Causes of Cardiovascular Hospitalization and Death in Patients With Transthyretin Amyloid Cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial [ATTR-ACT])

Alan B. Miller, MD[a,*], James L. Januzzi, MD[b], Blair J. O'Neill, MD[c], Balarama Gundapaneni, MS[d], Terrell A. Patterson, PhD[d], Marla B. Sultan, MD, MBA[e], and José López-Sendón, MD, PhD[f]

In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), tafamidis significantly reduced mortality and cardiovascular (CV)-related hospitalizations compared with placebo in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). This analysis aimed to assess the causes of CV-related death and hospitalization in ATTR-ACT to provide further insight into the progression of ATTR-CM and efficacy of tafamidis. ATTR-ACT was an international, double-blind, placebo-controlled, and randomized study. Patients with hereditary or wild-type ATTR-CM were randomized to tafamidis (n = 264) or placebo (n = 177) for 30 months. The independent Endpoint Adjudication Committee determined whether certain investigator-reported events met the definition of disease-related efficacy endpoints using predefined criteria. Cause-specific reasons for CV-related deaths (heart failure [HF], arrhythmia, myocardial infarction, sudden death, stroke, and other CV causes) and hospitalizations (HF, arrhythmia, myocardial infarction, transient ischemic attack/stroke, and other CV causes) were assessed. Total CV-related deaths was 53 (20.1%) with tafamidis and 50 (28.2%) with placebo, with HF (15.5% tafamidis, 22.6% placebo), followed by sudden death (2.7% tafamidis, 5.1% placebo), the most common causes. The number of patients with a CV-related hospitalization was 138 (52.3%) with tafamidis and 107 (60.5%) with placebo; with HF the most common cause (43.2% tafamidis, 50.3% placebo). All predefined causes of CV-related death or hospitalization were less frequent with tafamidis than placebo. In conclusion, these data provide further insight into CV disease progression in patients with ATTR-CM, with HF the most common adjudicated cause of CV-related hospitalization or death in ATTR-ACT.
Clinical trial registration ClinicalTrials.gov: NCT01994889. **© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)** **(Am J Cardiol 2021;148:146−150)**

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive cardiac disease leading to death within a few years, typically due to cardiac causes including heart failure (HF) and sudden death.[1-4] ATTR-CM remains both underdiagnosed and misdiagnosed.[5,6] Greater awareness of ATTR-CM, and what to expect during the course of the disease, could aid earlier diagnosis and improve treatment, which is crucial to facilitate effective patient care.[6] In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), tafamidis significantly reduced mortality and cardiovascular (CV)-related hospitalizations compared with placebo in patients with ATTR-CM.[7] All-cause mortality was significantly lower with tafamidis (29.5%) than with placebo (42.9%), as was the rate of CV-related hospitalization (0.48 per year with tafamidis compared with 0.70 per year with placebo).[7] There was also a reduction in all-cause mortality with tafamidis in patients with less and more severe disease and both hereditary and wild-type ATTR-CM.[8] Further information on the causes of hospitalization and death may help guide physicians on what to expect when treating patients with ATTR-CM. We therefore evaluated the causes of CV-related deaths and hospitalizations in ATTR-ACT.

Methods

ATTR-ACT was a phase 3, multicenter, international, 3-arm, parallel-design, placebo-controlled, double-blind, randomized study for which the design has been previously published (NCT01994889).[7,9] Briefly, those eligible to enroll were patients aged ≥18 and ≤90 years with a diagnosis of ATTR-CM defined by the presence of either variant *TTR* (ATTRv), or wild-type amyloid (ATTRwt) and a medical history of HF with at least 1 prior hospitalization due to HF, or clinical signs and symptoms associated with HF

[a]Department of Medicine, University of Florida Cardiovascular Center, Jacksonville, Florida; [b]Massachusetts General Hospital, Baim Institute for Clinical Research, Boston, Massachusetts; [c]University of Alberta, Edmonton, Alberta, Canada; [d]Pfizer Inc, Groton, Connecticut; [e]Pfizer Inc, New York, New York; and [f]Hospital Universitario La Paz, IdiPaz, CIBER-CV, Madrid, Spain. Manuscript received November 15, 2020; revised manuscript received and accepted February 26, 2021.

This study was sponsored by Pfizer.

See page 149 for disclosure information.

*Corresponding author: Tel: (904) 244-8232.
E-mail address: alan.miller@jax.ufl.edu (A.B. Miller).

