Title

Patient-Important Adverse Events of β-blockers in Frail Older Adults after Acute Myocardial Infarction

Journal

The Journals of Gerontology Series A, 74(8)

ISSN

1079-5006

Authors

Zullo, Andrew R
Olean, Matthew
Berry, Sarah D
et al.

Publication Date

2019-07-12

DOI

10.1093/gerona/gly191

Peer reviewed

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2019, Vol. 74, No. 8, 1277–1281
doi:10.1093/gerona/gly191
Advance Access publication August 20, 2018

OXFORD

Brief Report

Patient-Important Adverse Events of β-blockers in Frail Older Adults after Acute Myocardial Infarction

Andrew R. Zullo, PharmD, PhD,[1,2,3] Matthew Olean, PharmD,[1,3,4] Sarah D. Berry, MD, MPH,[5] Yoojin Lee, MS, MPH,[1] Jennifer Tjia, MD, MSCE,[6] and Michael A. Steinman, MD[7]

[1]Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island. [2]Center of Innovation in Long-Term Services and Supports, Providence Veterans Affairs Medical Center, Rhode Island. [3]Department of Pharmacy, Rhode Island Hospital, Providence. [4]University of Rhode Island College of Pharmacy, Kingston. [5]Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts. [6]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester. [7]Division of Geriatrics, University of California, San Francisco and San Francisco VA Medical Center.

Address correspondence to: Andrew R. Zullo, PharmD, PhD, Department of Health Services, Policy, and Practice, Brown University School of Public Health, 121 South Main Street, Box G-S121-8, Providence, RI 02912. E-mail: andrew_zullo@brown.edu

Received: May 24, 2018; Editorial Decision Date: August 13, 2018

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: We evaluated the burden of adverse events caused by β-blocker use after acute myocardial infarction (AMI) in frail, older nursing home (NH) residents.

Methods: This retrospective cohort study used national Medicare claims linked to Minimum Data Set assessments. The study population was individuals aged ≥65 years who resided in a U.S. NH for ≥30 days, had a hospitalized AMI between May 2007 and March 2010, and returned to the NH. Exposure was new use of β-blockers versus nonuse post-AMI. Orthostasis, general hypotension, falls, dizziness, syncope, and breathlessness outcomes were measured over 90 days of follow-up. Odds ratios (ORs) with 95% confidence intervals (CIs) for outcomes were estimated using multinomial logistic regression models after 1:1 propensity score-matching of β-blocker users to nonusers.

Results: Among the 10,992 NH propensity score-matched residents with an AMI, the mean age was 84 years and 70.9% were female. β-blocker users were more likely than nonusers to be hospitalized for hypotension (OR = 1.20, 95% CI 1.03–1.39) or experience breathlessness (OR = 1.10, 95% CI 1.01–1.20) after AMI. With the exception of falls, other outcome estimates, though imprecise, were compatible with a potential elevated risk of orthostasis (OR = 1.14, 95% CI 0.96–1.35), syncope, (OR = 1.24, 95% CI 0.55–2.77), and dizziness (OR = 1.28, 95% CI 0.82–1.99) among β-blocker users.

Conclusions: Considered alongside prior evidence that β-blockers may worsen functional outcomes in NH residents with poor baseline functional and cognitive status, our results suggest that providers should exercise caution when prescribing for these vulnerable groups, balancing the mortality benefit against the potential for causing adverse events.

Keywords: Nursing homes, Adrenergic beta-antagonists, Myocardial infarction, Activities of daily living, Drug-related side effects and adverse reactions

β-blockers are recommended for all adults without a contraindication after an acute myocardial infarction (AMI) (1,2). However, β-blockers may have side effects like hypotension and fatigue, which are particularly detrimental to frail, older adults (3,4). These adverse events (AEs) could, in part, explain the results from a recent study that found an association between β-blocker use and functional decline in nursing home (NH) residents after AMI (5). Regardless, symptoms and AEs of cardiovascular medications are often the outcomes that older adults notice and care about. Little is known about whether β-blockers cause these AEs in frail, older adults or the magnitude of these potential effects. Therefore, we used a unique national data set to evaluate the association between β-blockers and AEs that could result in functional decline among frail, older NH residents. We hypothesized that β-blockers would increase the risk of all AEs, including hypotension, syncope, dizziness, breathlessness, and falls.

