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ORIGINAL RESEARCH ARTICLE

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

BACKGROUND: The 2018 US cholesterol management guidelines recommend additional lipid-lowering therapies for secondary prevention in patients with low-density lipoprotein cholesterol ≥70 mg/dL or non–high-density lipoprotein cholesterol ≥100 mg/dL despite maximum tolerated statin therapy. Such patients are considered at very high risk (VHR) based on a history of >1 major atherosclerotic cardiovascular disease (ASCVD) event or a single ASCVD event and multiple high-risk conditions. We investigated the association of US guideline-defined risk categories with the occurrence of ischemic events after acute coronary syndrome and reduction of those events by alirocumab, a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor.

METHODS: In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), patients with recent acute coronary syndrome and residual dyslipidemia despite optimal statin therapy were randomly assigned to alirocumab or placebo. The primary trial outcome (major adverse cardiovascular events, ie, coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina) was examined according to American College of Cardiology/American Heart Association risk category.

RESULTS: Of 18924 participants followed for a median of 2.8 years, 11935 (63.1%) were classified as VHR: 4450 (37.3%) had multiple prior ASCVD events and 7485 (62.7%) had 1 major ASCVD event and multiple high-risk conditions. Major adverse cardiovascular events occurred in 14.4% of placebo-treated patients at VHR versus 5.6% of those not at VHR. In the VHR category, major adverse cardiovascular events occurred in 20.4% with multiple prior ASCVD events versus 10.7% with 1 ASCVD event and multiple high-risk conditions. Alirocumab was associated with consistent relative risk reductions in both risk categories (hazard ratio=0.84 for VHR; hazard ratio=0.86 for not VHR; $P_{interaction}$=0.820) and by stratification within the VHR group (hazard ratio=0.86 for multiple prior ASCVD events; hazard ratio=0.82 for 1 major ASCVD event and multiple high-risk conditions; $P_{interaction}$=0.672). The absolute risk reduction for major adverse cardiovascular events with alirocumab was numerically greater (but not statistically different) in the VHR group versus those not at VHR (2.1% versus 0.8%; $P_{interaction}$=0.095) and among patients at VHR with multiple prior ASCVD events versus a single prior ASCVD event (2.4% versus 1.8%; $P_{interaction}$=0.661).

CONCLUSIONS: The US guideline criteria identify patients with recent acute coronary syndrome and dyslipidemia who are at VHR for recurrent ischemic events and who may derive a larger absolute benefit from treatment with alirocumab.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01663402.

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Clinical Perspective

What Is New?

- We evaluated the application of the 2018 American College of Cardiology/American Heart Association cholesterol management guideline recommendations for additional lipid-lowering therapies in patients with established atherosclerotic cardiovascular disease and residual dyslipidemia despite maximum tolerated statin therapy who were enrolled in the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab).
- Patients classified as very high risk, either because of a history of multiple atherosclerotic cardiovascular disease events or a single atherosclerotic cardiovascular disease event (trial-qualifying acute coronary syndrome) and multiple high-risk conditions, had more than double the risk of recurrent cardiovascular events as patients classified as not very high risk.
- The very-high-risk category also had a larger absolute benefit of alirocumab treatment.

What Are the Clinical Implications?

- Application of the new guideline recommendations for the risk stratification and use of additional lipid-lowering therapies in patients with established atherosclerotic cardiovascular disease clearly identifies patients at very high risk of recurrent cardiovascular events after an acute coronary syndrome, and who may derive substantial benefit from treatment with a proprotein convertase subtilisin/kexin type 9 inhibitor.

Secondary prevention treatment options for patients with established atherosclerotic cardiovascular disease (ASCVD) and elevated serum cholesterol values have evolved beyond statins since the publication of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines.[1] In the interim, large cardiovascular outcomes trials have evaluated nonstatin medications in patients with established ASCVD, including ezetimibe and inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9).[2–4] These trials demonstrated further reductions in the occurrence of major adverse cardiovascular events (MACE) when these therapies were added to statins.[2–4] Consequently, an update to the ACC/AHA cholesterol guidelines was published in 2018,[5] which specifically recommended shared decision making by clinicians and patients with established ASCVD to decide on the use of these nonstatin medications, informed by expected future risks of recurrent cardiovascular events. The guidelines categorize patients with established ASCVD as very high risk (VHR) or not VHR based on the presence of multiple prior ASCVD events or a single prior ASCVD event and multiple high-risk concomitant clinical conditions.

We evaluated the application of the 2018 ACC/AHA cholesterol guideline recommendations for patients with established ASCVD using data from the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab).[4] The trial compared alirocumab, a PCSK9 inhibitor, with placebo in patients on optimized statin therapy after a recent acute coronary syndrome (ACS). A high percentage of these patients had been treated with revascularization for the index ACS event, and they were well treated with other secondary prevention medications. Specifically, we analyzed the association of the VHR categorization with the occurrence of cardiovascular events and the influence of this categorization on the treatment effect of intensive low-density lipoprotein cholesterol (LDL-C) lowering with alirocumab.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Qualified researchers may also request access to study documents, including the clinical study report, study protocol with amendments, blank case report form, statistical analysis plan, and data set specifications.

