Jesselson Integrated Heart Center
Shaare Zedek Medical Center, Jerusalem

מרכז הלב המשולב ע"ש יסלזון
מרכז רפואי שערי צדק, ירושלים

THERAPIES FOR ATTR: TREATMENTS FOR TODAY, EMERGING TREATMENTS FOR TOMORROW

Prof. Tal Hasin
Director, HF Unit

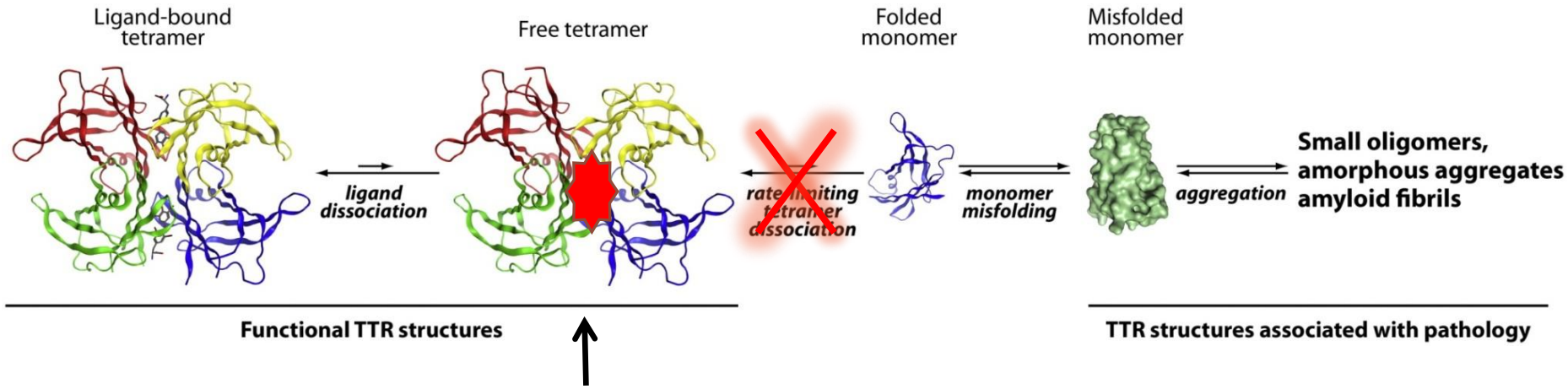
No relevant disclosures

AGENDA

- Case
- Treatment options
- Tafamidis- expanding population
- New medications

A 93 YEAR OLD FRAIL WOMEN WITH ATTR-CM

- w+3 alert, fully dependent (walker)
- Arthritis, HTN, s/p CTS
- 1yr dyspnea, edema, 3 HF hospitalizations, NYHA (???)
- Wt 40kg, Ht 130cm, frail
- Echocardiography: LV 2.8/1.7, preserved EF, walls 2.3/1.8
- Troponin 500-800, BNP 700
- DPD +2, Kappa/Lambda 1.86
- Negative genetic testing


Ligand-bound tetramer
Free tetramer
Folded monomer
Misfolded monomer
ligand dissociation
rate limiting tetramer dissociation
monomer misfolding
aggregation
Small oligomers, amorphous aggregates amyloid fibrils
Functional TTR structures
TTR structures associated with pathology

Tafamidis

INITIATE TAFAMIDIS (VYNDAMAX)?

"First we'll find out if your insurance covers the magic wand treatment."

European Heart Journal (2015) **36**, 2585–2594
doi:10.1093/eurheartj/ehv338

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*

[1]Heart Failure and Inherited Cardiac Diseases Unit, Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, Manuel de Falla, 2, Majadahonda, Madrid 28222,

- 120 patients, age ≥60 years, admitted for HFpEF (LVEF≥50%) with LVH (≥12mm by echocardiography).
- Prospectively screened for ATTR cardiac amyloidosis by Tc-DPD scintigraphy.
- 16 pts (13%) diagnosed of ATTR cardiac amyloidosis.
- **Mean age 82 ± 8** years, 59% women.

ESC European Society of Cardiology
European Heart Journal (2017) 38, 2879–2887
doi:10.1093/eurheartj/ehx350

CLINICAL RESEARCH
Heart failure/cardiomyopathy

המרכז הרפואי שערי צדק
SHAARE ZEDEK MEDICAL CENTER

Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement

Adam Castaño[1,2]*, David L. Narotsky[1], Nadira Hamid[3], Omar K. Khalique[3], Rachelle Morgenstern[2], Albert DeLuca[2], Jonah Rubin[1], Codruta Chiuzan[4], Tamim Nazif[3], Torsten Vahl[3], Isaac George[3], Susheel Kodali[3], Martin B. Leon[3], Rebecca Hahn[3], Sabahat Bokhari[2], and Mathew S. Maurer[1]

