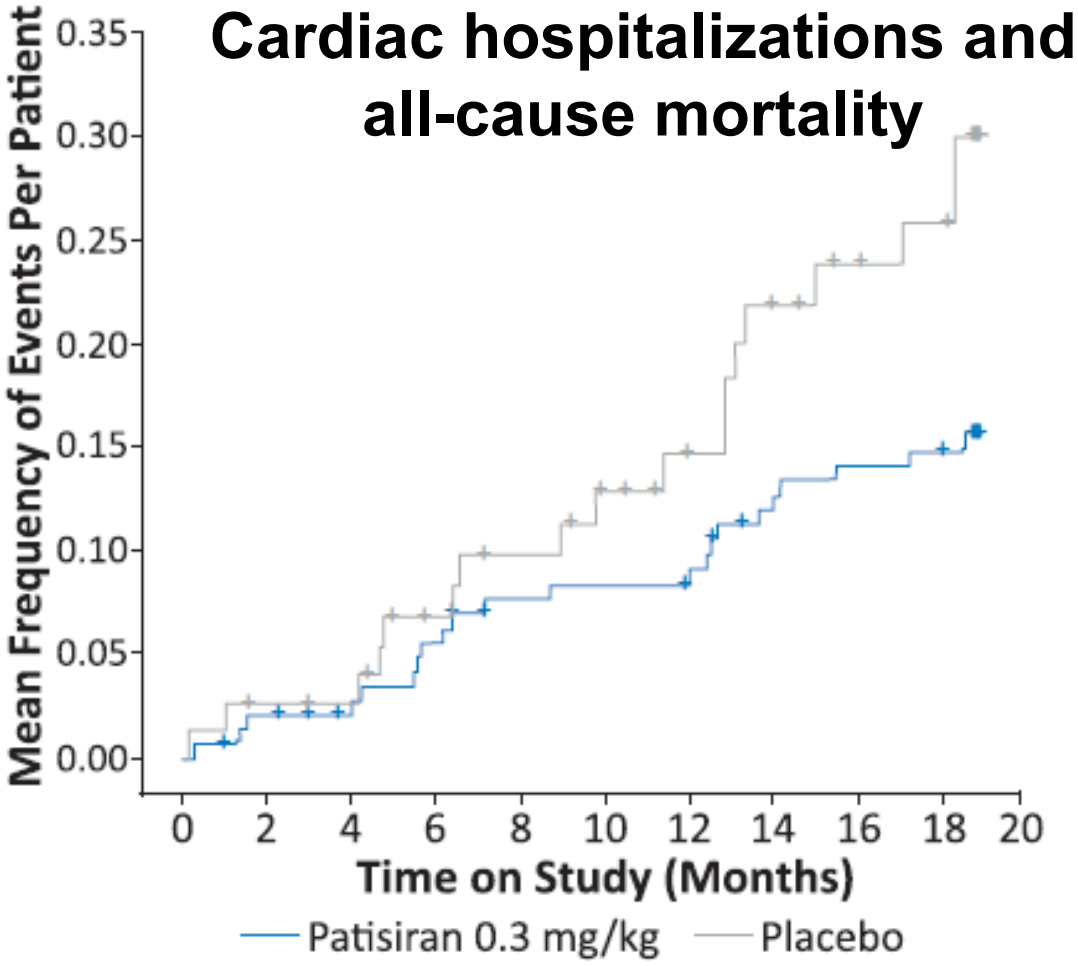
Patisiran – Improved Cardiac Endpoints

- APOLLO study sub-analysis of 126 pts with cardiac involvement

NTproBNP



Cardiac hospitalizations and all-cause mortality



- Similar results for LV mass and wall thickness, longitudinal systolic strain, 6MWD