Study Design and End Points

The design and primary findings from the ODYSSEY OUTCOMES trial have been published.[4,6] The trial was approved in each center by the responsible Institutional Review Board or Ethics Committee, and all patients provided written informed consent. A total of 18924 patients ≥40 years of age with a prior ACS hospitalization within 1 to 12 months on intensive or maximum tolerated statin therapy with residual dyslipidemia (LDL-C ≥70 mg/dL, non–high-density lipoprotein cholesterol ≥100 mg/dL, or apolipoprotein B ≥80 mg/dL) were randomly assigned to blinded treatment with alirocumab 75 mg every 2 weeks or placebo and followed for a median of 2.8 years. The dose of alirocumab was blindly adjusted during follow-up to target an on-treatment LDL-C level of 25 to 50 mg/dL.

The primary composite end point was MACE, comprising death attributable to coronary heart disease, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization.[6] All end points were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

Risk Categorization According to Guideline Recommendations

Patients were categorized as VHR with multiple major ASCVD events if they had at least 1 prior ASCVD event before the qualifying index ACS, including myocardial infarction,

ischemic stroke, or peripheral artery disease.[5] Patients who did not have multiple major ASCVD events could also be categorized as VHR based on the combination of 1 major ASCVD event (the qualifying index ACS for the trial) and at least 2 high-risk conditions (age ≥65 years, revascularization before the index ACS, diabetes mellitus, history of hypertension, baseline estimated glomerular filtration rate of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥100 mg/dL despite maximum tolerated statin therapy).[5] The presence of heterozygous familial hypercholesterolemia (another high-risk clinical condition specified in the guidelines) was not captured on the trial case report form. Analyses were performed by the categorization of VHR versus not VHR and then with further stratification of the patients at VHR according to the presence of multiple major ASCVD events versus 1 major ASCVD event with at least 2 high-risk clinical conditions.

Statistical Analysis

Summary statistics, such as mean values and proportions, were used to compare the baseline clinical characteristics of

Table 1. Baseline Clinical Characteristics by Very-High-Risk Categorization and by Substratification of Very-High-Risk Patients

Variable	All Patients		Non-VHR		VHR*		VHR* (Multiple Prior Major ASCVD Events)		VHR* (1 Major Prior ASCVD Event + Multiple High-Risk Conditions)	
	Placebo (n=9462)	Alirocumab (n=9462)	Placebo (n=3525)	Alirocumab (n=3464)	Placebo (n=5937)	Alirocumab (n=5998)	Placebo (n=2241)	Alirocumab (n=2209)	Placebo (n=3696)	Alirocumab (n=3789)
Demographics										
Age, y	58.6±9.4	58.5±9.3	54.7±7.6	54.6±7.5	61.0±9.6	60.8±9.5	60.2±9.5	60.6±9.2	61.4±9.6	60.9±9.6
Male sex	7090 (74.9)	7072 (74.7)	2876 (81.6)	2808 (81.1)	4214 (71.0)	4264 (71.1)	1749 (78.0)	1677 (75.9)	2465 (66.7)	2587 (68.3)
Cardiovascular risk factors										
Smoking status										
Current	2278 (24.1)	2282 (24.1)	576 (16.3)	548 (15.8)	1702 (28.7)	1734 (28.9)	544 (24.3)	521 (23.6)	1158 (31.3)	1213 (32.0)
Former or never	7183 (75.9)	7180 (75.9)	2948 (83.6)	2916 (84.2)	4235 (71.3)	4264 (71.1)	1697 (75.7)	1688 (76.4)	2538 (68.7)	2576 (68.0)
Hypertension	6044 (63.9)	6205 (65.6)	1079 (30.6)	1099 (31.7)	4965 (83.6)	5106 (85.1)	1766 (78.8)	1801 (81.5)	3199 (86.6)	3305 (87.2)
Diabetes mellitus	2751 (29.1)	2693 (28.5)	255 (7.2)	242 (7.0)	2496 (42.0)	2451 (40.9)	852 (38.0)	776 (35.1)	1644 (44.5)	1675 (44.2)
Prior medical history										
Peripheral artery disease	386 (4.1)	373 (3.9)	0	0	386 (6.5)	373 (6.2)	386 (17.2)	373 (16.9)	0	0
Congestive heart failure	1449 (15.3)	1365 (14.4)	79 (2.2)	62 (1.8)	1370 (23.1)	1303 (21.7)	596 (26.6)	545 (24.7)	774 (20.9)	758 (20.0)
Myocardial infarction	1843 (19.5)	1790 (18.9)	0	0	1843 (31.0)	1790 (29.8)	1843 (82.2)	1790 (81.0)	0	0
PCI	1615 (17.1)	1626 (17.2)	26 (0.7)	20 (0.6)	1589 (26.8)	1606 (26.8)	1262 (56.3)	1244 (56.3)	327 (8.8)	362 (9.6)
CABG	526 (5.6)	521 (5.5)	4 (0.1)	6 (0.2)	522 (8.8)	515 (8.6)	402 (17.9)	374 (16.9)	120 (3.2)	141 (3.7)
Ischemic stroke	256 (2.7)	268 (2.8)	0	0	256 (4.3)	268 (4.5)	256 (11.4)	268 (12.1)	0	0
Laboratory values										
eGFR, mL/min	79.8±19.1	79.5±19.4	84.9±16.0	84.5±16.0	76.8±20.2	76.6±20.5	77.2±20.1	76.3±19.8	76.6±20.2	76.7±21.0
LDL-C, mg/dL	92.3±30.8	92.4±31.1	89.8±28.6	89.8±27.5	93.8±31.9	94.0±32.9	96.1±32.7	98.1±35.6	92.4±31.4	91.5±31.0
Non–HDL-C, mg/dL	122±35.5	122±35.0	118±32.9	118±31.4	125±36.7	125±36.7	128±38.0	130±39.6	123±35.8	122±34.7
HDL-C, mg/dL	44.2±11.4	44.4±11.3	44.2±11.2	44.6±11.2	44.1±11.5	44.2±11.4	43.6±11.2	44.2±11.4	44.5±11.7	44.3±11.4
Triglycerides, mg/dL, median (quartile 1, quartile 3)	129 (94.7,183)	129 (93.8, 181)	121 (89.4, 172)	122 (88.5, 169)	135 (97.0, 188)	135 (97.0, 188)	136 (98.0, 193)	136 (97.3, 189)	133 (96.5, 186)	133 (97.0, 187)
Apolipoprotein B, mg/dL	83.3±21.6	83.0±21.3	80.6±20.1	80.2±19.1	84.9±22.3	84.6±22.3	86.6±22.4	87.6±23.7	83.8±22.1	82.9±21.3