[1]Division of Cardiology, Department of Internal Medicine, Center for Advanced Cardiac Care, Columbia University Medical Center, 622 W 168 St, P.H. 12-1291, New York, NY

- 151 patients with severe symptomatic aortic stenosis undergoing TAVR
- Prospectively screened for ATTR cardiac amyloidosis by Tc-PYP scintigraphy, echocardiography, strain imaging
- 24 pts (16%) diagnosed of ATTR cardiac amyloidosis
- Cardiac amyloidosis was significantly associated with the low-flow low-gradient phenotype
- **mean age 84 ± 6 years**, 68% men

The NEW ENGLAND JOURNAL of MEDICINE

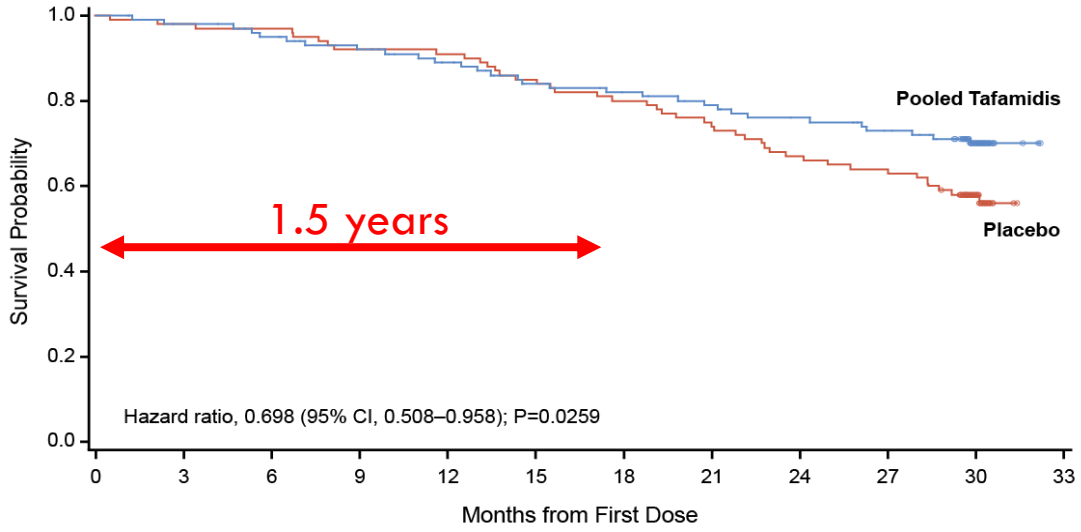
ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

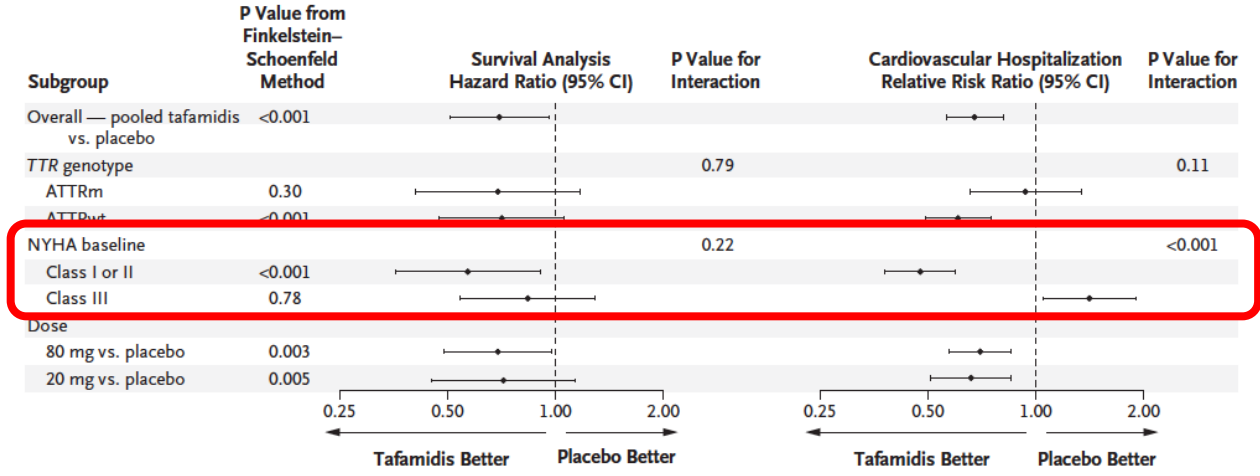
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

- 441 pts with symptomatic ATTR cardiac amyloidosis (76% wt)
- Randomized in 2:1:2 ratio to tafamidis 80mg, tafamidis 20mg and placebo for 30 months
- Age 18-90, **median age 75yr, 90% males**