Methods

Study Design and Data Source

We used a previously established national, retrospective cohort of NH residents who return to the NH after AMI (5). The data source was national Medicare data linked to the Minimum Data Set (MDS) version 2.0 and Online Survey Certification and Reporting System (OSCAR) data. The MDS is a quarterly assessment tool of resident characteristics that is required for all facilities that are certified to receive Medicare or Medicaid funding. The OSCAR data provides facility-level information on NH characteristics, staffing levels, and quality indicators. Medicare claims include information on inpatient care (Part A), outpatient care (Part B), and prescription drug dispensings (Part D). This study was approved by the institutional review boards of the University of California, San Francisco, and the Department of Veterans Affairs.

Study Population

Our study population consisted of U.S. NH residents aged 65 years or older who were hospitalized for AMI between May 1, 2007 to March 31, 2010; had resided in a NH for at least 30 days before AMI hospitalization; had not used a β-blocker for at least 4 months before hospitalization; and returned to the NH after hospital discharge. We defined hospitalization with AMI based on a Part A hospital claim with *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9) code 410.XX or 411.1 as the primary or secondary diagnosis. Additional details about the study population have been previously published (5–8).

Exposures and Causal Contrast of Interest

Initiation of an oral β-blocker was ascertained using Medicare Part D claims. No prevalent (prior) β-blocker users were included. The causal contrast of interest was defined as the effect of initiating β-blocker versus not initiating β-blocker, regardless of subsequent treatment discontinuation or switching among treatment groups (ie, intention-to-treat).

Outcomes

We identified 90-day orthostasis and general hypotension outcomes using ICD-9 codes 458.0 and 458.XX, respectively, in any coding position on hospital claims (5). Falls were similarly identified using codes E880-E888 in any position on the Part A hospital claims. All coding positions were permitted because orthostasis, general hypotension, and falls are very rarely the principal cause for hospital admission. We ascertained 90-day dizziness, syncope, and breathlessness outcomes using checkboxes in Section J (Health Conditions) of the MDS version 2.0 assessments (5).

Baseline Characteristics

Potential common causes (or proxies of common causes) of β-blocker use and outcomes were prespecified based on existing literature (5,7,9–13) and measured prior to β-blocker use. Additional details about the measurement of baseline characteristics and which characteristics were included have been previously described (5). In brief, variables were measured in inpatient claims, outpatient claims, MDS records, and OSCAR data, and included demographic characteristics, medical history, medication use, risk factors for AMI, health services utilization, and NH facility characteristics (14). MDS data were used to generate several validated scales including the Cognitive Performance Scale (CPS), the Morris Activities of Daily Living (ADL) scale, and the Changes in Health, End-stage disease, Symptoms and Signs (CHESS) score, a measure of global prognosis.

Statistical Analyses

We adjusted for confounding by nearly 100 baseline covariates using methods that rely on estimating the propensity score (ie, the probability of receiving β-blocker vs not, conditional on covariates). Propensity scores were estimated using a logistic regression model. The model used restricted cubic splines with four knots for continuous variables and interaction terms wherever indicated based on prior literature (5,7,9–13). We included a pretreatment history of all AEs in the model. We also included concomitant medications that could be associated with the AEs, including antidepressants, opioids, sedative-hypnotics, antipsychotics, diuretics, and direct-acting vasodilators.

We used the propensity score to match one new user of β-blockers to one nonuser after the AMI. We applied a greedy 5-to-1 digit matching algorithm without replacement to do so. Propensity score distributions in each treatment group were examined using histograms and descriptive statistics. We used standardized mean differences after matching to assess covariate balance between treatment groups.

We estimated odds ratios (ORs) with 95% confidence intervals (CIs) using multinomial logistic regression models to compare β-blocker initiators to nonusers for all outcomes of interest while accounting for the competing risk of death.

In a noncausal preliminary analysis to begin to assess whether AE outcomes may have contributed to a previously observed association between β-blockers and functional decline (5), we estimated treatment effects within strata defined by post-AMI functional decline (had a 3-point increase on the 28-point MDS ADL scale vs did not). Specifically, we used a multinomial regression model with treatment (β-blocker initiation vs nonuse) term, post-AMI functional decline term, and a treatment × post-AMI functional decline term as independent variables.