Data presented as n (%) or mean±SD unless otherwise indicated.

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; and VHR, very high risk.

*Patients were categorized as very-high-risk with (a) multiple major ASCVD events if they had ≥1 prior ischemic event before the qualifying index ACS event, including myocardial infarction, ischemic stroke, or peripheral artery disease; or (b) 1 major ASCVD event (the qualifying index ACS event) and ≥2 high-risk conditions (age ≥65 years, revascularization before the index ACS event, diabetes mellitus, history of hypertension, baseline eGFR of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe).[5]

patients among the categorized subgroups by risk status. The background frequencies in incidence rates of MACE and its components, also cardiovascular and all-cause death, among the categorized subgroups by risk status were compared only among patients receiving placebo to limit confounding by randomized treatment. The association of baseline LDL-C values and the absolute risk increase in MACE and death among the categorized subgroups by risk status was evaluated by using generalized linear regression models by treatment groups separately. Kaplan-Meier curves for survival probability over time were plotted by treatment groups and by risk status. Both relative risk reductions (RRRs) and absolute risk reductions (ARRs) by treatment assignment were calculated to evaluate the alirocumab treatment effect by subgroup interaction. The estimates and tests for hazard ratios (HRs) between treatment groups and treatment by risk status interaction used proportional hazard models for RRRs and the Gail-Simon method for ARRs.[7] Marginal Cox regression models were used to estimate treatment HRs and testing of treatment by risk status interaction for total (ie, first and potentially subsequent) nonfatal MACE and all-cause death events. Nonparametric mean cumulative function curves were created for total events, representing the expected (ie, mean) cumulative number of events per 100 patients at a given point in time after randomization. The SAS 9.4 analytic software package was used to perform the statistical analyses.

Table 2. Frequency of Ischemic Events Among Placebo-Treated Patients by Very-High-Risk Categorization and by Substratification of Very-High-Risk Patients

End Point	All Patients	Non-VHR	VHR	VHR* (Multiple Prior Major ASCVD Events)	VHR* (1 Major Prior ASCVD Event + Multiple High-Risk Conditions)
MACE					
Events	1052	198	854	458	396
Patient-years	25271	9699	15571	5720	9851
Incidence rate, /100 patient-years	4.16	2.04	5.48	8.01	4.02
Myocardial infarction					
Events	756	150	606	349	257
Patient-years	25530	9754	15776	5820	9955
Incidence rate, /100 patient-years	2.96	1.54	3.84	6.00	2.58
Stroke					
Events	152	13	139	68	71
Patient-years	26501	9974	16526	6250	10277
Incidence rate, /100 patient-years	0.57	0.13	0.84	1.09	0.69
CHD death					
Events	222	31	191	105	86
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	0.82	0.31	1.13	1.64	0.82
Unstable angina requiring hospitalization					
Events	60	15	45	25	20
Patient-years	26601	9969	16632	6302	10330
Incidence rate, /100 patient-years	0.23	0.15	0.27	0.40	0.19
Cardiovascular death					
Events	271	33	238	127	111
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	1.01	0.33	1.41	1.99	1.06
All-cause death					
Events	392	56	336	169	167
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	1.46	0.56	2.00	2.64	1.60

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; and VHR, very high risk.