ATTR-ACT RESULTS, MORTALITY

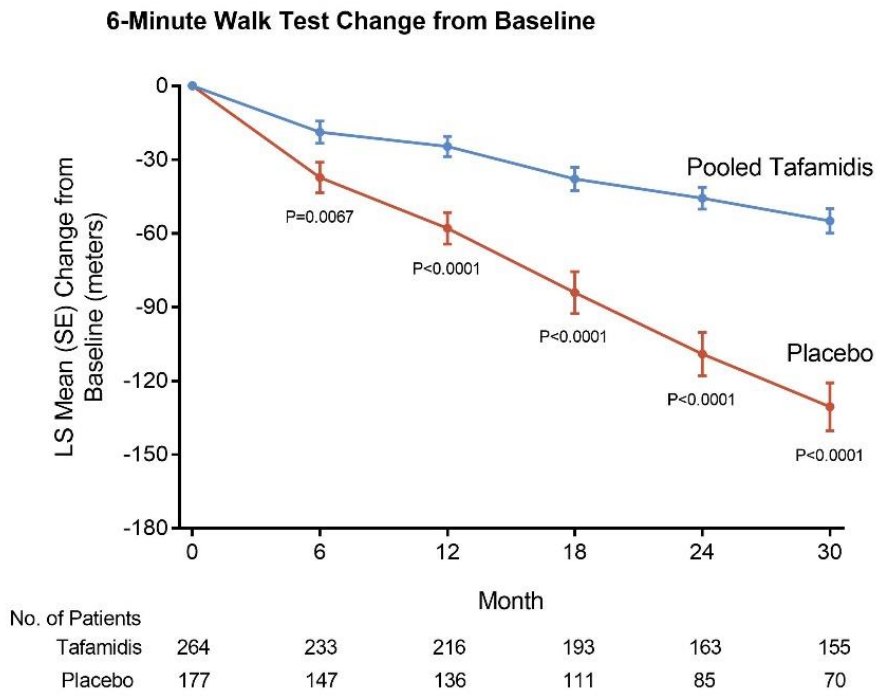


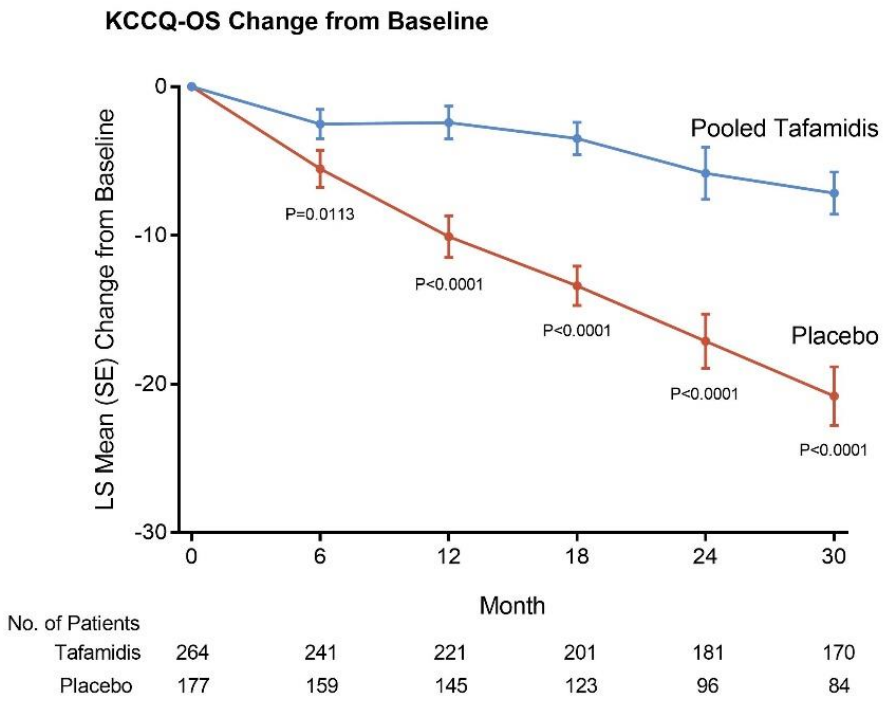


Maurer MS, et al. N Engl J Med. 2018 Aug 27

ATTR-ACT RESULTS, QOL

Immediate benefit!





