Risk Differences in Secondary Prevention Patients Who Present With Acute Coronary Syndrome and Implications of Guideline-Directed Cholesterol Management

Nathan W. Kong, MD[a,*], Aakash Bavishi, MD[b], Ansel Philip Amaral, MD, PhD[b], Anjan Tibrewala, MD[b], Arif Jivan, MD, PhD[b], Philip Silberman, MA[c], and Neil J. Stone, MD[b]

The 2018 American College of Cardiology/American Heart Association cholesterol guidelines for secondary prevention identified a group of "very high risk" (VHR) patients, those with multiple major atherosclerotic cardiovascular disease (ASCVD) events or 1 major ASCVD event with multiple high-risk features. A second group, "high risk" (HR), was defined as patients without any of the risk features in the VHR group. The incidence and relative risk differences of these 2 groups in a nontrial population has not been well characterized. Using the Northwestern Medicine Enterprise Data Warehouse, we compared the incidence of VHR and HR patients as well as their relative risk for cardiovascular morbidity and mortality in a single-center, large, academic, retrospective cohort study. Total 1,483 patients with acute coronary events from January 2014 to December 2016 were risk stratified into VHR and HR groups. International Classification of Diseases versions 9 and 10 were used to assess for composite events of unstable angina pectoris, non-ST elevation myocardial infarction, or ST-elevation myocardial infarction, ischemic stroke, or all-cause death with a median follow-up of 3.3 years. VHR patients were found to have 87 ± 5.4 composite events per 1,000 patient-years compared with HR patients who had 33 ± 5.1 events per 1,000 patient-years (p <0.001). VHR group had increased risk of future events as compared to the HR group (multivariable adjusted hazard ratio 1.66 [1.01 to 2.74], p = 0.047). In conclusion, these results support the stratification of patients into the VHR and HR risk groups for secondary prevention. **(Am J Cardiol 2020;133:1−6)**

Multiple large randomized control trials have shown that statin therapy is effective at preventing recurrent acute coronary syndrome (ACS) events.[1−4] The 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on cholesterol management recommended high-intensity statin therapy to lower low-density lipoprotein cholesterol (LDL-C) for patients with clinical atherosclerotic cardiovascular disease (ASCVD).[5] In these secondary prevention patients, the guidelines call for a risk stratification paradigm that separates patients into very high risk (VHR) versus high risk (HR). The VHR group was defined by multiple major ASCVD events or 1 major ASCVD event with multiple high-risk features. This risk stratification is important as previous studies have indicated that patients with more risk markers have greater mortality benefit from lipid lowering therapy than those with less risk markers.[6] However, less is known regarding the incidence of these 2 risk groups in nontrial cohorts as well as the relative risk differences. We seek to compare the incidence of VHR and HR patients as well as their relative risk for cardiovascular morbidity and mortality in a single-center, large, academic, retrospective cohort study.

Methods

The Northwestern Medicine Enterprise Data Warehouse (NMEDW) was queried to identify adult patients (age ≥18) who had an ACS event at Northwestern Memorial Hospital between January 1, 2014 and December 31, 2016. In the present study, ACS was defined as a left heart catheterization (LHC) with an associated International Classification of Disease versions 9 and 10 (ICD9/10) diagnosis of unstable angina pectoris, non-ST elevation myocardial infarction, or ST-elevation myocardial infarction. The NMEDW is an electronic database that collects information from the electronic health record (EHR) of Northwestern Memorial Hospital and codifies the data into a searchable format. For our analysis, patient's demographics, co-morbidities, medications, laboratory values, and variables necessary for determination of risk strata were extracted. Patients were then followed in the EHR until January 31, 2019, for repeat ACS events, ischemic stroke, or death. ACS events were determined using the same criteria as above, whereas ischemic stroke events were determined using ICD 9/10 codes.

[a]Department of Internal Medicine, University of Chicago, Chicago, Illinois; [b]Bluhm Cardiovascular Institute, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and [c]Clinical and Translational Sciences Institute, Northwestern University, Chicago, Illinois. Manuscript received May 18, 2020; revised manuscript received and accepted July 20, 2020.

Funding: None.

See page 6 for disclosure information.

*Corresponding author: Tel: (724) 325-7047; fax: (878) 201-5792

E-mail address: nathan.kong@uchospitals.edu (N.W. Kong).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.07.039

All-cause death was determined by the death date listed in the NMEDW. To limit misclassification from using ICD codes alone, patients who did not get a LHC and those with missing data which prevented risk stratification were excluded from our analysis. The institutional review board reviewed and approved the study (STU00209384).