Results

Study Cohort

Propensity score-matching yielded a cohort of 5,496 β-blocker users and an equal number of nonusers. The cohort had a mean (*SD*) age of 84 (8) years and 70.9% female. Of the 10,992 NH residents in the propensity score-matched cohort, 396 (3.6%) had a pre-β-blocker hospitalization with orthostasis, 526 (4.8%) with general hypotension, and 274 (2.5%) with falls; 109 (1.0%) individuals had a history of pretreatment dizziness, 30 (0.3%) had a history of syncope, and 916 (8.3%) has a history of breathlessness. Characteristics between β-blocker users and nonusers in the cohort were well-balanced after matching (Table 1). All standardized differences between treatment groups were ≤0.06. Further description of the cohort's baseline characteristics has been previously published (5).

Treatment Effects

After AMI, β-blocker users were more likely than nonusers to be hospitalized for hypotension (OR = 1.20, 95% CI 1.03–1.39) or experience breathlessness (OR = 1.10, 95% CI 1.01–1.20) (Table 2). With the exception of falls, other outcome estimates, though imprecise, were consistent with a potential elevated risk of orthostasis (OR = 1.14, 95% CI 0.96–1.35), syncope, (OR = 1.24, 95% CI 0.55–2.77), and dizziness (OR = 1.28, 95% CI 0.82–1.99) among β-blocker users.

Table 1. Characteristics of β-blocker Users and Nonusers After Propensity Score Matching

	n (%)	
	β-blocker Users (*n* = 5,496)	β-blocker Nonusers (*n* = 5,496)
Age, mean (*SD*) years	84 (8)	84 (8)
Female sex	3,901 (71.0)	3,887 (70.7)
Race		
Caucasian	4,485 (81.6)	4,497 (81.8)
African American	644 (11.7)	646 (11.8)
Other	367 (6.7)	353 (6.4)
Adverse events prior to AMI hospitalization		
Breathlessness	461 (8.4)	455 (8.3)
Syncope	15 (0.3)	15 (0.3)
Dizziness	54 (1.0)	55 (1.0)
Falls	124 (2.3)	150 (2.7)
General hypotension	264 (4.8)	262 (4.8)
Orthostasis	200 (3.6)	196 (3.6)
ADL status prior to AMI hospitalization		
Independent to limited assistance required	1,834 (33.4)	1,866 (34.0)
Extensive assistance required	1,801 (32.8)	1,778 (32.4)
Extensive dependency	1,861 (33.9)	1,852 (33.7)
Cognitive status prior to AMI hospitalization		
Intact or borderline intact	1,580 (28.8)	1,585 (28.8)
Mild to moderate dementia	3,294 (59.9)	3,305 (60.1)
Moderately severe to very severe dementia	622 (11.3)	606 (11.0)
Chronic conditions prior to AMI hospitalization		
Diabetes	1,567 (28.5)	1,582 (28.8)
Dyslipidemia	297 (11.8)	288 (11.9)
Hypertension	3,055 (55.6)	3,018 (54.9)
Renal failure	297 (11.8)	288 (11.9)
COPD	1,498 (27.3)	1,504 (27.4)
Heart failure	2,554 (46.5)	2,562 (46.6)
PVD	409 (7.4)	399 (7.3)
Number of medications prior to AMI hospitalization	11 (8–15)	12 (8–15)
Medication use prior to AMI hospitalization		
Statins	1,559 (28.4)	1,580 (28.8)
Antiplatelets	914 (16.6)	916 (16.7)
Warfarin	707 (12.9)	723 (13.2)
Length of hospital stay for AMI, median (IQR) days	6 (4–9)	6 (4–9)
Number of days in ICU/CCU during AMI stay		
None	2,374 (43.2)	2,361 (43.0)
1–2	1,376 (25.0)	1,396 (25.4)
3 or more	1,746 (31.8)	1,739 (31.6)
PCI or CABG during AMI hospitalization	126 (2.3)	98 (1.8)

Note: AMI = Acute myocardial infarction; ADL = Activities of daily living; CABG = Coronary artery bypass graft; HF = Heart failure; ICU/CCU = Intensive care unit/coronary care unit; IQR = Interquartile range; PCI = Percutaneous coronary intervention; PVD = Peripheral vascular disease; SD = Standard deviation.