*Patients were categorized as very high risk with (a) multiple major ASCVD events if they had ≥1 prior ischemic event before the qualifying index ACS event, including myocardial infarction, ischemic stroke, or peripheral artery disease; or (b) 1 major ASCVD event (the qualifying index ACS event) and ≥2 high-risk conditions (age ≥65 years, revascularization before the index ACS event, diabetes mellitus, history of hypertension, baseline eGFR of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe).[5]

RESULTS

A total of 18 924 patients were randomly assigned at 1315 sites in 57 countries, with 9462 patients randomly assigned to alirocumab and 9462 patients to placebo. Median (quartile 1, quartile 3) follow-up was 2.8 (2.3, 3.4) years. Among the overall population, 11 935 patients (63.1%) were categorized as VHR, with 4450 of these (37.3%) having multiple major ASCVD events and 7485 (62.7%) having 1 major ASCVD event (index ACS event) and at least 2 high-risk clinical conditions. Among the 7485 patients classified as at VHR because of 1 major ASCVD event and at least 2 high-risk clinical conditions, 2568 (41.2%) qualified because of the presence of age ≥65 years and hypertension, 1045 (14.0%) qualified because of age ≥65 years and diabetes mellitus, and 403 (5.4%) qualified because of age ≥65 years and current smoking (the 3 qualification categories may not be mutually exclusive). In comparison with patients categorized as not VHR, patients at VHR were older, more commonly female, and more likely to have cardiovascular risk factors and prior cardiovascular events and procedures, and, in general, they had higher baseline lipid values (Table 1). Comparing patients in the VHR group with multiple major ASCVD events to those with a single ASCVD event and multiple risk factors, the former were more frequently male and had fewer cardiovascular risk factors.

Among patients in the placebo group, the rates of all events were substantially higher in the patients at VHR than in those categorized as not VHR (Table 2). When placebo-treated, patients at VHR were further stratified by the presence of multiple major ASCVD events or 1 major ASCVD event and multiple risk factors; the frequencies of ischemic end points were higher among those with multiple major ASCVD events.

Treatment with alirocumab was associated with similar reductions in LDL-C levels among patients categorized as VHR or not VHR (Figure 1A), and also among the patients at VHR further stratified by the presence of multiple major ASCVD events or 1 major ASCVD event and multiple risk factors (Figure 1B).

The Kaplan-Meier curves depicting the longitudinal occurrence of MACE events over time demonstrate a substantially higher risk of events among those categorized as VHR in comparison with those categorized as not VHR, with an earlier and more sustained separation of the event curves by alirocumab versus placebo treatment among the patients at VHR (Figure 2A). Similarly, the risk of death was greater among patients categorized as VHR, with a separation of the event curves by alirocumab versus placebo treatment observed only in the VHR group (Figure 2B).

The HR for MACE observed with alirocumab treatment was similar in the VHR (HR, 0.84; 95% CI, 0.76–0.93) and not VHR (HR, 0.86; 95% CI, 0.70–1.06; $P_{interaction}$=0.820) categories and was also similar among the patients at VHR further stratified by the presence of multiple major ASCVD events (HR, 0.86; 95% CI, 0.75–0.98) or 1 major ASCVD event and multiple risk factors (HR, 0.82; 95% CI, 0.71–0.95; $P_{interaction}$=0.672) (Figure 3A). A greater ARR in MACE was observed with alirocumab among those categorized as VHR (ARR, 2.13%; 95% CI, 0.91–3.35) versus those not at VHR (ARR, 0.77%; 95% CI, –0.28 to 1.81), but it was not statistically different ($P_{interaction}$=0.095). The ARR for alirocumab treatment was similar among the patients at VHR with multiple major ASCVD events (ARR, 2.42%; 95% CI, 0.11–4.73) or with 1 major ASCVD event and multiple risk factors (ARR, 1.82%; 95% CI, 0.47–3.17; $P_{interaction}$=0.661) (Figure 3A). Similar findings were observed with alirocumab treatment for all-cause death (Figure 3B).

An exploratory analysis that stratified patients as VHR by the presence of baseline (prerandomization) LDL-C levels ≥100 mg/dL demonstrated higher MACE and death rates among those with baseline LDL-C levels above this threshold and significantly greater RRRs and ARRs for both MACE and all-cause death with alirocumab treatment (Figure 3A and 3B). Nonsignificant but numerically greater RRR and ARR results were observed with alirocumab treatment in the patients not at VHR among those with baseline LDL-C levels ≥100 mg/dL.

The treatment effect of alirocumab according to risk status was further investigated by total nonfatal MACE events and all-cause death (Figure 4A). The RRR was identical irrespective of risk status (HRs 0.84 for both VHR and not VHR; $P_{interaction}$=0.98). However, the accrual of events was markedly higher among patients classified as VHR, with greater ARR by alirocumab, with nearly 5 events avoided over 4 years per 100 patients in the VHR subgroup in comparison with 1.6 events avoided over 4 years per 100 patients in the not VHR patient subgroup (Figure 4B).

DISCUSSION

Approximately two-thirds of patients with recent ACS and residual dyslipidemia despite optimal statin therapy who were enrolled in a contemporary cardiovascular outcomes trial were categorized as VHR for future ASCVD events based on recently published updates to the ACC/AHA cholesterol treatment guidelines.[5] The guideline-defined risk categories correlated well with the observed risk in this post-ACS population. Moreover, we observed that in the VHR category, patients with multiple major ASCVD events had an even greater risk of MACE and all-cause death during longitudinal follow-up than patients who had only 1 prior major ASCVD event (the qualifying index ACS event) with at least 2 high-risk clinical conditions. Although alirocumab was