Patients' were risk stratified according to the AHA/ACC 2018 Cholesterol Guidelines. VHR was defined as either the presence of another major ASCVD event (history of MI, ischemic stroke, or peripheral artery disease) or as having ≥2 high-risk conditions: age greater than or equal to 65 years old, history of coronary artery bypass surgery or percutaneous coronary intervention, diabetes mellitus, hypertension, estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2, current smoker, congestive heart failure, LDL-C greater than or equal to 100 mg/dL despite being on high-intensity statin therapy and ezetimibe, or LDL-C greater than or equal to 220 mg/dL, which was used as a surrogate for heterozygous familial hypercholesteremia (HeFH) (Figure 1). Patients without another major ASCVD event or with <2 high-risk conditions were classified as HR ASCVD.

Our primary outcome was the composite events of repeat ACS, ischemic stroke, and all-cause death. Other prespecified outcomes were individual occurrences of repeat ACS, ischemic stroke, and all-cause death. Lost to follow-up was defined as last date of follow-up within 7 days of index ACS event.

All analysis was performed on R 3.5.0 (R Core Team, 2018) using the "tableone" and "survival" packages. All event rates are reported in 1,000 patient-years (PY). Multivariable Cox regression modeling was used to generate adjusted hazard ratios. Variables included in multivariable analysis were gender, race, BMI, diastolic blood pressure, levels of LDL-C, HDL-C, non-HDL-C, and medication usage. Variables inclusion for analysis was determined by significant differences in baseline characteristics (Table 1). A 2-tailed, $p < 0.05$ was considered statistically significant for all analyses.

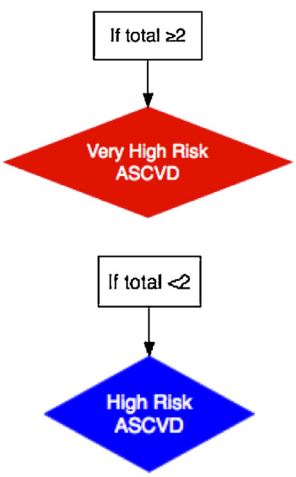
Results

Total 1,483 patients with 4,191 PY of follow-up were included (Figure 2). Median follow-up time was 3.3 years. Thirty-five percent of patients were female, 19% were African American, and the average age was 64 ± 13 years. About 1,027 (69%) were VHR and 456 (31%) were HR patients. There were 256 (25%) VHR patients who experienced the composite outcome compared with 41 (9%) of HR patients ($p < 0.001$, Table 1).

The overall composite event incidence rate for our cohort was 61 ± 4.1 per 1,000 PY. In the VHR group, the incidence rate for composite events was 87 ± 5.4 per 1,000 PY compared with the HR group which had an event rate of 33 ± 5.1 per 1,000 PY ($p < 0.001$, Figure 3). Our prespecified secondary outcomes of stroke (28 ± 3.1 vs 5.6 ± 2.1, $p < 0.001$), all-cause death (36 ± 3.5 vs 7.2 ± 2.4, $p < 0.001$), and repeat ACS events (38 ± 3.6 vs 23 ± 4.3, $p = 0.018$) were also significantly different between the VHR and HR ASCVD risk groups respectively (Figure 3).

Kaplan-Meier survival curves showed that the VHR group had significantly decreased event-free survival rates compared with the HR group ($p < 0.001$; Figure 4). Cox regression analysis revealed increased risk of composite

Risk Condition	Points
Previous Major ASCVD Event	
Myocardial Infarction	2
Ischemic Stroke	2
Peripheral Artery Disease	2
High-Risk Conditions	
Age ≥65 years old	1
Previous CABG/PCI	1
Congestive heart failure	1
Diabetes mellitus	1
Hypertension	1
eGFR <60 mL/min/1.73 m^2	1
Current smoker	1
LDL-C ≥100 mg/dL on max statin & ezetimibe	1
LDL-C ≥220 mg/dL[a]	1
Total Possible	15



CABG, coronary artery bypass surgery; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention

[a] Used to approximate heterozygous familial hypercholesterolemia

Figure 1. Risk stratification method. Patients were considered very high risk if they had a total score greater than or equal to 2. Patients with scores of 0 and 1 were considered high risk. Previous major ASCVD events were given 2 points while all high-risk conditions received a score of 1.