0002-9149/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

https://doi.org/10.1016/j.amjcard.2021.02.035

(volume overload or elevated intracardiac pressures) that required treatment with a diuretic. Eligible patients also had end-diastolic intraventricular septal wall thickness >12 mm demonstrated by echocardiography, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥ 600 pg/ml and confirmed the presence of amyloid deposits in biopsy tissue from cardiac and noncardiac sites. Patients were randomized (2:1:2) to tafamidis 80 mg, tafamidis 20 mg, or matching placebo once daily for 30 months, with analyses performed on the pooled tafamidis treatment group (combined tafamidis 80 mg and 20 mg groups) compared with placebo.

The primary efficacy endpoint of ATTR-ACT was a hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations comparing tafamidis with placebo. CV-related mortality (in which heart transplant or durable cardiac mechanical assist device (CMAD) implantation [for circulatory support] counted as death) and the rate of CV-related hospitalizations were also assessed by Cox proportional hazards model and Poisson regression analysis, respectively.[9]

The study was approved by the independent review boards or ethics committees at each participating site and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

The independent Endpoint Adjudication Committee conducted a blinded review of all potential study endpoints to determine whether investigator-reported events met the definition of disease-related efficacy endpoints using predefined criteria. All cases of death during the study were reported to the Endpoint Adjudication Committee, which reviewed the case to determine the cause of death. Death due to any cause was included in the primary efficacy evaluation (together with a heart transplant and implantation of a durable CMAD, which were counted as death for the efficacy analyses). All deaths were reviewed to determine if they were CV-related or not, with CV-related causes recorded as HF, arrhythmia, myocardial infarction (MI), sudden death, stroke, and other CV causes (see Supplementary Table 1).

At each visit, it was reported by the investigator if the patient had been hospitalized (including the reason for hospitalization), with all hospitalizations reported to the Endpoint Adjudication Committee. Hospitalization for endpoint adjudication was defined as a nonelective admission to an acute care setting for medical therapy that resulted in at least a 24-hour stay (or a date change if the time of admission/discharge was not available). Hospitalization reports were also reviewed by the Endpoint Adjudication Committee to determine if they were CV-related or not, with CV-related causes recorded as HF, arrhythmia, MI, transient ischemic attack/stroke, and other CV causes (see Supplementary Table 2).

The hazard ratio for time to mortality was derived from a Cox proportional hazards model with genotype (ATTRv and ATTRwt) and New York Heart Association (NYHA) baseline classification (NYHA classes I and II combined, and NYHA class III) in the model. Frequency of all-cause hospitalization was compared using a Poisson regression model with treatment, genotype (ATTRv and ATTRwt), NYHA baseline classification (NYHA classes I and II combined, and NYHA class III), treatment-by-genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors adjusted for treatment duration.[7]

Comorbidities, numbers of deaths, and hospitalizations are shown using descriptive statistics. Causes of hospitalization are shown with multiple occurrences of the same hospitalization admittance reason in a single patient counted once. For efficacy analyses and frequency of hospitalization, all hospitalizations in each patient are counted.

Results

As previously reported,[7] demographic and clinical characteristics were similar in the tafamidis and placebo groups, with the majority of patients being male, with a mean age of 74 years, and over 75% ATTRwt. Most patients (approximately 60%) were NYHA class II with median NT-proBNP concentrations being approximately 3,000 pg/ml, and mean left ventricular ejection fraction approximately 48%.[7] Patients had a number of CV-related comorbidities, with the most common being hypertension (54.9% of tafamidis patients; 47.5% of placebo patients), atrial fibrillation (53.0% tafamidis; 50.3% placebo), congestive cardiac failure (25.0% tafamidis; 27.7% placebo), and coronary artery disease (19.3% tafamidis; 22.6% placebo).

There was a significant 30.9% reduction in the risk of CV-related death with tafamidis compared with placebo (Figure 1). The majority of deaths in the study were CV-related (103 of 144 total deaths, 71.5%). Total deaths were less frequent with tafamidis compared with placebo, as were both CV-related and non-CV-related deaths (Table 1). All predefined causes of death were less frequent with tafamidis than with placebo (Table 1). There was a nonsignificant 30.2% reduction in the risk of HF death with tafamidis (Figure 1). Within each treatment group, the proportions of each cause of CV-related death were similar, with HF the most common cause of CV-related death, followed by sudden death.