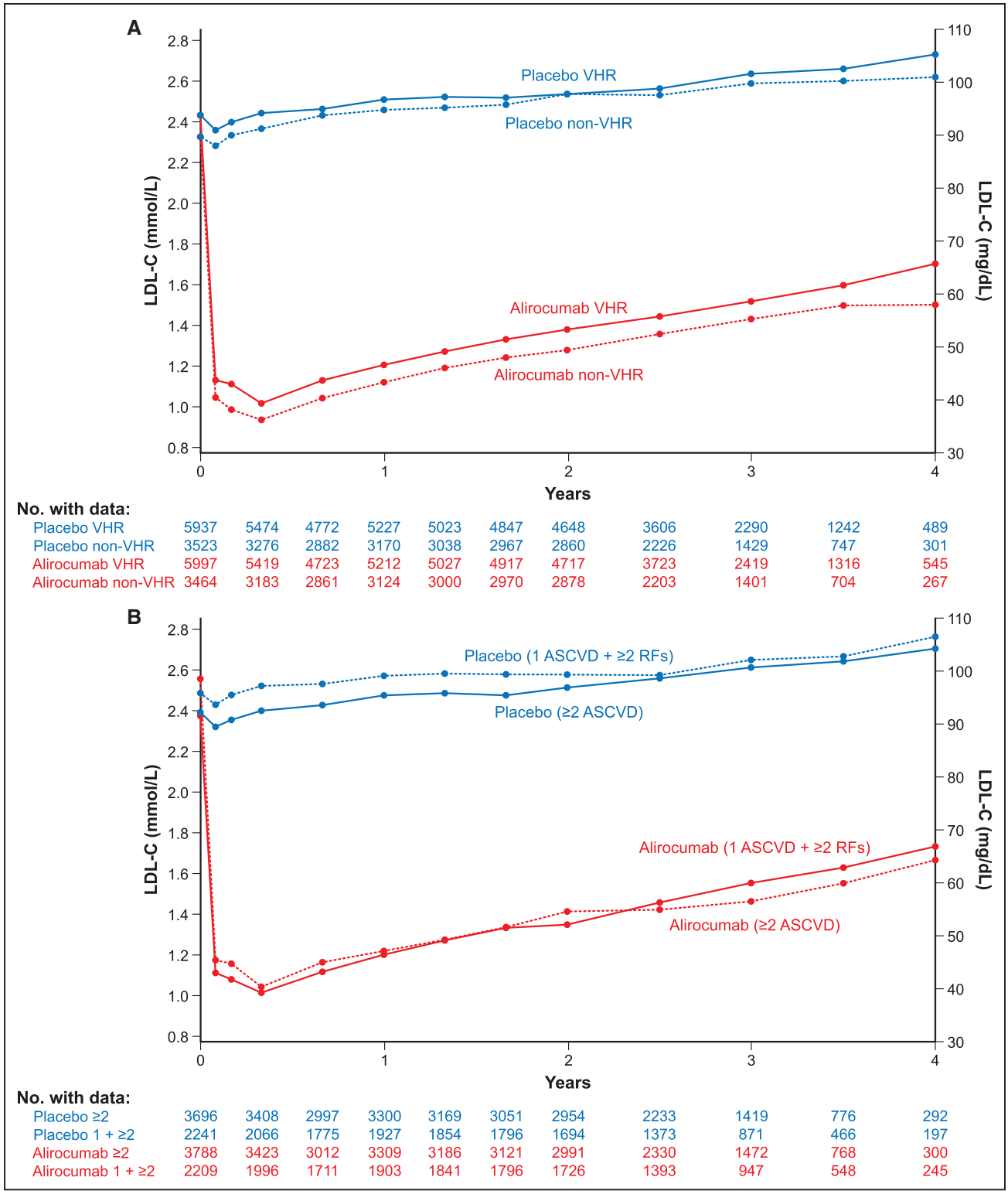

Figure 1. Impact of alirocumab treatment on temporal changes in achieved LDL-C values.
Very high-risk categorization (**A**) and substratification of very high-risk patients (**B**). ASCVD indicates major atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; and VHR, very high risk.

associated with consistent LDL-C lowering and relative reductions in the risk of MACE and all-cause death across guideline-defined risk categories, we observed a numerically greater, but not statistically different, ARR for time to first event with alirocumab in patients categorized as VHR in comparison with those categorized as not at VHR. These findings were further informed by a total events analysis that demonstrated a larger

