Review of the new cardio literature

Disclosures

Hippocrates refusing the gift of Artaxerxes by Anne-Louis Girodet 1792

Disclosure

- Speaker has no conflict of interest

Learning objectives

- As a result of attending this session, participants will be able to:
  - Recognize new developments in the field of cardiology
  - Review the evidence for colchicine and omega-3s in CVD protection
  - Identify situations in which NOAC use is appropriate in valvular a.fib
  - Recognize the role of the placebo effect in patients complaining of statin side effects
  - Recognize the equivalence of ticagrelor and clopidogrel in some clinical situations
  - Find true happiness in their lives

What's new in cardiology?

- (Relatively) new studies:
  - Colchicine for cardiac disease
  - High dose Omega-3s
  - Anti-coagulating valvular a.fib
  - Side-effects of statins
  - Polypill for treating CAD
  - Alpheus – Ticagrelor vs. Clopidogrel post PCI

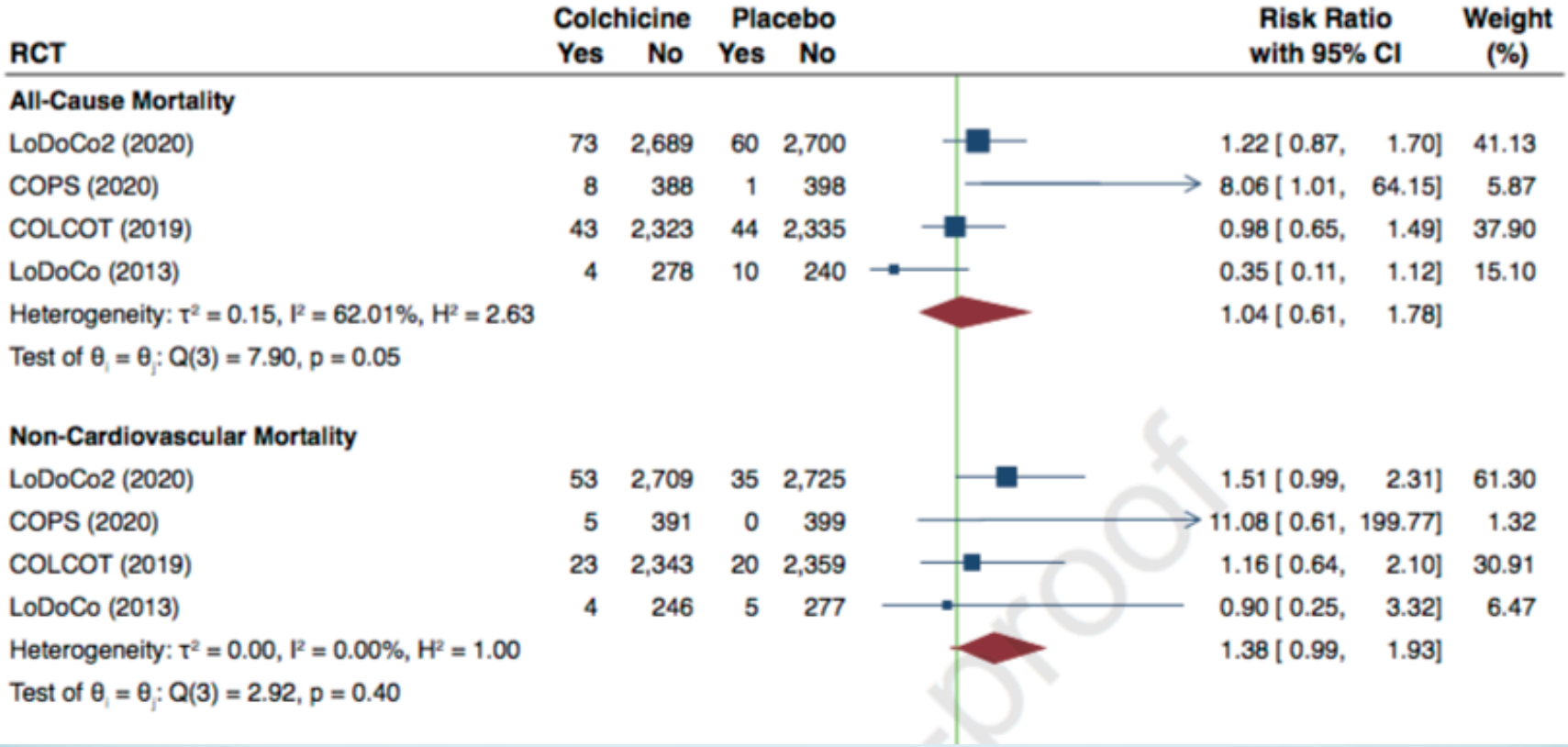
Colchicine for CAD

- 4 trials
  - COLCOT
    - Post ACS patients
    - No mortality benefit, no reduction in MI
    - Benefit in stroke and angina leading to angiography
  - COPS
    - Post ACS patients
    - Increased risk of mortality with colchicine
    - No benefit in stroke
    - Less revascularization