The total number of patients with at least 1 hospitalization during the study was 326; 190 (72.0%) in the tafamidis group and 136 (76.8%) in the placebo group. There was a significant 32.4% reduction in the rate of CV-related hospitalizations, and a significant 20.7% reduction in the rate of all-cause hospitalization, with tafamidis compared with placebo (Figure 2). The total proportion of patients hospitalized, and the proportion with CV-related hospitalizations, was greater with placebo than with tafamidis (Table 2). All predefined causes of CV-related hospitalization were less frequent with tafamidis than placebo (Table 2). There was a significant 35.1% reduction in the rate of HF hospitalization, and nonsignificant reductions in the rate of arrhythmia hospitalization (27.9% reduction) and other CV-related hospitalizations (30.6% reduction) with tafamidis compared with placebo (Figure 2). Within each treatment group, the proportions of each cause of CV-related hospitalization were similar,

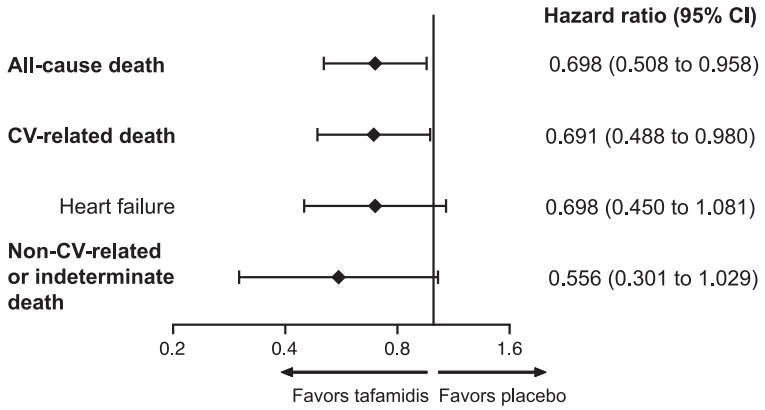

Figure 1. Risk of death with tafamidis compared with placebo. Time to all-cause mortality and most common causes. Hazard ratios and relative risk ratios were assessed for causes in >5% of patients treated with tafamidis. In the mortality analysis, heart transplant and implantation of a durable CMAD were counted as death. CI = confidence interval; CMAD = cardiac mechanical assist device; CV = cardiovascular.

with HF the most common cause of CV-related hospitalization, followed by other CV causes and arrhythmia.

Discussion

In ATTR-ACT, tafamidis was shown to significantly reduce mortality and CV-related hospitalizations in patients with ATTR-CM.[7] In order to better characterize this outcome, this analysis evaluated the causes of death and hospitalization. The large majority of deaths were CV-related and the most common cause of CV-related death and hospitalization was HF. Our findings provide insight into the burden of this disease in terms of morbidity and mortality confirming that ATTR-CM is a disease of advanced HF.

ATTR-CM is a systemic disease and treatment may impact not only cardiac-related events. CV-related death was more prevalent than non-CV-related death in both groups and comparatively lower in the tafamidis group. While sudden death has been discussed as an important cause of death in patients with all forms of amyloidosis,[4,10,11] in ATTR-ACT there were relatively few instances of CV-related sudden death, affecting 2.7% of all tafamidis-treated patients compared with 5.1% of placebo-treated patients over 30 months. In recent trials in patients with HF with reduced ejection fraction in which cause of death was adjudicated, a lower incidence of sudden cardiac death has been noted.[12] This reduction has been attributed to the use of evidence-based therapies.[12] However, patients with ATTR-CM typically have preserved ejection fraction[13,14] with the mean ejection fraction in ATTR-ACT being approximately 48%.[7] In the TOPCAT trial in patients with HF with preserved ejection fraction (median ejection fraction of 56%), the cause of death, as a percentage of all patients enrolled in the trial, was more commonly adjudicated as sudden death (3.2% of all patients enrolled) than HF (1.9%).[15] In ATTR-ACT, there were 16 deaths adjudicated as sudden death (11.1% of the 144 total deaths) and 81 adjudicated as HF (56.3% of the 144 total deaths). In TOPCAT, there were 526 total deaths, 111 adjudicated as sudden death (21.1%), and 67 adjudicated as HF (12.7%). Based on this comparison, it appears that in patients with ATTR-CM, in contrast to other patients with HF with preserved ejection fraction, the predominant cause of death is HF.