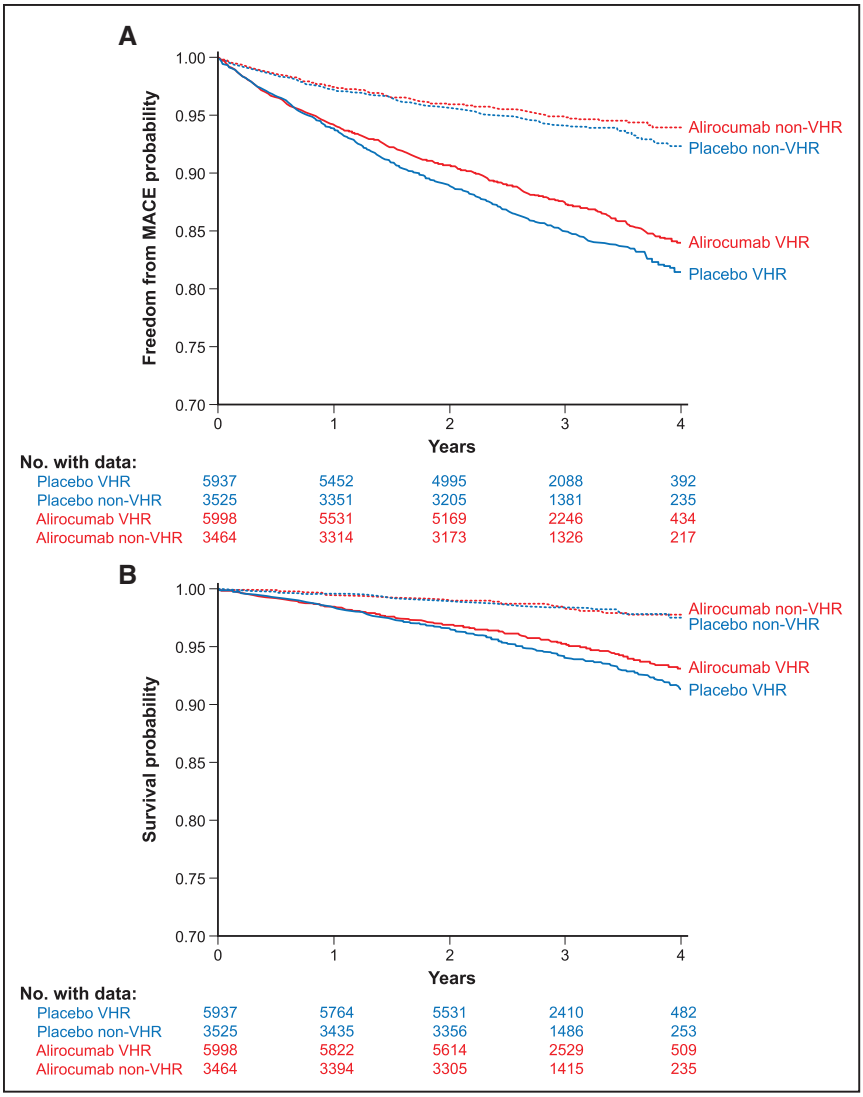

Figure 2. Occurrence of recurrent ischemic events by alirocumab treatment by very-high-risk categorization and by substratification of very-high-risk patients.
The frequency of MACE (**A**) and all-cause death (**B**). MACE indicates major adverse cardiovascular event; and VHR, very high risk.

number of events avoided over 4 years with alirocumab in the VHR versus not VHR subgroups. Furthermore, within the VHR category, we observed similar ARRs for time to first event with alirocumab among those who had multiple major ASCVD events and those who had only 1 prior major ASCVD event and multiple risk factors. In summary, these findings provide support for the application of the updated ACC/AHA cholesterol treatment guidelines[5] to select the highest-risk patients for treatment with additional LDL-C–lowering therapies (beyond statins) in the post-ACS setting.

Contemporary trials that evaluated further LDL-C lowering with ezetimibe or PCSK9 inhibitors, in addition to statin therapy, focused on patients with established ASCVD confirmed by a prior ischemic event.[2–4] Within this context, secondary analyses from these trials have shown that multiple high-risk subgroups derive enhanced benefit from additional LDL-C lowering, including those with peripheral artery disease, diabetes mellitus, multivessel coronary disease with prior coronary artery bypass surgery, and multiple prior myocardial infarction events.[8–13] Our findings provide further confirmation of the incremental benefit of additional LDL-C lowering for patients with established ASCVD (leveraging both time to first event and total events analyses) using a comprehensive, integrated risk-stratification approach recommended by recently updated cholesterol guidelines in comparison with binary attributions of risk based on the presence or absence of a single high-risk clinical characteristic.[5] Thus, the present data indicate the utility of the ACC/AHA cholesterol treatment guidelines[5] risk categories to inform decisions on the selection of patients with established ASCVD for PCSK9 inhibitor therapy to achieve the greatest benefits of intensive LDL-C–lowering therapies.

In the post-ACS setting, the risk of recurrent ischemic events is greatest in the first 3 to 6 months following the index ACS event, so the timing and sequencing of additional LDL-C–lowering therapies may need to be more front-loaded to have the greatest treatment benefit and impact. Treatment with high-intensity statin therapy starting at the time of ACS has been shown to be superior to placebo and to moderate-intensity statin