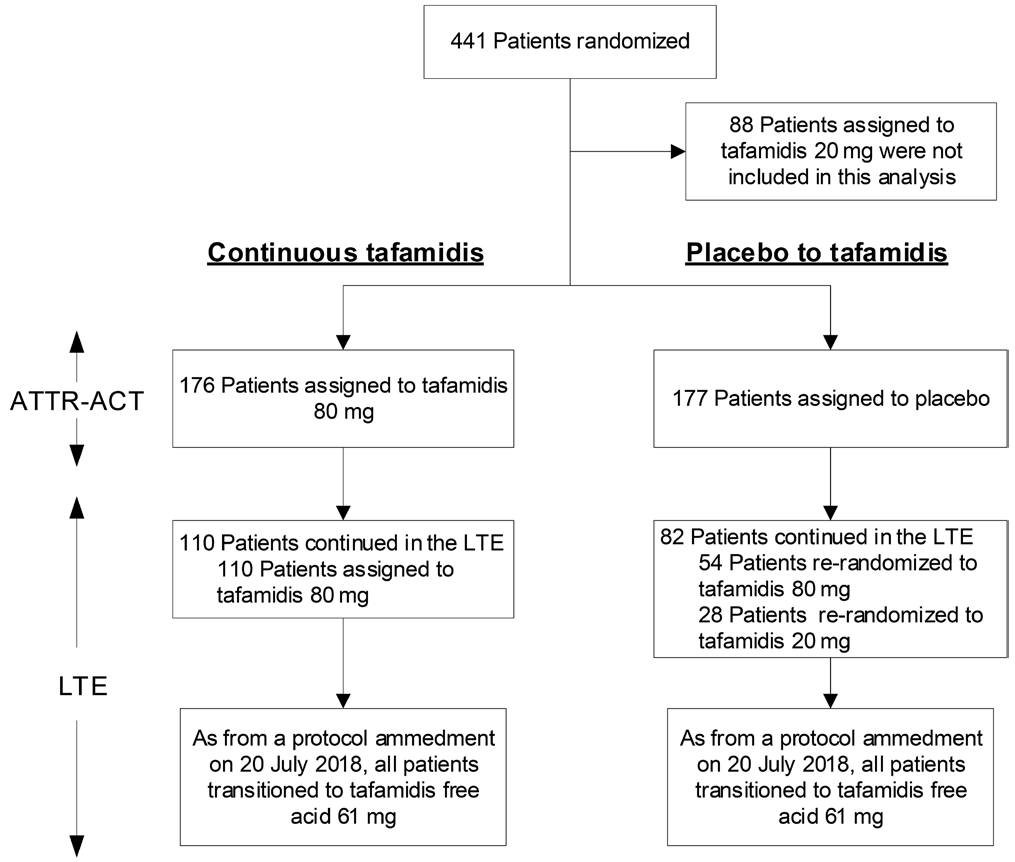
Maurer MS, et al. N Engl J Med. 2018 Aug 27

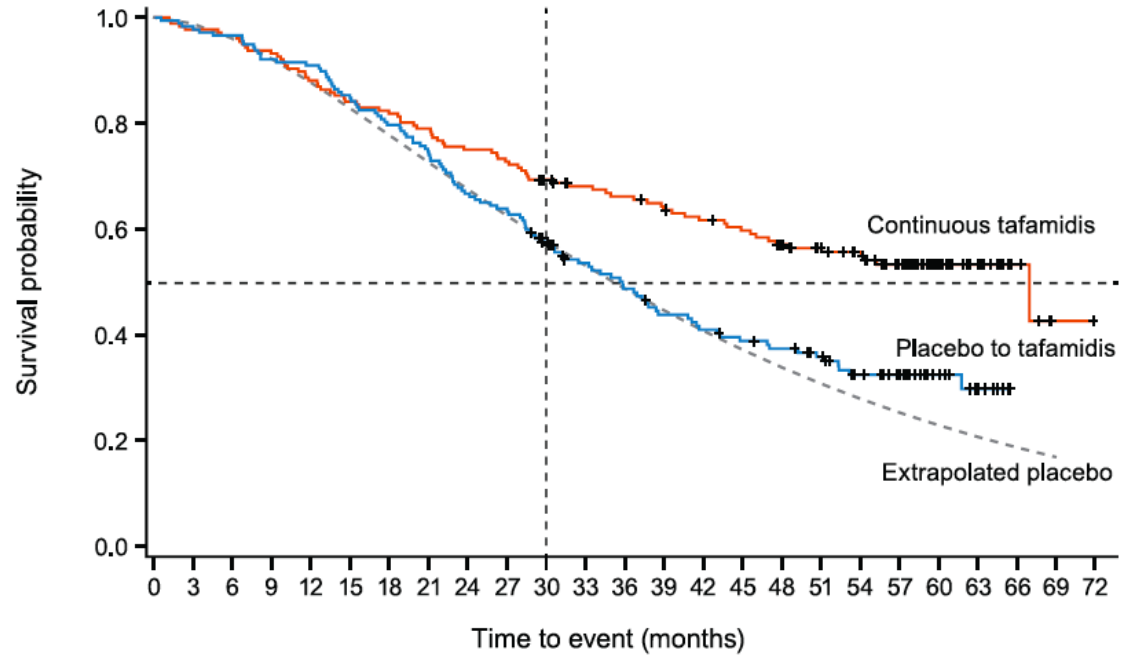
BACK TO THE PATIENT

- Now 95yr, still frail
- In 2 years 5 hospitalizations (UTI, Cellulitis, elective cataract, CVA, COVID-19+AF and ARF), no HF events
- Echocardiography