Colchicine for CAD

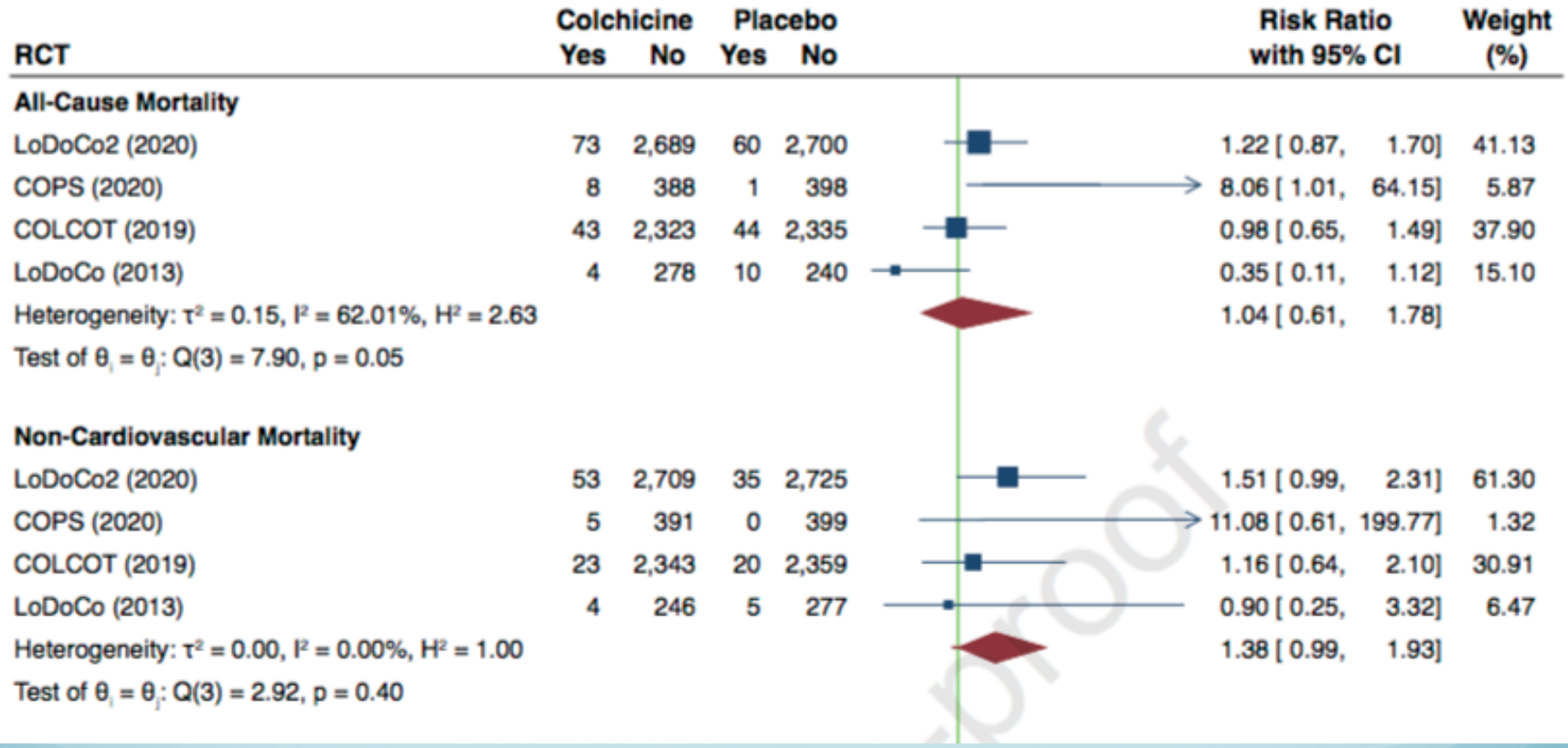
- LoDoCo2
  - Chronic CAD
  - Reduced MI but not stroke
  - Reduced CV death, but increased not CV death
- LoDoCo
  - Open label precursor of LoDoCo2