Stratification by Functional Decline

When the data were jointly stratified by post-AMI β-blocker use and functional decline, there was no evidence that the risk of AEs was substantially greater among those with β-blocker use and functional decline compared to those without (Table 3). This suggests that the AEs we evaluated were unlikely to be major mediators of the previously observed association between β-blockers and functional decline (5).

Discussion

In this retrospective cohort study, new use of β-blockers after AMI was associated with a slightly increased risk of hypotension and breathlessness in frail older adults, but not other AEs. Additionally, there was little evidence that potential AEs that we studied were likely to be responsible for the association between β-blockers and functional decline. Emerging evidence suggests that the benefits of β-blockers after AMI may be especially concentrated in individuals with reduced ejection fraction mediated by the AMI, and individuals with preserved ejection fraction may benefit less. Nonetheless, β-blockers remain the standard of care and are associated with reductions in mortality in the overall population of vulnerable older adults after AMI (5). For as long as β-blockers remain the standard of care, information on AEs that frail, older adults notice and care about is necessary to guide treatment decision-making.

Several pharmacokinetic and pharmacodynamic studies have suggested that frail older adults may experience more AEs from β-blockers, but few have examined the clinical significance of these findings in older adults by empirically examining outcomes (15). Meta-analyses of trials enrolling younger patients suggested that β-blockers were associated with dizziness, but conflicted on whether they were associated hypotension, breathlessness, or syncope (16,17).

Just one prior study examined the prevalence of orthostasis among NH residents and found that individuals with orthostasis received β-blockers more often than those without orthostasis (18). That study was not designed to analyze the effect of β-blockers on AEs, did not examine residents after AMI, and only examined orthostasis, but provides some of the only available prior evidence that a relationship may exist between β-blockers and important AEs among older NH residents. One other cross-sectional study using 2004 National Nursing Home Survey data found that β-blockers were associated with an increased likelihood of falls (OR = 1.14, 95% CI = 1.04–1.27), but the cross-sectional design precluded causal inference (19). Our study adds to the existing literature by providing the highest quality evidence to date on the relationship between β-blockers and AE outcomes among frail, older adults in NHs. In doing so, it provides information on outcomes that are important to a variety of geriatric healthcare professionals (3). Such information can be used to guide and support prescribing decisions in the NH setting.

Limitations of our study include the possibility of outcome misclassification due to a lack of validated outcome definitions for our data; the inability to look at fatigue and depression as outcomes despite their clinical importance; and the low incidence of the outcomes that limited our statistical power to detect a difference across subgroups of patient characteristics or by β-blocker type (ie, lipophilicity or cardioselectivity) (5). Another notable limitation of our study cohort was the lack of information on left ventricular ejection fraction (LVEF) since the data from younger individuals suggests that the mortality benefit is greatest for those with a LVEF of less than 40%. Due to the nature of our data, we were also unable to assess dose–response relationships with AE outcomes. Future studies using Veterans Affairs or other data should aim to address whether the harm-benefit balance of β-blockers in highly vulnerable older adults differs across strata of LVEF and by β-blocker dose.

Table 2. Association of β-blocker Use Versus Nonuse With Potential Adverse Event Outcomes

	Events, *n*		Risk, %			
Adverse Event Outcome	β-blocker Users (*n* = 5,496)	β-blocker Nonusers (*n* = 5,496)	β-blocker Users	β-blocker Nonusers	OR (95% CI)	*p* Value
Hypotension	394	347	7.2	6.3	1.20 (1.03, 1.39)	.02
Orthostatic Hypotension	283	261	5.2	4.8	1.14 (0.96, 1.35)	.14
Syncope	13	11	0.2	0.2	1.24 (0.55, 2.77)	.60
Dizziness	44	36	0.8	0.7	1.28 (0.82, 1.99)	.27
Breathlessness	1,596	1,525	29.0	27.8	1.10 (1.01, 1.20)	.03
Falls	100	118	1.8	2.2	0.88 (0.68, 1.16)	.37

Note: CI = Confidence interval; OR = Odds ratio.