	05.2020	06.2022
LV end diastolic	2.8	4.1
LV end systolic	1.7	3.0
Septum	2.3	1.5
Free wall	1.8	1.4

ATTR-ACT EXTENDED PROTOCOL





Patients remaining at risk (cumulative events)

Continuous tafamidis	176 (0)	172 (4)	170 (6)	164 (12)	155 (21)	148 (28)	144 (32)	139 (37)	132 (44)	128 (48)	117 (54)	107 (56)	104 (59)	99 (63)	95 (66)	91 (69)	85 (73)	78 (74)	72 (75)	56 (78)	30 (78)	17 (78)	6 (78)	1 (79)	0 (79)
Placebo to tafamidis	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	93 (75)	77 (81)	70 (88)	62 (95)	58 (99)	54 (102)	51 (104)	45 (106)	36 (110)	29 (110)	15 (110)	8 (111)	0 (111)	0 (111)	0 (111)

Elliott P. Circ-HF 2022

HEART FAILURE TREATMENT

- Diuretics, salt restriction (carefully)
- BB, ACEi usually not tolerated in AL (ATTR?)
- Hypotension- stockings, midodrine
- Maintain sinus as possible
- Anticoagulation?
  - Small A wave (<20cm/s)
  - <30-40cm/s LAA velocity
- ICDs?

NEUROHORMONAL BLOCKADE IN ATTR-CM

309 registry patients NYHA 1-4 (most 2-3), EF 45%

Baseline and time-varying use analysis

Neutral effect on mortality

Stopping BB may have a beneficial effect

Cheng R.K. JAHA 2021

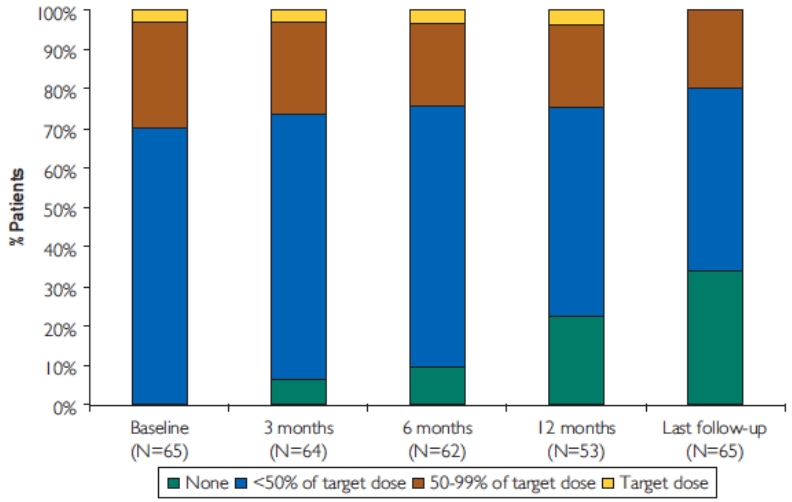
BETA BLOCKERS MAY BE PROTECTIVE IN ATTR-CM

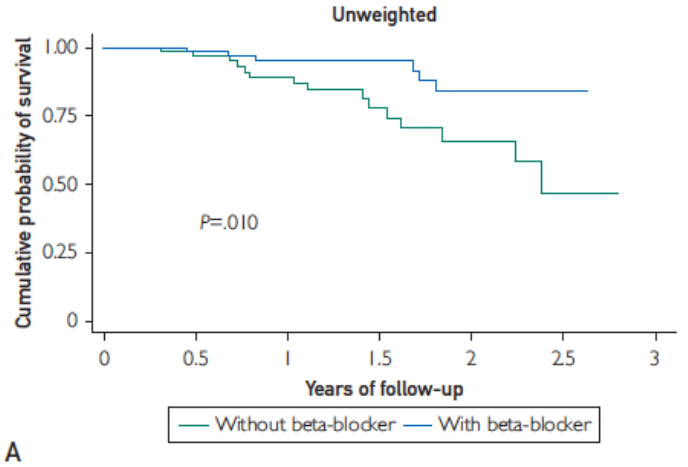
128 ATTR-CM registry, EF 53%, 53% on Tafamidis

63 without BB; 65 with BB (sicker)