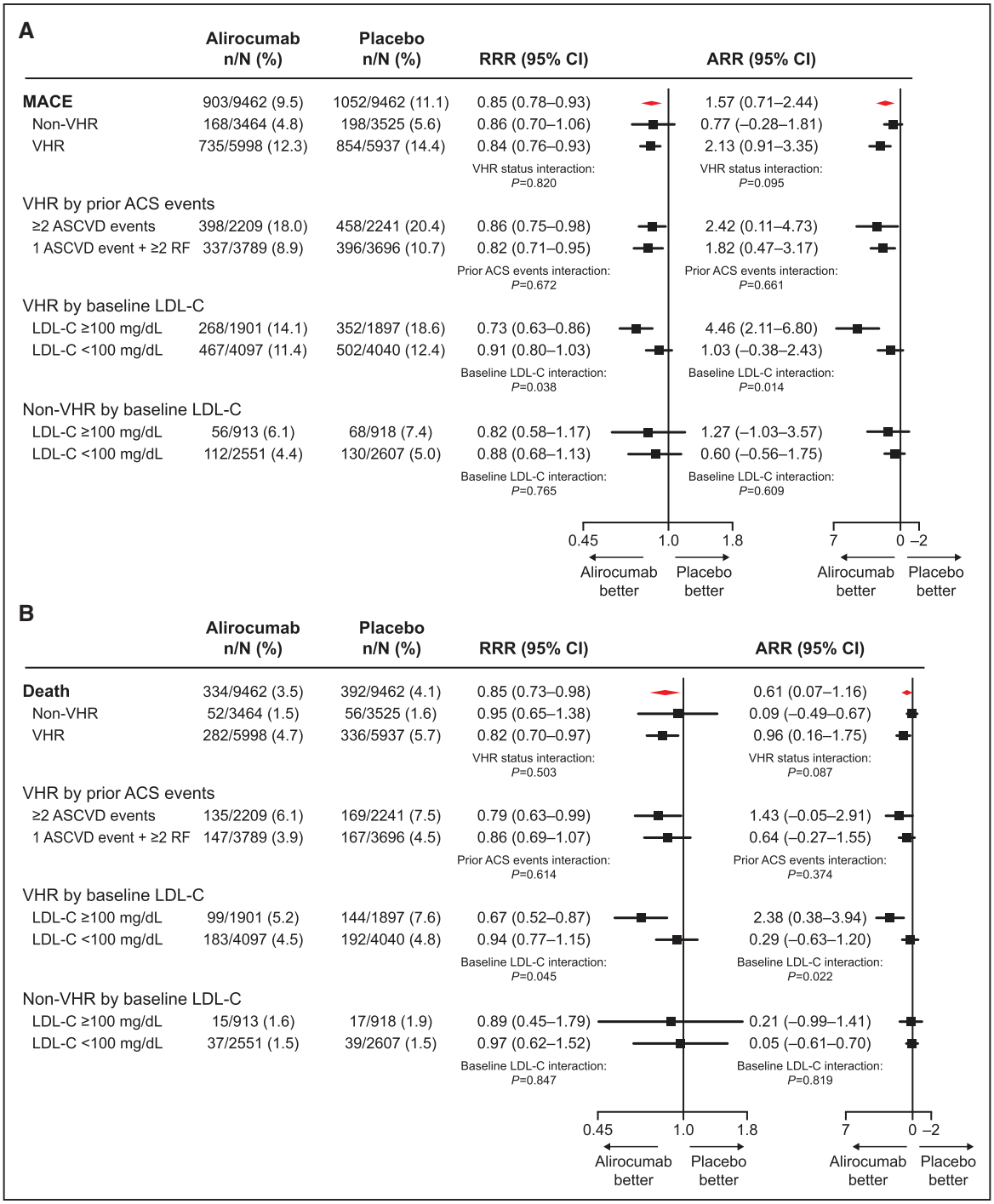

Figure 3. Risk reductions associated by treatment, and very-high-risk categorization, substratification of very-high-risk patients, and baseline LDL-C for very-high-risk and non–very-high-risk patients.

MACE (**A**) and all-cause death (**B**). An LDL-C value of 100 mg/dL equates to 2.6 mmol/L. ACS indicates acute coronary syndrome; ARR, absolute risk reduction; ASCVD, major atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; RF, risk factor; RRR, relative risk reduction; and VHR, very high risk.

therapy for reducing the early risk of recurrent ischemic events and correlated with greater relative reductions in LDL-C values in the MIRACL trial (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) and PROVE IT–TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22), respectively.[14,15] Further LDL-C lowering with ezetimibe, added to statin therapy, started within 10 days of an ACS event, is associated with a modest reduction in LDL-C values and recurrent ischemic events, but the benefits observed were apparent only after 1 year of treatment exposure.[2] Similar findings were observed in the ODYSSEY OUTCOMES trial with alirocumab, in which treatment was initiated at a

