Patient Phenotypes, Cardiovascular Risk, and Ezetimibe Treatment in Patients After Acute Coronary Syndromes (from IMPROVE-IT)

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Risk prediction following acute coronary syndrome (ACS) remains challenging. Data-driven machine-learning algorithms can potentially identify patients at high risk of clinical events. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial randomized 18,144 post-ACS patients to ezetimibe + simvastatin or placebo + simvastatin. We performed hierarchical cluster analysis to identify patients at high risk of adverse events. Associations between clusters and outcomes were assessed using Cox proportional hazards models. The primary outcome was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina hospitalization, or coronary revascularization ≥30 days after randomization. We evaluated ezetimibe's impact on outcomes across clusters and the ability of the cluster analysis to discriminate for outcomes compared with the Global Registry of Acute Coronary Events (GRACE) score. Five clusters were identified. In cluster 1 (n = 13,252), most patients experienced a non-STEMI (54.8%). Cluster 2 patients (n = 2,719) had the highest incidence of unstable angina (n = 83.3%). Cluster 3 patients (n = 782) all identified as Spanish descent, whereas cluster 4 patients (n = 803) were primarily from South America (56.2%). In cluster 5 (n = 587), all patients had ST elevation. Cluster analysis identified patients at high risk of adverse outcomes (log-rank p <0.0001); Cluster 2 (vs 1) patients had the highest risk of outcomes (hazards ratio 1.33, 95% confidence interval 1.24 to 1.43). Compared with GRACE risk, cluster analysis did not provide superior outcome discrimination. A consistent ezetimibe treatment effect was identified across clusters (interaction p = 0.882). In conclusion, cluster analysis identified significant difference in risk of outcomes across cluster groups. Data-driven strategies to identify patients who may differentially benefit from therapies and for risk stratification require further evaluation. **(Am J Cardiol 2019;123:1193−1201)**

Despite our growing understanding of how best to manage patients after acute coronary syndrome (ACS), morbidity and mortality remain high. Many of these patients appear to have a high risk of recurrent cardiovascular events, potentially related to differential responses to secondary preventive therapies.[1] A number of strategies to identify these high-risk patients have been developed.[1−8] Cluster analysis (a form of machine learning) has been used in a variety of disease states, without the need for historical or arbitrary a priori assumptions, to identify patients with distinct phenotypes that have a varying natural history of disease and differential response to therapies.[9−17]

It remains unclear whether data-driven approaches can identify high-risk patient phenotypes that derive greater benefit from such preventative therapies. Using data from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), our primary objective was to determine whether a cluster analysis could group and identify post-ACS patients at higher differential risk of adverse cardiovascular events.

Furthermore, we evaluated whether cluster analysis would identify a consistent treatment response of ezetimibe on top of simvastatin across different risk profiles. Finally, we evaluated whether cluster analysis could provide superior discrimination of cardiovascular events compared with traditional risk models.

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See page 1200 for disclosure information.

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Methods

The details and results of IMPROVE-IT have been previously reported.[18,19] Briefly, IMPROVE-IT was a multinational, double-blind, placebo-controlled trial that randomized 18,144 patients stabilized after ACS to simvastatin (40 mg/day) in addition to placebo *or* simvastatin (40 mg/day) in addition to ezetimibe (10 mg/day). Patients had to be at least 50 years of age and hospitalized for ACS (including myocardial infarction [MI] with or without ST-segment elevation or high-risk unstable angina [UA]) within the preceding 10 days. For patients receiving long-term prescription lipid-lowering therapy, low-density lipoprotein cholesterol (LDL-C) levels were required to be 50 to 100 mg/dl; otherwise, LDL-C levels were required to be 50 to 125 mg/dl. Exclusion criteria included baseline ezetimibe use (in combination with a statin), creatinine clearance <30 ml/min, statin therapy with a potency >40 mg simvastatin, hemodynamic instability, or revascularization by coronary artery bypass grafting (CABG) for the index event. The analyzed population in the present study included all patients in IMPROVE-IT. All participants in IMPROVE-IT provided written informed consent to participate, and the study complied with the Declaration of Helsinki. The study received approval by the ethics committee at each participating site and was monitored by an independent data and safety monitoring board.

For both the present study and IMPROVE-IT, the primary outcome was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for UA, or coronary revascularization ≥30 days after randomization. We also evaluated cardiovascular death and all-cause mortality.