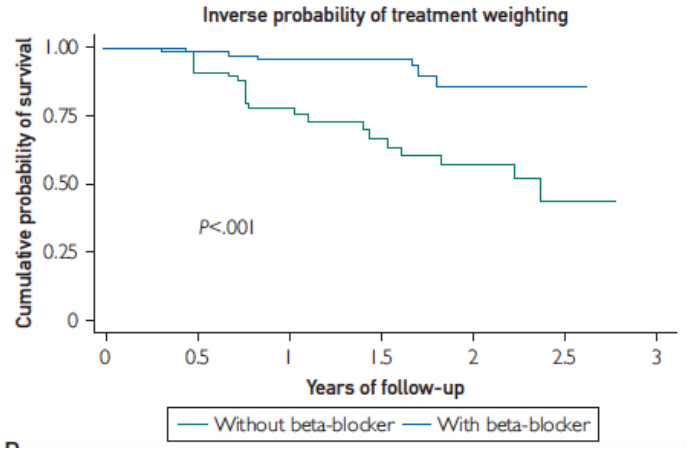
Low dose, 25% stopped BB

Lower mortality



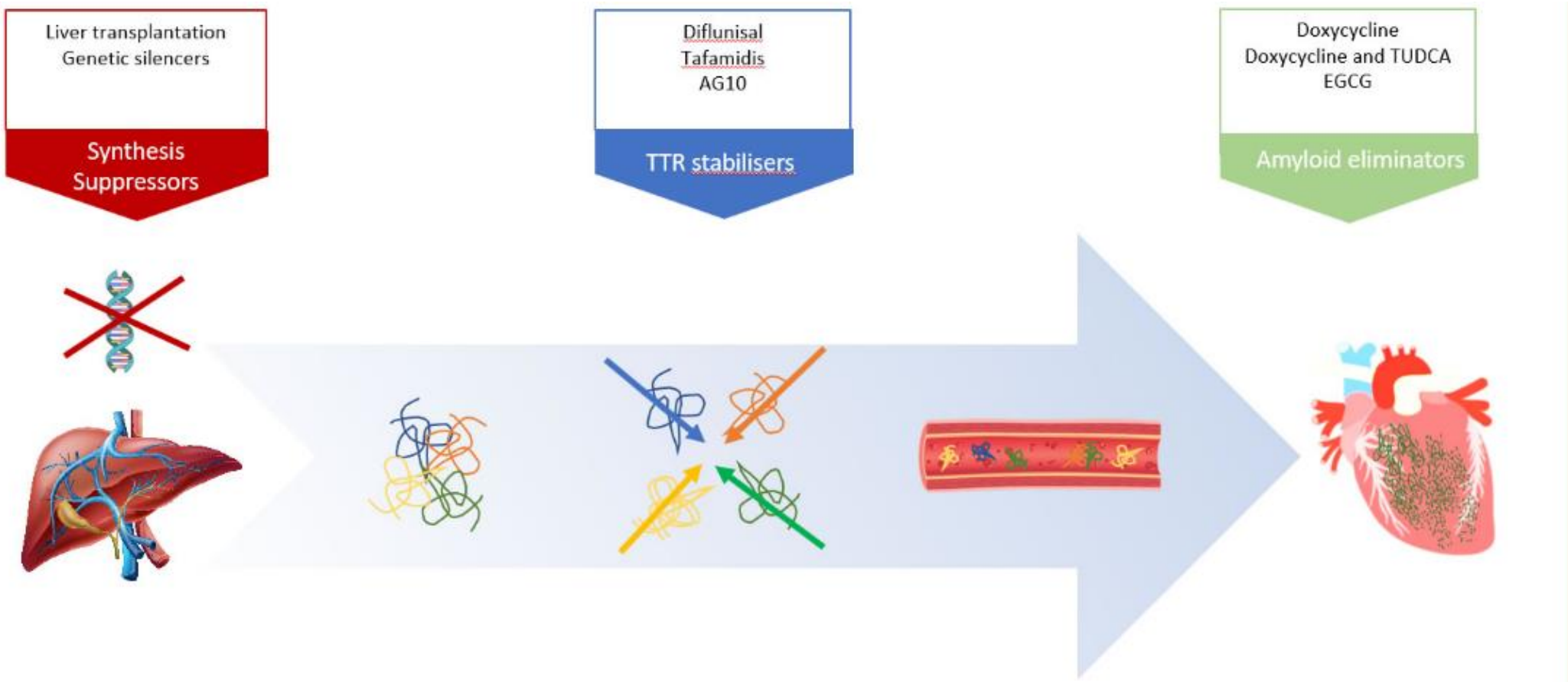


A



Barge-Caballero G. Mayo clinic proc. 2022: 97(2)