Colchicine for CAD



From: Samuel et al. Canadian Journal of Cardiology (2020). https://doi.org/10.1016/j.cjca.2020.10.006

Colchicine for CAD



RCT	Colchicine Yes	Colchicine No	Placebo Yes	Placebo No	Risk Ratio with 95% CI	Weight (%)
All-Cause Mortality						
LoDoCo2 (2020)	73	2,689	60	2,700	1.22 [0.87, 1.70]	41.13
COPS (2020)	8	388	1	398	8.06 [1.01, 64.15]	5.87
COLCOT (2019)	43	2,323	44	2,335	0.98 [0.65, 1.49]	37.90
LoDoCo (2013)	4	278	10	240	0.35 [0.11, 1.12]	15.10
Heterogeneity: $\tau^2 = 0.15$, $I^2 = 62.01\%$, $H^2 = 2.63$					1.04 [0.61, 1.78]	
Test of $\theta_i = \theta_j$: Q(3) = 7.90, p = 0.05						
Non-Cardiovascular Mortality						
LoDoCo2 (2020)	53	2,709	35	2,725	1.51 [0.99, 2.31]	61.30
COPS (2020)	5	391	0	399	11.08 [0.61, 199.77]	1.32
COLCOT (2019)	23	2,343	20	2,359	1.16 [0.64, 2.10]	30.91
LoDoCo (2013)	4	246	5	277	0.90 [0.25, 3.32]	6.47
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					1.38 [0.99, 1.93]	
Test of $\theta_i = \theta_j$: Q(3) = 2.92, p = 0.40						

Colchicine for CAD

- Great enthusiasm by some
- Restrained ambivalence by others
- Future trials will likely settle uncertainty

Omega-3s for CVD

- Reduce-IT trial – NEJM 2019
  - High dose EPA
  - Less MI and CV death
    - But…
  - More atrial fibrillation
  - More bleeding
- STRENGTH trial – JAMA Nov 2020
  - Presented this month at AHA
  - High dose EPA/DHA omega-3
  - Stopped early for futility – no benefit

Original Investigation

March 2018

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77917 Individuals

Theingi Aung, MBBS, FRCP[1,2,3]; Jim Halsey, BSc[1,2]; Daan Kromhout, PhD[4]; et al

» Author Affiliations | Article Information

JAMA Cardiol. 2018;3(3):225-233. doi:10.1001/jamacardio.2017.5205

Related Articles

Multimedia

Key Points

Question Does supplementation with marine-derived omega-3 fatty acids have any associations with reductions in fatal or nonfatal coronary heart disease in people at high risk of cardiovascular disease?

Findings This meta-analysis of 10 trials involving 77 917 participants demonstrated that supplementation with marine-derived omega-3 fatty acids for a mean of 4.4 years had no significant association with reductions in fatal or nonfatal coronary heart disease or any major vascular events.

Meaning The results provide no support for current recommendations to use omega-3 fatty acid supplements for the prevention of fatal coronary heart disease or any cardiovascular disease in people who have or at high risk of developing cardiovascular disease.

Omega-3s for CVD

- Benefit for omega-3s unclear
  - Not simply a dose issue
  - Would need to assume that
    - EPA is beneficial
    - DHA is harmful
    - They perfectly balance each other out

Valvular A.fib

From 2014 CCS A.fib guidelines

Table 5. Expert opinion survey regarding the clinical use of a NOAC in relation to the following commonly encountered scenarios: Would you consider NOAC use to be: (1) contraindicated or (2) not contraindicated (ie, reasonable to use) with the following valvular disorders?

NOAC use is contraindicated	NOAC use is reasonable
Mechanical heart valves • In any position (100% agreement)	**Bioprosthetic heart valve** • Aortic position (82% agreement) • Mitral position (73% agreement)
Rheumatic mitral stenosis • Mild (47% agreement) • Moderate-severe (88% agreement) • After commissurotomy (42% agreement)	**Mitral annuloplasty** • With or without prosthetic ring (88% agreement) **Nonrheumatic mitral stenosis** • Mild (97% agreement) **Mitral regurgitation** • _Mild (97% agreement) • Moderate-severe (>90% agreement) **Tricuspid regurgitation** • Any severity (98% agreement)
Non-rheumatic mitral stenosis • Moderate or severe (69% agreement)	**Aortic stenosis or regurgitation** • Mild (98% agreement) • Moderate to severe (80% agreement)

NOAC, novel non-vitamin K antagonist.