The frequency of CV-related hospitalizations per year (per patient) with tafamidis (0.48) compared with placebo (0.70), with the relative risk ratio for the treatment difference, were previously reported as part of the predefined secondary outcomes from ATTR-ACT.[7] The high number of CV-related hospitalizations per patient reflects the extraordinary impact of amyloidosis in the evolution of the disease. In other contemporary trials, repeated hospitalizations were not usually measured. In the SHIFT trial, comparing ivabradine with placebo in a large number of patients with HF with reduced ejection fraction (n = 6,505) and with a similar follow-up time (median follow-up 22.9 months), repeated HF hospitalizations occurred in only 32.5% of patients,[16] a fraction of the hospitalizations reported in

Table 1
Patient deaths and adjudicated causes of death

Deaths	Tafamidis (N = 264)	Placebo (N = 177)
Total deaths	72 (27.3%)	72 (40.7%)
CV-related deaths	53 (20.1%)	50 (28.2%)
Cause of CV-related death		
Heart failure	41 (15.5%)	40 (22.6%)
Sudden death	7 (2.7%)	9 (5.1%)
Stroke	0	1 (0.6%)*
Other CV	5 (1.9%)†	0
Non-CV-related deaths	14 (5.3%)	13 (7.3%)
Indeterminate deaths	5 (1.9%)	9 (5.1%)

CV = cardiovascular.

Not counted in this table are heart transplant (7 with tafamidis, 4 with placebo) and implantation of a durable cardiac mechanical assist device (2 with tafamidis, 0 with placebo), which were counted as death in the mortality analysis.

* Reported as "hypoxic ischemic encephalopathy with cardiac arrest due to disease progression."

† Including 1 case each reported as "withdrawal of total artificial heart support due to right frontal lobe hemorrhagic cerebrovascular accident," "multiple organ dysfunction syndrome caused by disease under study," "brain hemorrhage," "cardiomyopathy caused by disease under study," and "disease progression (disease under study)."

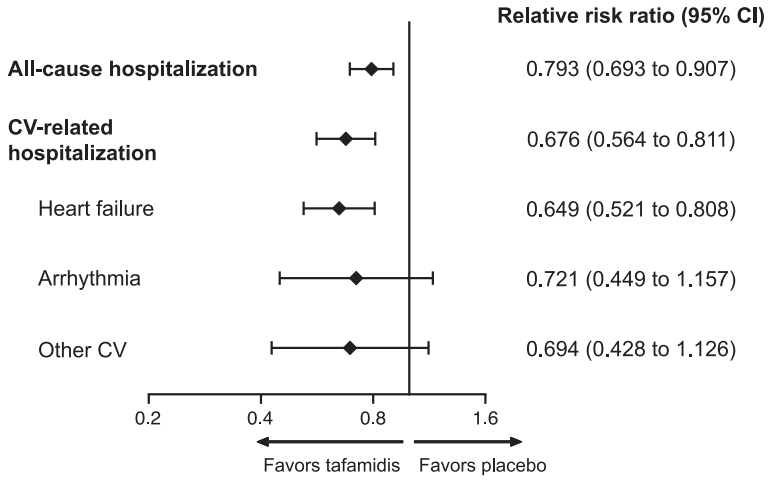

Figure 2. Relative risk of hospitalization with tafamidis compared with placebo. Frequency of all-cause hospitalization and CV-related hospitalization, and most common causes. Hazard ratios and relative risk ratios were assessed for causes in >5% of patients treated with tafamidis. CI = confidence interval; CV = cardiovascular.

ATTR-ACT. The majority of CV hospitalizations in both groups were due to HF, followed by arrhythmias, with a higher prevalence in the placebo groups; this was similar to other contemporary HF clinical trials.

ATTR-CM is a systemic disease and is associated with a large and complex number of comorbidities in this elderly population. Consequently, adjudication of events, in particular the main reason for hospitalization, is always challenging. However, all events were adjudicated blindly by an experienced endpoint adjudication committee with predefined criteria to classify CV causes. Counting the number of repeated hospitalizations during follow-up may be misleading if, as was the case, mortality is high. Nevertheless, higher mortality imposes a bias on the total number of hospitalizations, which may be artificially more frequent in the group with a lower death rate. In spite of this possible bias, total and CV-related hospitalizations were less frequent with tafamidis compared with placebo.

Table 2
Patients hospitalized and adjudicated cause of hospitalization

Hospitalizations	Tafamidis (N = 264)	Placebo (N = 177)
Total patients with ≥1 hospitalization	190 (72.0%)	136 (76.8%)
Patients with ≥1 CV-related hospitalization	138 (52.3%)	107 (60.5%)
Patients with ≥1 non-CV-related hospitalization	125 (47.3%)	80 (45.2%)
Patients with ≥1 indeterminate hospitalization	3 (1.1%)	0
Cause of CV-related hospitalization		
Heart failure	114 (43.2%)	89 (50.3%)
Arrhythmia	40 (15.2%)	38 (21.5%)
TIA/stroke	7 (2.7%)	8 (4.5%)
Myocardial infarction	2 (0.8%)	5 (2.8%)
Other CV	45 (17.0%)	35 (19.8%)

CV = cardiovascular; TIA = transient ischemic attack.