ATTR-CM, THERAPEUTIC SITES OF ACTION



The NEW ENGLAND JOURNAL of MEDICINE

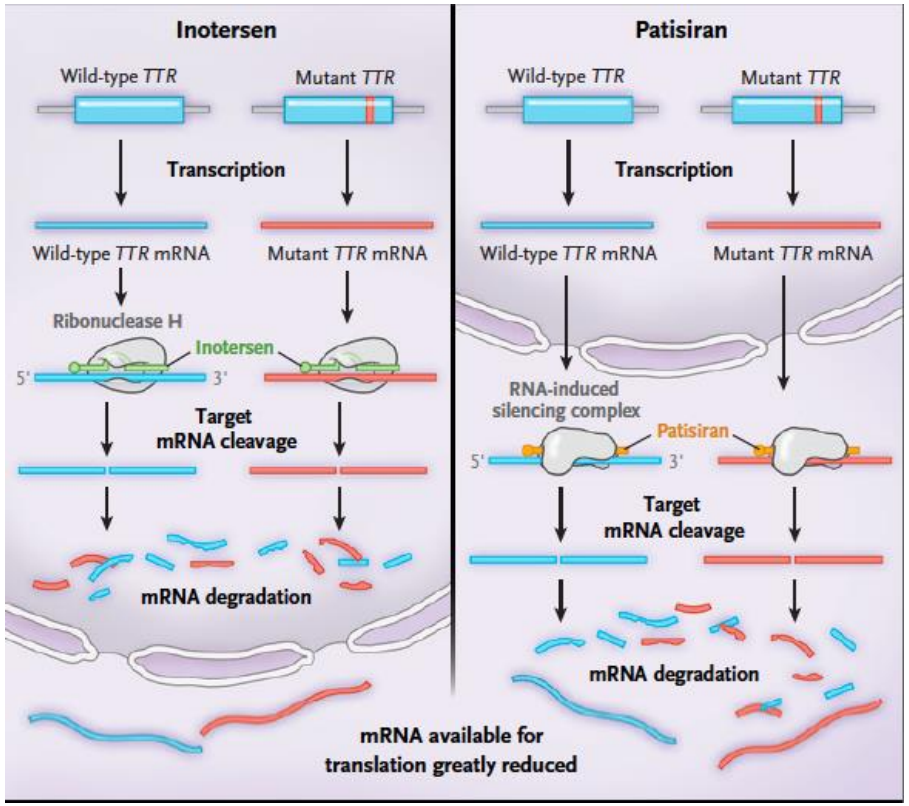
ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

OLIGONUCLEOTIDES TO DECREASE TTR SYNTHESIS

- Tested for hereditary TTR with polyneuropathy
- Reduce serum TTR by 71-81%
- Reduced neurological progression
- Thrombocytopenia with Inotersen, transfusion related with Patisiran



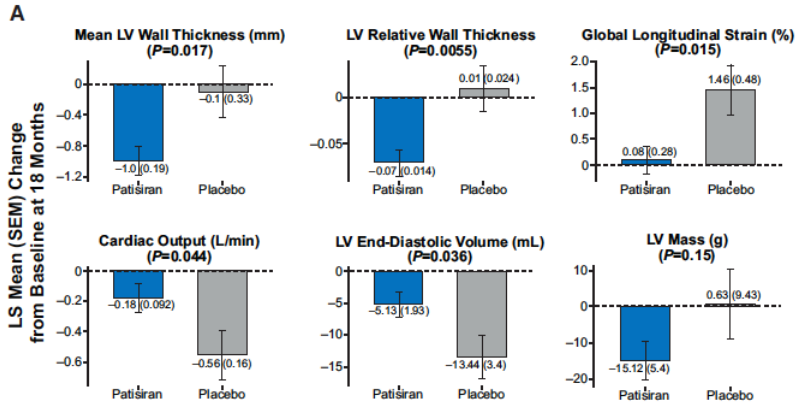
Benson M.D. NEJM 379(1) 2018
Adams D. NEJM 379(1) 2018

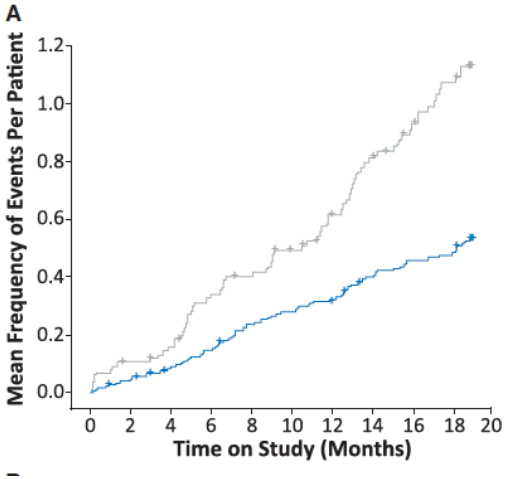
PATISIRAN (APOLLO) CARDIAC SUBSTUDY

In a **pre-specified cardiac subpopulation (n=126, 56%)**

LV wall thickness ≥13 mm; no HTN or AS
*reduced wall thickness
* improved global longitudinal strain
*increased cardiac output at month 18.
*Lowering of PRO-BNP as early as 9 month.

In a **post hoc exploratory analysis**, lower cardiac hospitalizations and/or all-cause death.