ORIGINAL ARTICLE FREE PREVIEW

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

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November 14, 2020
DOI: 10.1056/NEJMoa2029603

Abstract

BACKGROUND The effects of rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve remain uncertain.

METHODS In this randomized trial, we compared rivaroxaban (20 mg once daily) with dose-adjusted warfarin (target international normalized ratio, 2.0 to 3.0) in patients with atrial fibrillation and a bioprosthetic mitral valve. The primary outcome was a composite of death, major cardiovascular events (stroke, transient ischemic attack, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months.

RESULTS A total of 1005 patients were enrolled at 49 sites in Brazil. A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference calculated as restricted mean survival time, 7.4 days; 95% confidence interval [CI], −1.4 to 16.3; P<0.001 for noninferiority). Death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20). The incidence of stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI, 0.07 to 0.88). Major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35). The frequency of other serious adverse events was similar in the two groups.

CONCLUSIONS In patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months. (Funded by PROADI-SUS and Bayer; RIVER ClinicalTrials.gov number, NCT02303795.)

Statin side effects

CORRESPONDENCE

N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects

TO THE EDITOR:

Statins are often discontinued because of side effects,[1,2] even though some blinded trials have not shown an excess of symptoms with statins as compared with placebo.[3,4] Patients who had previously discontinued statins because of side effects that occurred within 2 weeks after the initiation of treatment were enrolled in a double-blind, three-group, n-of-1 trial to test whether symptoms would be induced by a statin or placebo. Details of the trial methods are provided in Section S2 in the Supplementary Appendix (available with the full text of this letter at NEJM.org); the trial protocol and statistical analysis plan are also available at NEJM.org.

The patients received four bottles containing atorvastatin at a dose of 20 mg, four bottles containing placebo, and four empty bottles; each bottle was to be used for a 1-month period according to a random sequence. The patients used a smartphone application to report symptom intensity daily. Symptom scores ranged from 0 (no symptoms) to 100 (worst imaginable symptoms). If the patients determined that their symptoms were unacceptably severe, they could discontinue the tablets for that month.

The primary end point was symptom intensity as assessed with the use of the nocebo ratio (i.e., the ratio of symptom intensity induced by taking placebo to the symptom intensity induced by taking a statin). This ratio was calculated as the symptom intensity with placebo minus the symptom

November 15, 2020
DOI: 10.1056/NEJMc2031173
Metrics

ORIGINAL ARTICLE FREE PREVIEW

Polypill with or without Aspirin in Persons without Cardiovascular Disease

Salim Yusuf, D.Phil., Philip Joseph, M.D., Antonio Dans, M.D., Peggy Gao, M.Sc., Koon Teo, Ph.D., Denis Xavier, M.D., Patricio López-Jaramillo, Ph.D., Khalid Yusoff, M.B., B.S., Anwar Santoso, Ph.D., Habib Gamra, M.D., Shamim Talukder, M.B., B.S., Courtney Christou, B.Sc., et al., for the International Polycap Study 3 Investigators*

November 13, 2020
DOI: 10.1056/NEJMoa2028220

Abstract

BACKGROUND A polypill comprising statins, multiple blood-pressure–lowering drugs, and aspirin has been proposed to reduce the risk of cardiovascular disease.

METHODS Using a 2-by-2-by-2 factorial design, we randomly assigned participants without cardiovascular disease who had an elevated INTERHEART Risk Score to receive a polypill (containing 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril) or placebo daily, aspirin (75 mg) or placebo daily, and vitamin D or placebo monthly. We report here the outcomes for the polypill alone as compared with matching placebo, for aspirin alone as compared with matching placebo, and for the polypill plus aspirin as compared with double placebo. For the polypill-alone and polypill-plus-aspirin comparisons, the primary outcome was death from cardiovascular causes, myocardial infarction, stroke, resuscitated cardiac arrest, heart failure, or revascularization. For the aspirin comparison, the primary outcome was death from cardiovascular causes, myocardial infarction, or stroke. Safety was also assessed.

RESULTS A total of 5713 participants underwent randomization, and the mean follow-up was 4.6 years. The low-density lipoprotein cholesterol level was lower by approximately 19 mg per deciliter and systolic blood pressure was lower by approximately 5.8 mm Hg with the polypill and with combination therapy than with placebo. The primary outcome for the polypill comparison occurred in 126 participants (4.4%) in the polypill group and in 157 (5.5%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.63 to 1.00). The primary outcome for the aspirin comparison occurred in 116 participants (4.1%) in the aspirin group and in 134 (4.7%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.67 to 1.10). The primary outcome for the polypill-plus-aspirin comparison occurred in 59 participants (4.1%) in the combined-treatment group and in 83 (5.8%) in the double-placebo group (hazard ratio, 0.69; CI, 0.50 to 0.97). The incidence of hypotension or dizziness was higher in groups that received the polypill than in their respective placebo groups.