Table 1
Baseline and follow-up demographics

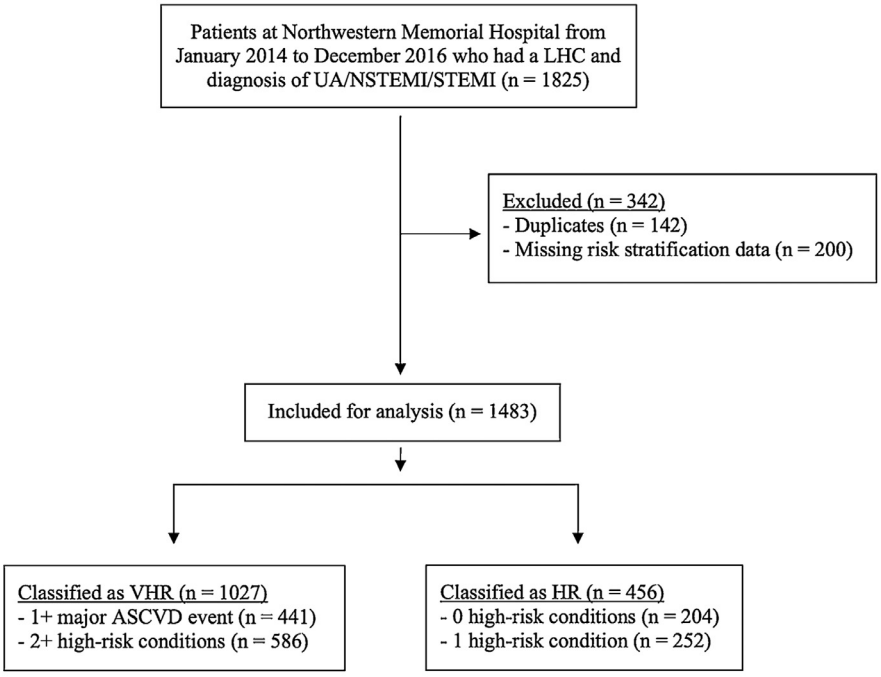
Variable	Very high risk n = 1,027	High risk n = 456	p Value
Age (years)	67.5 ± 11.9	55.6 ± 10.9	<0.01
Men	655 (63.8%)	310 (68.0%)	0.13
Black	198 (19.5%)	82 (18.3%)	0.65
BMI (kg/m^2)	29.6 ± 6.8	29.8 ± 6.6	0.55
History of myocardial infarction	261 (25.5 %)	0	<0.01
History of stroke	144 (14.1%)	0	<0.01
History of peripheral artery disease	191 (18.7%)	0	<0.01
Age ≥65 years	648 (63.1%)	72 (15.8%)	<0.01
Previous bypass/stent	145 (14.4%)	44 (10.2%)	0.04
History of heart failure	421 (43.5%)	23 (5.6%)	<0.01
Diabetes mellitus	339 (33.2%)	11 (2.4%)	<0.01
Hypertension	489 (47.8%)	17 (3.9%)	<0.01
eGFR <60 mL/min/1.73m^3	884 (86.1%)	85 (18.6%)	<0.01
Current smoker	246 (24.0%)	5 (1.1%)	<0.01
Heterozygous familial hypercholesterolemia	3 (0.5%)	1 (0.3%)	1
Index ACS event			
Associated diagnosis			
Unstable angina pectoris	246 (24.0%)	98 (21.5%)	0.36
Non-ST elevation myocardial infarction	184 (17.9%)	94 (20.6%)	
ST elevation myocardial infarction	597 (58.1%)	264 (57.9%)	
Systolic blood pressure (mm Hg)	147.0 ± 28.3	144.4 ± 27.0	0.1
Diastolic blood pressure (mm Hg)	76.5 ± 14.8	81.4 ± 14.9	<0.01
Heart rate (mm Hg)	78.0 ± 19.8	78.3 ± 18.7	0.79
Low-density lipoprotein (mg/dL)	83.9 ± 36.5	103.0 ± 37.3	<0.01
High-density lipoprotein (mg/dL)	41.5 ± 13.5	43.8 ± 13.3	0.02
Non−high-density lipoprotein (mg/dL)	114.2 ± 45.3	130.8 ± 44.8	<0.01
Triglycerides (mg/dL)	109.0 [74.5, 168.5]	109.0 [79.0, 169.0]	0.95
Total cholesterol (mg/dL)	155.2 ± 47.8	174.3 ± 47.7	<0.01
Medications			
Statins	681 (66.3%)	126 (27.65%)	<0.01
ACE inhibitor/angiotensin receptor blockers	526 (51.2%)	68 (14.9)	<0.01
Beta-blockers	513 (50.0%)	74 (16.2%)	<0.01
Calcium channel blockers	258 (25.1%)	16 (3.5%)	<0.01
Thiazide diuretics	194 (18.9%)	16 (3.5%)	<0.01
Loop diuretics	151 (14.7%)	4 (0.9%)	<0.01
Diabetic	296 (28.8%)	11 (2.4%)	<0.01
Aspirin	685 (66.7%)	132 (28.9%)	<0.01
Non-statin lipid lowering	40 (3.9%)	6 (1.3%)	0.01
Outcomes			
Repeat acute coronary syndrome	112 (10.9%)	29 (6.4%)	0.01
Stroke	83 (8.1%)	7 (1.5%)	<0.01
All-cause death	105 (10.2%)	9 (2.0%)	<0.01
Composite events	256 (24.9%)	41 (9.0%)	<0.01