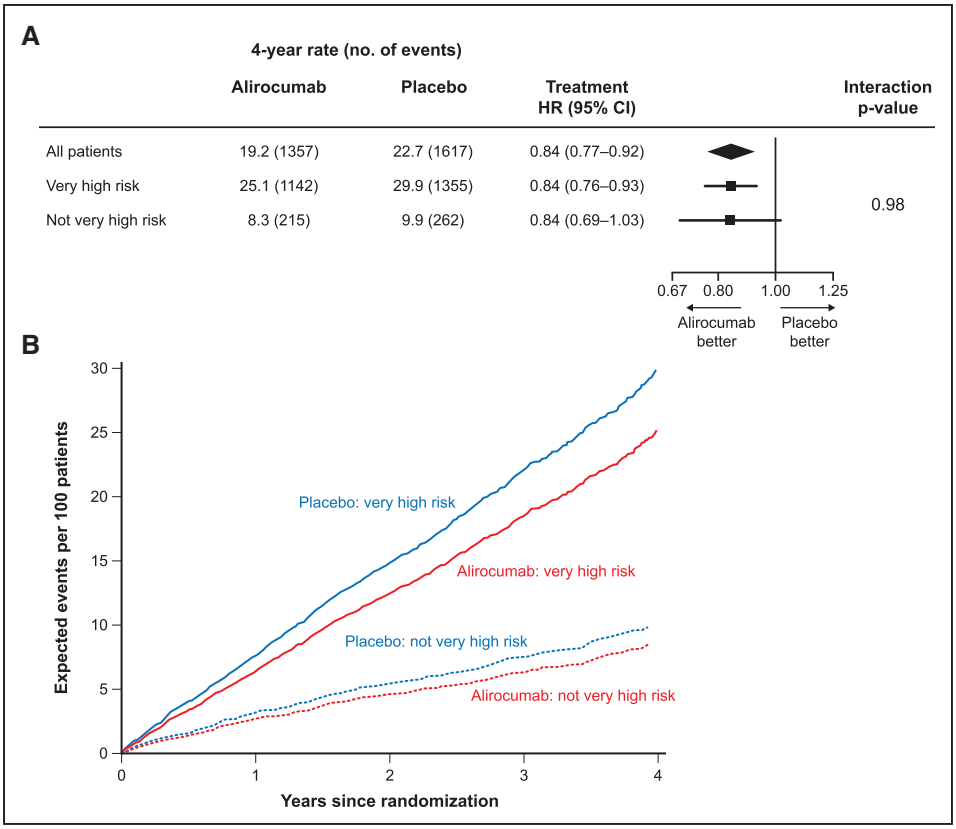

Figure 4. Total nonfatal MACE events and death by very high-risk categorization and treatment assignment to 4 years.
A, Treatment group rates represent the expected number of events per 100 patients for total nonfatal MACE and all-cause death events based on mean cumulative function estimates at 4 years; the total number of events observed are in parentheses. Treatment HRs and associated CIs and high-risk categorization by treatment assignment interaction *P* value are from marginal Cox regression models. **B**, Accrual of events per 100 patients. The expected number of nonfatal MACE and all-cause death events per 100 patients in the placebo and alirocumab groups at 4 years were 29.9 and 25.1, respectively, for patients classified as very high risk and 9.9 and 8.3, respectively, for patients classified as not very high risk. HR indicates hazard ratio; and MACE, major adverse cardiovascular event.

median of 2.6 months after the index ACS event and a separation of event curves became apparent at ≈1 year.[4] In this context, when considering additional LDL-C–lowering therapies for patients at VHR with ASCVD, the 2018 ACC/AHA cholesterol treatment guidelines recommend starting with high-intensity statin therapy, then adding ezetimibe if LDL-C values remain ≥70 mg/dL, and finally adding a PCSK9 inhibitor if LDL-C values continue to remain ≥70 mg/dL.[5] No clinical trial has investigated such a sequential approach to the addition of lipid-lowering therapies to intensive statin treatment. Nonetheless, LDL-C reduction with ezetimibe reaches a steady state ≈2 weeks after commencing treatment,[16] allowing assessment of the need for further addition of a PCSK9 inhibitor within a relatively short period of time, perhaps as early as 4 weeks after commencing treatment, and in line with the recommended time window of 4 to 12 weeks for repeat LDL-C measurement in the 2018 guidelines.[5] In this regard, the new ACC/AHA guidelines[5] are logical and pragmatic.

The ODYSSEY OUTCOMES trial showed that patients with ACS and LDL-C ≥100 mg/dL despite high-intensity statin therapy derived a greater absolute treatment benefit with alirocumab than those with LDL-C in the 70 to 100 mg/dL range.[4,17] In the present analysis, we demonstrate that, among patients with recent ACS classified as VHR according to ACC/AHA criteria, the benefit of alirocumab treatment was particularly pronounced among those statin-treated patients with LDL-C ≥100 mg/dL. Therefore, the presence of residual elevated LDL-C levels ≥100 mg/dL despite optimal statin therapy may be an important criterion to select those patients at VHR who will derive substantial benefit from the addition of a PCSK9 inhibitor.[5,18]

Limitations

Limitations of this analysis include insufficient data elements to identify patients in the ODYSSEY OUTCOMES trial with heterozygous familial hypercholesterolemia, which is 1 of the designated criteria for VHR. Second, the current analysis applies guideline categories only to patients with recent ACS, and not to the broader population of patients with chronic ASCVD. Third, the analysis of treatment benefit in patients at VHR according to baseline LDL-C should be considered in the context of trial design. The ODYSSEY OUTCOMES protocol specified blinded substitution of placebo for alirocumab in

patients with persistent on-treatment LDL-C levels <15 mg/dL. As attainment of LDL-C <15 mg/dL on alirocumab was infrequent among patients with baseline LDL-C levels >100 mg/dL, that subgroup was more likely to have persistent alirocumab treatment than those with baseline LDL-C levels <100 mg/dL. Finally, the present results should be considered hypothesis-generating because the analyses were not prespecified, but rather were conducted in an ad hoc manner in response to publication of the 2018 cholesterol guidelines update[5] in November 2018 (after conclusion of the trial earlier in 2018). Future studies may prespecify analyses of data according to guideline criteria for risk categories. In addition, meta-analyses of patient-level data from existing PCSK9 inhibitor trials may help to generalize the observations from the present analysis, which are limited to patients with recent ACS.

CONCLUSIONS

New recommendations for the risk stratification of patients with established ASCVD from the 2018 ACC/AHA cholesterol guidelines[5] for the selection of LDL-C–lowering therapies appear to identify patients with recent ACS and dyslipidemia who are at VHR for recurrent cardiovascular events and who may have an accentuated benefit from alirocumab treatment. Within this context, prospective evaluation of decision-support tools based on these guidelines will be helpful to determine the optimal approaches for improving the cholesterol management of patients in the post-ACS setting.

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