For cause of hospitalization, all new hospitalizations are counted, with multiple occurrences of the same hospitalization reason in a single patient counted once.

In conclusion, among patients randomized in ATTR-ACT, all adjudicated causes of CV-related death and hospitalization were less common with tafamidis than with placebo, with most deaths CV-related. HF was the most common cause of CV-related death and hospitalization.

Data sharing

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Author contributions

Alan B. Miller: Conceptualization, Methodology, Writing—Original Draft, Visualization. James L. Januzzi: Conceptualization, Methodology, Writing—Review & Editing. Blair J. O'Neill: Conceptualization, Methodology, Writing—Review & Editing. Balarama Gundapaneni: Conceptualization, Methodology, Formal analysis Writing—Review & Editing, Visualization. Marla B. Sultan: Conceptualization, Methodology, Writing—Review & Editing, Visualization. José López-Sendón: Conceptualization, Methodology, Writing—Original Draft, Visualization.

Disclosures

Alan B. Miller reports consultancy fees from Pfizer, AbbVie, Boehringer Ingelheim, Abbott, CVRx, and Respicardia. James L. Januzzi is a Trustee of the American College of Cardiology, has received grant support from Novartis and Abbott Diagnostics, consulting income from Abbott, Janssen, Novartis, and Roche, and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia, and Takeda. Blair J. O'Neill reports support from Pfizer and AstraZeneca. Balarama Gundapaneni, Terrell A.

Patterson, and Marla B. Sultan are full-time employees of Pfizer and own stock and/or stock options with Pfizer. José López-Sendón reports research grants from Pfizer, related to the study, and research grants from Boehringer Ingelheim, Merck, Bayer, Sanofi, and Amgen. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions, and funded by Pfizer.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.035.

1. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;39:2799–2806.
2. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RM, Bacchi-Reggiani L, Sangiorgi D, Ferlini A, Cavo M, Zamagni E, Fonte ML, Palladini G, Salinaro F, Musca F, Obici L, Branzi A, Perlini S. Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. *Circulation* 2009;120:1203–1212.
3. Castaño A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: Emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev* 2015;20:163–178.
4. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, Packman J, Grogan DR. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: The Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012;164:222–228. .e221.
5. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;73:2872–2891.
6. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, Gospodinova M, Obici L, Rapezzi C, Garcia-Pavia P. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail* 2019;7:709–716.
7. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;379:1007–1016.
8. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, Boman K, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: Further analyses from ATTR-ACT. *JACC Heart Fail* 2021;9:115–123.
9. Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, Gundapaneni B, Hahn C, Riley S, Schwartz J, Sultan MB, Rapezzi C. Design and rationale of the phase 3 ATTR-ACT clinical trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Circ Heart Fail* 2017;10:e003815.
10. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, Ciliberti P, Biagini E, Salvi F, Branzi A. Transthyretin-related amyloidoses and the heart: A clinical overview. *Nat Rev Cardiol* 2010;7:398–408.
11. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. *Heart Fail Rev* 2015;20:155–162.
12. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Kober L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining risk of sudden death in heart failure. *N Engl J Med* 2017;377:41–51.
13. Damy T, Costes B, Hagege AA, Donal E, Eicher JC, Slama M, Guellich A, Rappeneau S, Gueffet JP, Logeart D, Planté-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Rande JL, Goossens M, Canoui-Poitrine F, Buxbaum JN. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 2016;37:1826–1834.
14. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, Judge DP, Lenihan DJ, Gottlieb SS, Shah SJ, Steidley DE, Ventura H, Murali S, Silver MA, Jacoby D, Fedson S, Hummel SL, Kristen AV, Damy T, Planté-Bordeneuve V, Coelho T, Mundayat R, Suhr OB, Waddington Cruz M, Rapezzi C. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol* 2016;68:161–172.
15. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;370:1383–1392.
16. Borer JS, Bohm M, Ford I, Komajda M, Tavazzi L, Sendon JL, Alings M, Lopez-de-Sa E, Swedberg K. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *Eur Heart J* 2012;33:2813–2820.