Baseline and follow-up characteristics as stratified by risk category. Continuous variables are represented as mean ± standard deviation or median (interquartile range) if non-normal; categorical variables are represented as count (percent).

events in the VHR group compared with the HR group (univariate hazard ratio 2.72, 95% confidence interval 1.95 to 3.78, p <0.001; multivariate adjusted hazard ratio 1.66, 95% confidence interval 1.01 to 2.74, p = 0.047; Figure 4). One hundred fifty-four (10%) patients were lost to follow-up. Sensitivity analysis on those that were lost to follow-up revealed no changes to our primary or secondary outcomes.

Discussion

Our data from a large urban academic medical center showed that more than two-thirds (69%) of patients with an ACS event are considered VHR according the new 2018 ACC/AHA Cholesterol Guidelines. Our study is one of the first "real-world" estimates of this number in a US cohort. Although results may vary in different settings, we confirm that VHR patients are at significantly increased risk of developing cardiovascular morbidity and mortality following an ACS event. There were significantly higher rates of total recurrent ACS, stroke, and all-cause death among patients who were considered VHR compared with HR patients in both unadjusted and multivariable adjusted Cox proportion analyses. Twenty-five percent of VHR patients experienced a composite event compared with 9% of HR ASCVD patient, a 2.8 times increased risk. It is interesting to note that VHR patients had lower LDL-C



ASCVD, atherosclerotic cardiovascular disease; HR, high risk; LHC, left heart catheterization; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; UA, unstable angina; VHR, very high risk

Figure 2. Flow diagram of patient selection, including breakdown of "very high risk" and "high risk" patients. Breakdown of number of patients meeting criteria for risk stratification was included.