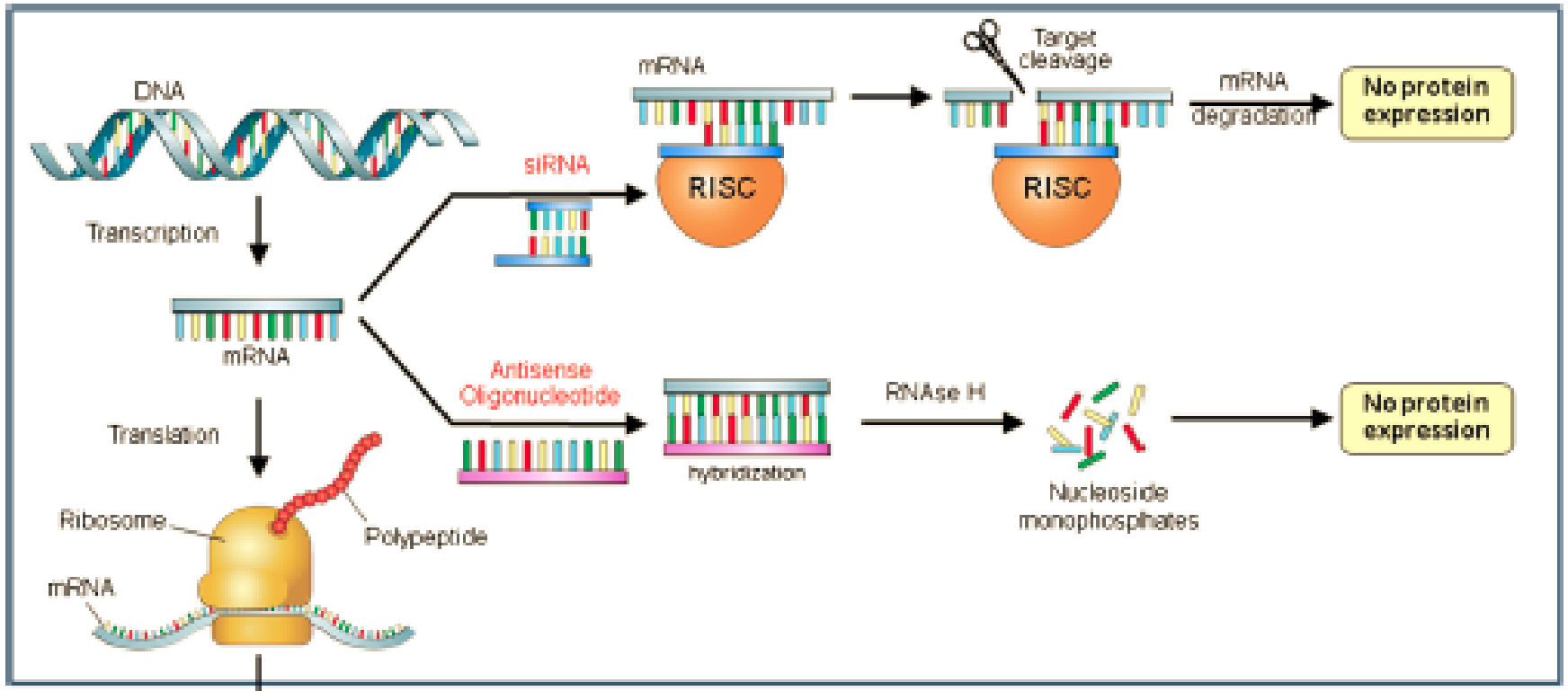
Solomon et al. Circ 2019;139:431

TTR Stabilizers

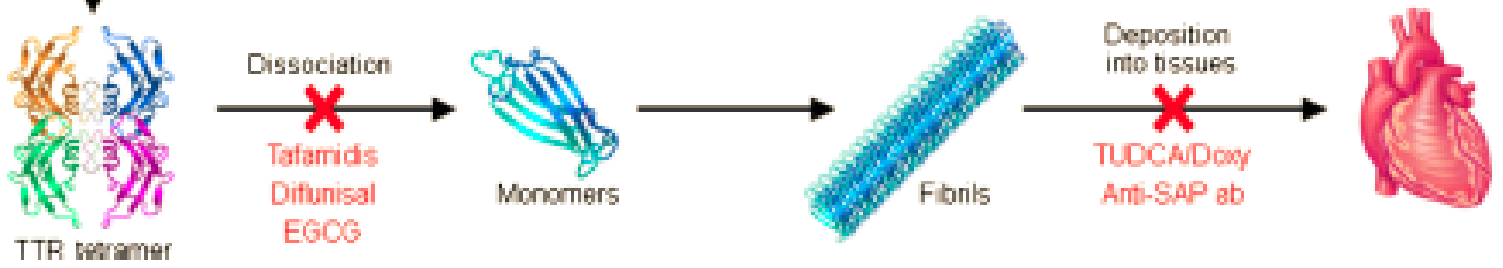
- Bind to the TTR tetramer and prevent its dissociation into monomers
  - Tafamidis
  - Diflunisal
  - AG10