CONCLUSIONS Combined treatment with a polypill plus aspirin led to a lower incidence of cardiovascular events than did placebo among participants without cardiovascular disease who were at intermediate cardiovascular risk. (Funded by the Wellcome Trust and others; TIPS-3 ClinicalTrials.gov number, NCT01646437.)

Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial

*Johanne Silvain, Benoit Lattuca, Farzin Beygui, Grégoire Rangé, Zuzana Motovska, Jean-Guillaume Dillinger, Ziad Boueri, Philippe Brunel, Thibault Lhermusier, Christophe Pouillot, Elisa Larrieu-Ardilouze, Franck Boccara, Jean-Noël Labeque, Paul Guedeney, Mohamad El Kasty, Mikael Laredo, Raphaëlle Dumaine, Grégory Ducrocq, Jean-Philippe Collet, Guillaume Cayla, Katrien Blanchart, Petr Kala, Eric Vicaut, Gilles Montalescot, on behalf of the ALPHEUS investigators**

Summary

Background Percutaneous coronary intervention (PCI)-related myonecrosis is frequent and can affect the long-term prognosis of patients. To our knowledge, ticagrelor has not been evaluated in elective PCI and could reduce periprocedural ischaemic complications compared with clopidogrel, the currently recommended treatment. The aim of the ALPHEUS study was to examine if ticagrelor was superior to clopidogrel in reducing periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI.

Methods The ALPHEUS study, a phase 3b, randomised, open-label trial, was done at 49 hospitals in France and Czech Republic. Patients with stable coronary artery disease were eligible for the study if they had an indication for PCI and at least one high-risk characteristic. Eligible patients were randomly assigned (1:1) to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter for 30 days) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter for 30 days) by use of an interactive web response system, and stratified by centre. The primary outcome was a composite of PCI-related type 4 (a or b) myocardial infarction or major myocardial injury and the primary safety outcome was major bleeding, both of which were evaluated within 48 h of PCI (or at hospital discharge if earlier). The primary analysis was based on all events that occurred in the intention-to-treat population. The trial was registered with ClinicalTrials.gov, NCT02617290.

Findings Between Jan 9, 2017, and May 28, 2020, 1910 patients were randomly assigned at 49 sites, 956 to the ticagrelor group and 954 to the clopidogrel group. 15 patients were excluded from the ticagrelor group and 12 from the clopidogrel group. At 48 h, the primary outcome was observed in 334 (35%) of 941 patients in the ticagrelor group and 341 (36%) of 942 patients in the clopidogrel group (odds ratio [OR] 0·97, 95% CI 0·80–1·17; p=0·75). The primary safety outcome did not differ between the two groups, but minor bleeding events were more frequently observed with ticagrelor than clopidogrel at 30 days (105 [11%] of 941 patients in the ticagrelor group *vs* 71 [8%] of 942 patients in the clopidogrel group; OR 1·54, 95% CI 1·12–2·11; p=0·0070).

Interpretation Ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis after elective PCI and did not cause an increase in major bleeding, but did increase the rate of minor bleeding at 30 days. These

Published Online November 14, 2020 https://doi.org/10.1016/S0140-6736(20)32236-4

*A complete list of the ALP investigators is provided in appendix

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Other not really new stuff

Amyloidosis

ORIGINAL ARTICLE

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., et al., for the ATTR-ACT Study Investigators*

September 13, 2018
N Engl J Med 2018; 379:1007-1016
DOI: 10.1056/NEJMoa1805689
Chinese Translation 中文翻译

Abstract

BACKGROUND

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.

METHODS

In a multicenter, international, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 441 patients with transthyretin amyloid cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. In the primary analysis, we hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations according to the Finkelstein–Schoenfeld method. Key secondary end points were the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), in which higher scores indicate better health status.

Related Articles

EDITORIAL SEP 13, 2018
Stabilizing Transthyretin to Treat ATTR Cardiomyopathy
C.C. Quarta and S.D. Solomon

CORRESPONDENCE JAN 10, 2019
Tafamidis for Transthyretin Amyloid Cardiomyopathy