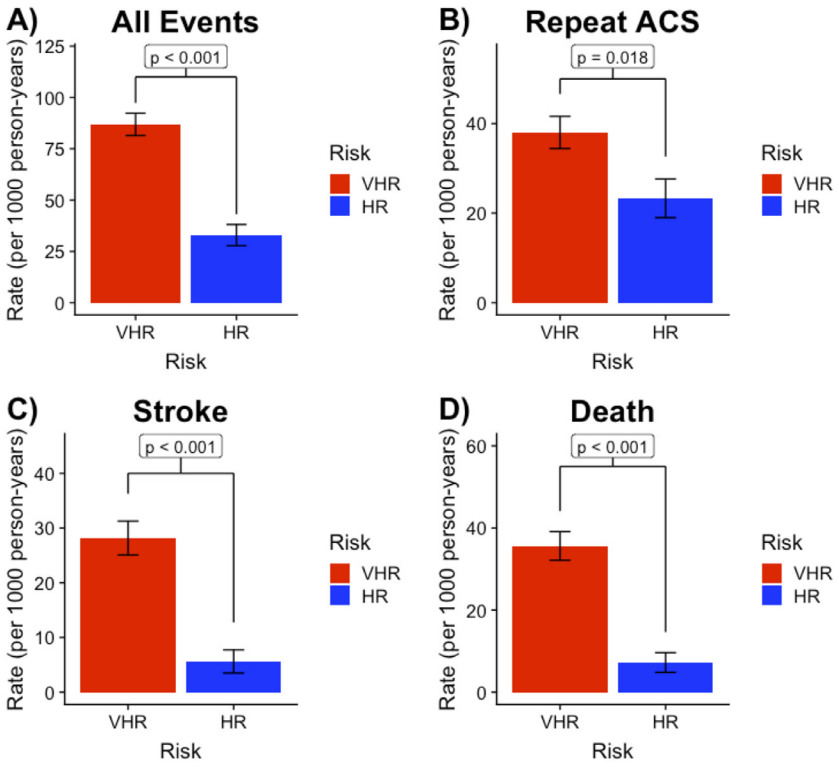
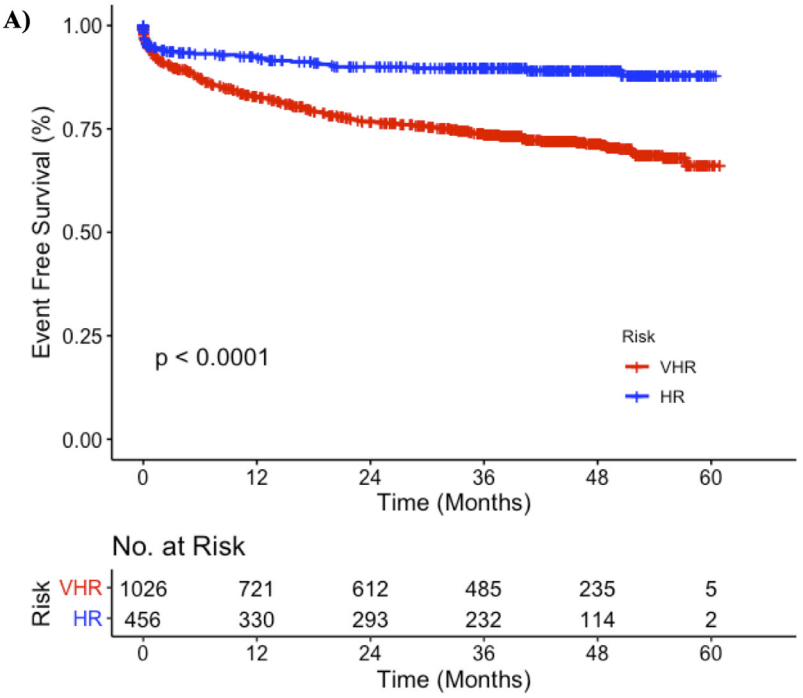


Figure 3. Incident rate of (**A**) composite events, (**B**) repeat ACS, (**C**) ischemic stroke, and (**D**) all-cause death for high risk (blue) atherosclerotic cardiovascular disease patients and very high risk (red) ASCVD patients.



B)

	Very High Risk	High Risk
No. of patients	1027	456
No. of events	256	41
Event Rate (per 1000PY)	86.9	32.9
Hazard ratio[a] [95% CI]	2.72 [1.95 – 3.78]	ref
p-value[a]	< 0.001	ref
Adjusted hazard ratio[b] [95% CI]	1.66 [1.01 – 2.74]	ref
Adjusted p-value[b]	0.047	ref

Figure 4. Survival analysis including (**A**) Kaplan-Meier survival curve and (**B**) univariate and multivariate Cox proportion hazard ratio analysis.

levels at baseline, likely because 66% of VHR patients were on a statin compared with only 28% of HR patients. This supports the idea that VHR patients are at an increased risk of an ACS event at any LDL-C level. Although statistically different, it should also be noted that these differences are quite large and the outcomes analyzed were clinically relevant.

Our cohort is well representative of the surrounding Chicago community. The Chicago Heart Association Detection Project in Industry (CHA) followed participants in the Chicago area from 1967 to 1973.[7] Among non−low-risk patients in CHA, 35% were female, and 14% were black. This is comparable to our cohort where 35% were female and 19% were black. Interestingly, our cohort had significantly fewer current smokers (17%) compared with CHA, where 47% of participants were current smokers. This likely reflects nationwide trends of decreasing prevalence of smokers in the last few decades.

Our results add to those found by Roe et al who examined the VHR and HR groups in the setting of the ODYSSEY OUTCOMES trial.[8] They found that 63.1% of trial patients were considered VHR, a similar number to our nontrial cohort. Interestingly, placebo-treated VHR patients in the ODYSSEY OUTCOMES trial had an event rate of 14.4% compared with 5.6% of HR patients for a relative risk difference of 2.6, again a similar finding to our nontrial cohort.