Solomon S. Circulation. 2019;139:431

DIFLUNISAL

- Nonsteroidal anti-inflammatory drug that has been repurposed as a TTR kinetic stabilizer
- Metanalysis: 400pts 6 trials 4 open-label, single-center studies, 2 compared to no Tx.
- generally well tolerated, GI and reversible renal dysfunction
- Improvements in: TTR concentration, left atrial volume index, cardiac troponin I, and global longitudinal strain. Overall decreased mortality and number of orthotopic heart transplant
- **Low cost**

Ibrahim M. HF reviews. 2022;27

AG-10

Selective TTR stabilizer

phase 2, randomized, double-blind, placebo-controlled

49 patients NYHA 2-3, ATTR-CM, (variant and wt)

AG10 (400 mg or 800mg per os twice daily for 28 days)

well tolerated, increased circulating TTR levels (considered as a positive effect, possibly linked to lower tissue deposition), and induced near-complete stabilization of TTR.

Phase 3 trial-

Judge, JACC (2019), 74 (3)

DOXYCYCLINE AND TAUROURSODEOXYCHOLIC ACID (TUDCA)

Tetracyclines, including doxycycline: disaggregation of amyloid fibres in vitro

The combination of doxycycline and tauroursodeoxycholic acid (TUDCA): more effective- complete amyloid clearance from tissues in animal models

In a small phase 2 trial, 28 patients with ATTR received doxycycline and TUDCA for 12months followed by a 6-month withdrawal period.

Results were modest and difficult to interpret because of a very high dropout rate (86%) due to treatment failure (expressed as >30% NT-proBNP increase), side effects and voluntary dropouts.

In a phase 2, open-label study, the treatment was well tolerated, and no progression of cardiac involvement and neuropathy was found in a preliminary analysis on 20 patients.

Emdin ET AL. European Heart Journal (2019) 0, 1–10

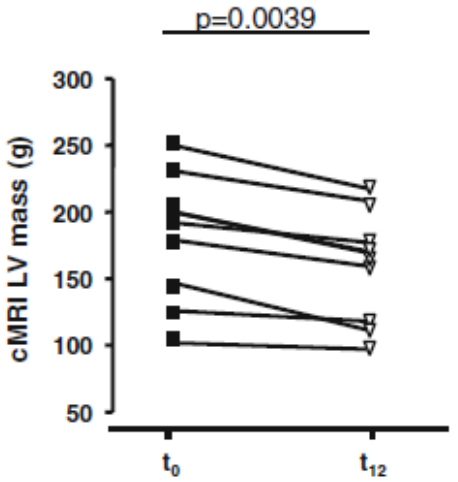
ECGC

Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea.

EGCG binds to soluble TTR decreasing the likelihood of tetramer dissociation, inhibits oligomer aggregation into amyloid fibres, thus promoting the disaggregation of TTR amyloid fibres.

In a single centre, open-label study, **30 patients** with cardiac ATTR (both variant and wt) received EGCG 675mg/day compared with 35 cardiac ATTR patients on HF supportive therapy over **12 months** of treatment

A mean **decrease of LV myocardial mass**, accompanied by an increase of mean mitral annular systolic velocity of % 9, suggests an inhibitory effect on the progression of cardiac amyloidosis. EGCG **did not improve survival**.



Kristen et al. Clin Res Cardiol (2012) 101:805–813

CONCLUSIONS

- Tafamidis improves ATTR-CM
- may be considered in frail nonagenarians
- benefit of routine HF treatment is debatable
- Novel treatments for TTR synthesis, stabilization and elimination are en-route
- Drink green tea (if you like it)


Thank you: HasintaI@gmail.com

המרכז הרפואי
שערי צדק
SHAARE ZEDEK
MEDICAL CENTER

י״ז אדר, תשפ״א
1 מרץ, 2021
מס׳: 3/2021

<u>הנדון: הרחבת סל שירותי הבריאות לשנת 2021</u>

64. הוראות לשימוש בתרופה TAFAMIDIS (Vyndamax)

א. התרופה תינתן לטיפול בחולים העונים על כל אלה:

1. קרדיומיופתיה מסוג wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM)
2. אבחנה של ATTR.

לעניין זה אבחנה של ATTR תקבע על פי שני התנאים הבאים:

א. קליניקה אופיינית ובדיקות דימות (אקו או MRI)

ב. קליטה דרגה 2 או 3 במיפוי עם bone-seeking tracers .

במידה ושני התנאים דלעיל לא מתקיימים במלואם וקיים חשד קליני משמעותי יש להמשיך לבירור בביופסיה והאבחנה תקבע על פיה.

3. דרגות תפקוד NYHA 1 או NYHA 2.

ב. מתן התרופה ייעשה לפי מרשם של רופא מומחה בקרדיולוגיה.