Table 3. Risk (%) of Each Adverse Event Stratified by β-blocker Use and Functional Decline

	Functional Decline (*n* = 1,328)		Alive With No Functional Decline (*n* = 8,201)		
Adverse Event Outcome	β-blocker users (*n* = 717)	β-blocker Nonusers (*n* = 611)	β-blocker users (*n* = 4,157)	β-blocker Nonusers (*n* = 4,044)	*p* Value[a]
Hypotension	7.4	7.3	7.1	6.1	.55
Orthostatic Hypotension	5.1	4.9	5.0	4.6	.88
Syncope	0.0	<1.8[b]	0.3	<0.3[b]	.97
Dizziness	<1.5[b]	<1.8[b]	0.7	1.0	.32
Breathlessness	30.1	29.3	26.5	26.2	.88
Falls	1.6	2.0	1.8	2.1	.95

[a]*p* value for whether the risk of an adverse event was different among β-blocker users versus nonusers for individuals with a functional decline versus without a decline; [b]Cells suppressed in compliance with the Centers for Medicare and Medicare Services Cell Size Suppression Policy stipulating that no cell can be reported that allows a value of 1 to 10 to be derived from other reported cells or information.

Since this study is observational, we cannot rule out the possibility of confounding. In addition to the absence of information on LVEF, we were unable to accurately differentiate ST-elevation MI (STEMI) from non-ST-elevation MI (NSTEMI) or identify the infarct location. However, several factors support the robustness of our findings. First, our linked clinical and administrative databases provide detailed patient information beyond what is captured in administrative data alone. Second, we also obtained excellent balance on nearly 100 baseline covariates between treatment groups. We were also unable to assess whether AE outcomes differed between individuals who persisted with versus discontinued β-blockers. Such an analysis would likely be subject to substantial selection bias even with many covariates available for adjustment since β-blockers reduce the risk of mortality and death was the primary reason individuals "discontinued" β-blockers. Findings from previous work using our study cohort suggest that nearly all people in NHs who start on a β-blocker after AMI remain on them for at least the first 90 days, so questions about continuation versus discontinuation of β-blockers may be less relevant for NH residents in the immediate post-AMI period (5,7).

It is important to note that causal inference cannot be drawn from our analysis stratifying on post-AMI functional decline. Functional decline was not temporally ordered to occur after AEs and a formal causal mediation analysis was not conducted. The stratified analysis was only intended to provide preliminary information about the plausibility of the hypothesis that functional decline could be mediated by AEs. While there is not a strong empirical justification for proceeding with a formal causal mediation analysis, such future work could be conducted.

In summary, β-blockers were associated with a small relative and absolute increase in hypotension and breathlessness in frail older adults, but there was not strong evidence that these AEs mediate functional decline. Compared to younger individuals, frail, older adults often prioritize maintaining function and avoiding AEs, as opposed to maximizing longevity (20). We hope our results will encourage providers to consider the net benefit-harm balance when prescribing β-blockers to older adults. For the minority of patients and their caregivers who prefer to maximize longevity, our results should reassure them that the risk of AEs associated with starting β-blockers is modest. Nonetheless, the potential negative effects of β-blockers on functional outcomes in frail NH residents with poor baseline functional and cognitive status merit caution when prescribing for these vulnerable groups, balancing the mortality benefit against the potential for causing AEs (5).

Funding

Financial support for this study was provided by the National Institute on Aging (5R01AG045441; K24AG049057; and P30AG044281), the National Heart, Lung, and Blood Institute (5R01HL111032), the Agency for Healthcare Research and Quality (5K12HS022998), and the U.S. Department of Veterans Affairs.

Conflict of Interest

S.D.B. serves as an author for the "Falls" chapters in UpToDate and receives royalties from Wolters Kluwer for this. J.T. is a paid consultant for CVS Health. M.A.S. has served as a paid consultant for iodine.com. All other authors have no relevant conflicts of interest.