ATTR Pharmacologic Therapies

Liver



Circulation



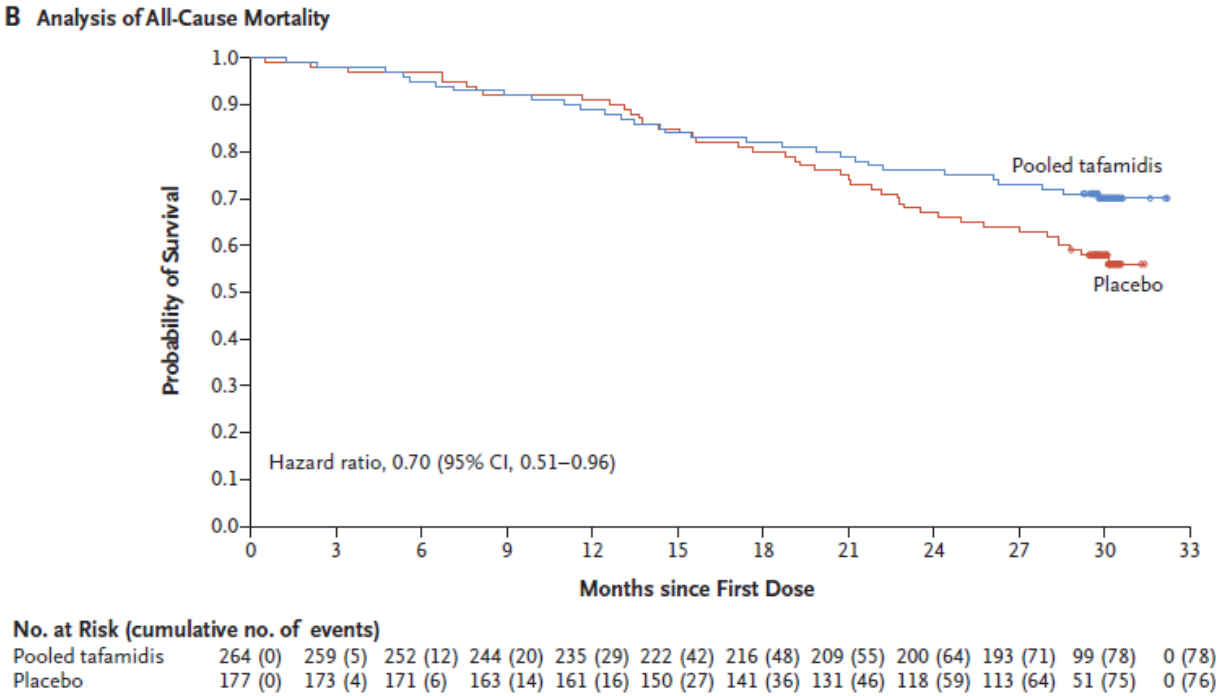
End-organs

Stabilizers

Vranian et al. Curr Cardiol Rep 2015;17:100

Tafamidis

- Once daily oral dosing
- ATTR-ACT RCT (N=441) enrolled patients with mutant (25%) or wtATTR (75%) cardiac amyloidosis, Tafamidis vs placebo, 30 months FU
- **Significant ↓ all-cause mortality**
- Reduced decline in 6WMD, QoL
- Similar adverse events b/w groups
- Under Health Canada review
  - FDA approval Monday