We had a relatively large, heterogeneous patient cohort with a mean follow-up of 3.3 years. Compared with large randomized trials, such as the recent ODYSSEY OUTCOMES trial, our study had more African Americans (18.9% in our study compared with 2.5% in the trial) and females (34.9% in our study compared with 25.2% in the trial).[9]

Several limitations should be noted. First, we performed a retrospective cohort study which introduces information bias if data are collected differently for the VHR and HR groups and is hypothesis seeking as opposed to hypothesis proving. Second, although the NMEDW, like other electronic databases, are powerful tools in analyzing large datasets, there are key limitations, specifically misclassification and omission. The NMEDW identifies diseases primarily through ICD codes. However, ACS is often difficult to diagnose, and many patients may be mistakenly classified. In order to limit misclassification, we limited our cohort to patients who had an ICD code of ACS and a LHC in the same hospitalization. We recognize that these strict criteria likely excluded patients who had ACS but were not managed with a LHC. Events within the NMEDW are only

documented if the event occurred at our institution or were reported within the EHR. Although we acknowledge that our adjudication of events is incomplete given that the NMEDW only documents events that occurred at our institution, it is unlikely to have changed our conclusions given the large differences and high numbers of patients. Finally, it was difficult to determine precisely those with HeFH in the NMEDW as there is no associated ICD-9/10 code. We used an LDL-C $\geq$220 mg/dL at the index ACS event as an approximation to capture those with phenotypically severe hypercholesterolemia but acknowledge that this overestimates those with HeFH. However, since only 4 patients met this criterion, an error in overestimating HeFH in our sample would be small.

In conclusion, post-ACS patients with at least 1 other ASCVD event or who have multiple high-risk conditions are at significantly increased risk for future cardiovascular morbidity and mortality. Our results support the stratification of secondary prevention ASCVD patients into VHR and HR groups as recommended by the 2018 ACC/AHA Multi-Society Guidelines on Cholesterol Management. This provides clinicians with a means of identifying those who would benefit the most from evidence-based intensive statin and nonstatin therapies to reduce ASCVD risk.

Author Contribution

Nathan W. Kong: Conceptualization, Methodology, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization Aakash Bavishi: Conceptualization, Methodology, Writing - Review & Editing Ansel Philip Amaral: Conceptualization, Methodology, Writing - Review & Editing Anjan Tibrewala: Conceptualization, Methodology, Writing - Review & Editing Arif Jivan: Conceptualization, Methodology, Writing - Review & Editing Philip Silberman: Software, Investigation, Data Curation Neil J. Stone: Conceptualization, Methodology, Writing - Review & Editing, Supervision

Disclosures

The authors have nothing to disclose.

Acknowledgments

We would like to thank Dr. Scott Grundy, MD, PhD at the University of Texas Southwestern Medical Center for providing feedback on our study. We would also like to recognize Liqi Chen of the Biostatistics Collaboration Center at Northwestern University for her insight and expertise into the statistical analysis of our data.

Data Availability

The datasets generated and used during the current study are available from the corresponding author on reasonable request.

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
2. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators I-I. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–2397.
3. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504.
4. Scandinavian Simvastatin Survival Study G. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
5. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;73:e285–e350.
6. Bohula EA, Morrow DA, Giugliano RP, Blazing MA, He P, Park JG, Murphy SA, White JA, Kesaniemi YA, Pedersen TR, Brady AJ, Mitchel Y, Cannon CP, Braunwald E. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol* 2017;69:911–921.
7. Pirzada A, Reid K, Kim D, Garside DB, Lu B, Vu TH, Lloyd-Jones DM, Zee P, Liu K, Stamler J, Daviglus ML. Chicago healthy aging study: objectives and design. *Am J Epidemiol* 2013;178:635–644.
8. Roe MT, Li QH, Bhatt DL, Bittner VA, Diaz R, Goodman SG, Harrington RA, Jukema JW, Lopez-Jaramillo P, Lopes RD, Louie MJ, Moriarty PM, Szarek M, Vogel R, White HD, Zeiher AM, Baccara-Dinet MT, Steg PG, Schwartz GG. Risk categorization using new American college of cardiology/American heart association guidelines for cholesterol management and its relation to alirocumab treatment following acute coronary syndromes. *Circulation* 2019;140:1578–1589.
9. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby J-F, Tricoci P, White HD, Zeiher AM. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097–2107.