References

1. Amsterdam EA, Wenger NK, Brindis RG, et al. AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–426. doi:10.1161/CIR.0000000000000134
2. O'Gara PT, Kushner FG, Ascheim DD, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555. doi:10.1161/CIR.0b013e3182742c84
3. Willham K, Covinsky K, Widera E. Geriatrics literature 2016 year in review. *J Am Geriatr Soc*. 2017;65:2146–2150. doi:10.1111/jgs.15064
4. Tjia J, Lapane K. Guideline-based prescribing in frail elderly patients. *JAMA Intern Med*. 2017;177:262–263. doi:10.1001/jamainternmed.2016.7714
5. Steinman MA, Zullo AR, Lee Y, et al. Association of β-Blockers with functional outcomes, death, and rehospitalization in older nursing home residents after acute myocardial infarction. *JAMA Intern Med*. 2017;177:254–262. doi:10.1001/jamainternmed.2016.7701
6. Zullo AR, Sharmin S, Lee Y, et al. Secondary prevention medication use after myocardial infarction in U.S. nursing home residents. *J Am Geriatr Soc*. 2017;65:2397–2404. doi:10.1111/jgs.15144
7. Zullo AR, Lee Y, Daiello LA, et al. Beta-blocker use in U.S. nursing home residents after myocardial infarction: a national study. *J Am Geriatr Soc*. 2017;65:754–762. doi:10.1111/jgs.14671
8. Zullo AR, Hersey M, Lee Y, et al. Outcomes of "diabetes-friendly" vs "diabetes-unfriendly" β-blockers in older nursing home residents with diabetes after acute myocardial infarction. *Diabetes, Obes Metab*. 2018. doi:10.1111/dom.13451. [Epub ahead of print].
9. Aronow WS. Prevalence of use of beta blockers and of calcium channel blockers in older patients with prior myocardial infarction at the time of admission to a nursing home. *J Am Geriatr Soc*. 1996;44:1075–1077. doi:10.1111/j.1532-5415.1996.tb02941.x
10. Ghosh S, Ziesmer V, Aronow WS. Underutilization of aspirin, beta blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs and overutilization of calcium channel blockers in older persons with coronary artery disease in an academic nursing home. *J Gerontol A Biol Sci Med Sci*. 2002;57:M398–M400. doi:10.1093/gerona/57.6.M398
11. Joseph J, Koka M, Aronow WS. Prevalence of use of antiplatelet drugs, beta blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in older patients with coronary artery disease in an academic nursing home. *J Am Med Dir Assoc*. 2008;9:124–127. doi:10.1016/j.jamda.2007.10.010
12. Levy CR, Radcliff TA, Williams ET, Hutt E. Acute myocardial infarction in nursing home residents: adherence to treatment guidelines reduces mortality, but why is adherence so low? *J Am Med Dir Assoc*. 2009;10:56–61. doi:10.1016/j.jamda.2008.08.009
13. Vitagliano G, Curtis JP, Concato J, Feinstein AR, Radford MJ, Krumholz HM. Association between functional status and use and effectiveness of beta-blocker prophylaxis in elderly survivors of acute myocardial infarction. *J Am Geriatr Soc*. 2004;52:495–501. doi:10.1111/j.1532-5415.2004.52153.x
14. Zullo AR, Zhang T, Banerjee G, et al. Facility and state variation in hip fracture in U.S. nursing home residents. *J Am Geriatr Soc*. 2018;66:539–545. doi:10.1111/jgs.15264
15. Mangoni AA. Cardiovascular drug therapy in elderly patients: specific age-related pharmacokinetic, pharmacodynamic and therapeutic considerations. *Drugs Aging*. 2005;22:913–941. doi:10.2165/00002512-200522110-00003
16. Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. *Arch Intern Med*. 2004;164:1389–1394. doi:10.1001/archinte.164.13.1389
17. Barron AJ, Zaman N, Cole GD, Wensel R, Okonko DO, Francis DP. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. *Int J Cardiol*. 2013;168:3572–3579. doi:10.1016/j.ijcard.2013.05.068
18. Valbusa F, Labat C, Salvi P, Vivian ME, Hanon O, Benetos A; PARTAGE investigators. Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE study. *J Hypertens*. 2012;30:53–60. doi:10.1097/HJH.0b013e32834d3d73
19. Simonson W, Han LF, Davidson HE. Hypertension treatment and outcomes in US nursing homes: results from the US National Nursing Home Survey. *J Am Med Dir Assoc*. 2011;12:44–49. doi:10.1016/j.jamda.2010.02.009.
20. Mitchell SL, Palmer JA, Volandes AE, Hanson LC, Habtemariam D, Shaffer ML. Level of care preferences among nursing home residents with advanced dementia. *J Pain Symptom Manage*. 2017;54:340–345. doi:10.1016/j.jpainsymman.2017.04.020