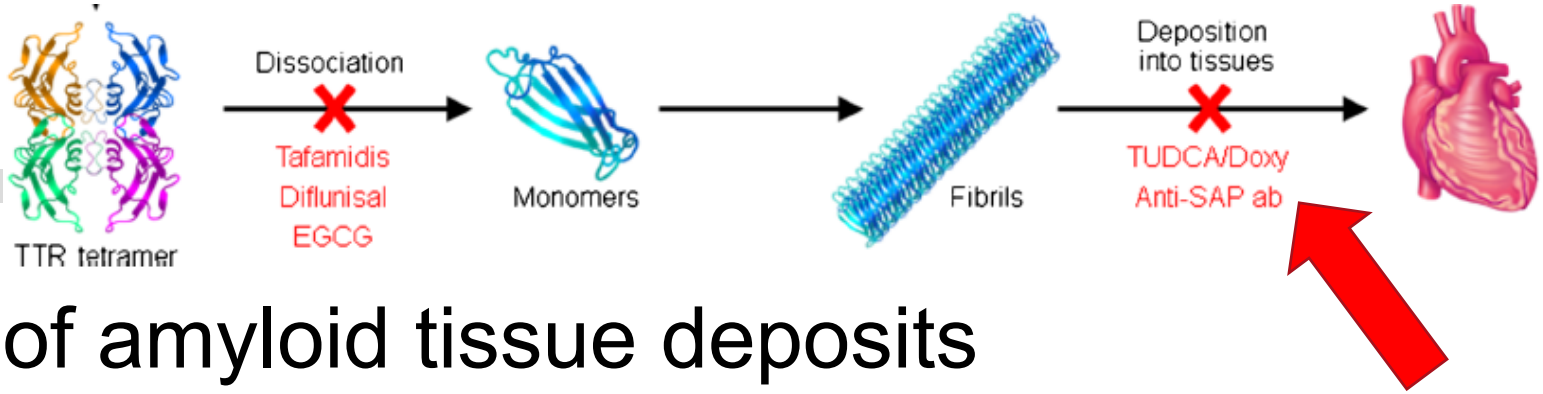
Maurer et al. NEJM 2018;379(11):1007

TTR Stabilizers

- **Diflunisal**
  - NSAID, twice daily oral dosing, limited cardiac data, no clear evidence of efficacy
  - Caution in patients with impaired renal function
  - Off-label use
- **AG10**
  - Twice daily oral dosing
  - Mimics stabilizing TTR mutation (T119M) – forms hydrogen bonds between serine residues on neighboring monomer
  - Well tolerated in phase II trial ATTR CA (N=49), 28 day FU
  - Normalized serum TTR levels
  - Phase III RCT starting

Castano et al. Congest Heart Fail 2012;310:2658
Judge et al. JACC 2019. In print.

ATTR Degraders

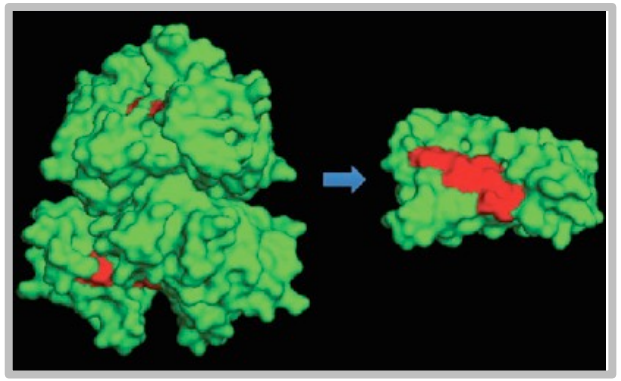


- Enhance resorption of amyloid tissue deposits
- **Doxycline Plus TUDCA/Ursodiol**
  - May attenuate disease progression
  - 10-15% intolerance, GI and derm
  - Off-label use
- **Epigallocatechin 3-gallate (EGCG, green tea extract)**
  - May attenuate disease progression
  - Well tolerated, rare GI side-effects

Vranian et al. Curr Cardiol Rep 2015;17:100
Obici et al. Amyloid 2012;19 (supple I):34
Karlstedt et al. J Card Fail 2019;25:147
Kristen et al. Clin Res Cardiol 2012;101:805
Cappelli et al. Intern Emerg Med 2018;12:873

Phase III RCTs for ATTR CA

- Inotersen
- Patisiran
- Vutrisiran
  - TTR silencer, siRNA, SC q 3 months
- AG10
- Doxy/TUDCA
- PRX004
  - Amyloid degrader, monoclonal Ab that binds to dissociated monomers, aggregates and amyloid deposits
  - Phase I trial



Higaki et al. Amyloid 2016;23:86

Summary

- Today there is no approved therapy for ATTR cardiac amyloidosis in Canada
  - **But not for long, the horizon is here!**
- Emerging therapeutic options act at different points in the TTR amyloidogenic cascade
  - ***Silencers*** – suppress TTR production
    - Inotersen, Patisiran – slow polyneuropathy progression, RCTs coming for CA
  - ***Stabilizers*** – stabilize TTR from dissociation
    - Tafamidis – survival benefit in ATTR CA
  - ***Degraders*** – reduce amyloid tissue deposit
    - Doxy/TUDCA, EGCG – role uncertain
- More therapies in development
- **Combination therapy??**

Promising Therapies On The Horizon For Treatment Of ATTR Amyloidosis

- Thank you
- Questions or comments?
- nmfine@ucalgary.ca

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