To obtain the patient clusters, we first conducted variable reduction on a set of 48 candidate baseline variables. Variable reduction grouped these baseline variables into disjoint variable clusters, and these variables were selected based on availability of baseline data. (The baseline variables representing patient characteristics, medical history, and labs used in the analysis are listed in the Supplementary Appendix.) Dimension reduction of this covariate list through variable clustering was conducted using the SAS PROC VARCLUS function. Using the results from variable reduction, we then clustered "similar" patients together using Ward's minimum variance method. Combining statistical criteria for cluster analysis and clinical judgment, we identified 5 patient clusters (full details provided in the Supplementary Appendix). One patient was removed from analysis due to an extreme triglyceride value.

Baseline patient characteristics, labs, and medications were described according to the identified 5 clusters. Continuous variables were described as medians with 25th and 75th percentiles; categorical variables were described as frequencies with percentages. Characteristics were compared across clusters using the Kruskal-Wallis test for continuous variables and the Pearson chi-squared test for categorical variables. The survival distributions for all the clinical endpoints were estimated using the Kaplan-Meier method and were compared between clusters using the log-rank test. Cox proportional hazards models were used to assess the associations between cluster groups and outcomes and to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) for each cluster in comparison with a reference cluster. Using interaction terms in a Cox regression model, we assessed whether cluster membership was associated with a differential response to ezetimibe on top of simvastatin therapy for each outcome. The ability of cluster membership to discriminate for the primary outcome, cardiovascular death, and all-cause death (using the c-statistic) was compared with the Global Registry of Acute Coronary Events (GRACE) score.

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Results

Hierarchical cluster analysis identified 5 patient clusters with varying distributions of baseline demographics and qualifying ACS events (Table 1).

Cluster 1 was the largest (n = 13,252). The median age was 63 years, and 92.1% of the patients were white (n = 12,188). Compared with other clusters, these patients had the lowest burden of congestive heart failure (2.2%, n = 285), diabetes (23.7%, n = 3,138), previous MI (15.1%, n = 2,004), and history of angina (32.9%, n = 4,351). Most patients had a non-ST elevation MI as the index ACS (54.8%, n = 7,253); furthermore, most patients had a percutaneous coronary intervention (PCI) catheterization after the index ACS (91.7%, n = 12,140).

In comparison, cluster 2 patients (n = 2,719) were the oldest (median age 66) and had the highest burden of comorbidities, including congestive heart failure (14.9%, n = 405), diabetes (40.8%, n = 1,108), previous MI (49.5%, n = 1,345), and history of angina (80.1%, n = 2,177). For the index ACS, most patients in cluster 2 had UA (n = 83.3%, n = 2,263), and they also had the lowest rate of catheterization (72.7%, n = 1,975) and PCI (44.6%, n = 1,210).

Patients in cluster 3 (n = 782) were among the youngest (median age 62), and all identified as having Spanish descent. They had a distribution of qualifying ACS events, and the majority came from South America (67%, n = 524).

Cluster 4 patients (n = 803, median age 63) were primarily identified as "other" (91.4%, n = 734) regarding race, and the majority were from South America (56.2%, n = 451). Cluster 4 patients had a distribution of qualifying ACS events and had the second-lowest rates of catheterization (76.8%, n = 615) and PCI (57.4%, n = 460).

Cluster 5 had the fewest patients (n = 587) and was one of the youngest clusters (median age 62); all patients had evidence of ST elevation. Cluster 5 patients also had the second-highest use of catheterization (89.4%, n = 525) and PCI (70.4%, n = 413) for the index ACS.

Medication use did not vary significantly across clusters; however, cluster 2 had the lowest use of angiotensin-converting enzyme inhibitors (Table 1).

Table 1
Baseline characteristic by cluster group

Characteristic	Cluster 1 (N = 13,252)	Cluster 2 (N = 2,719)	Cluster 3 (N = 782)	Cluster 4 (N = 803)	Cluster 5 (N = 587)
Age (yrs)	13,252, 63 (57−71)	2,719, 66 (59−73)	782, 62 (55−69)	803, 63 (56−70)	587, 62 (56−71)
Men	10,146/13,252 (76.6%)	1,984/2,719 (73.0%)	569/782 (72.8%)	575/803 (71.6%)	453/587 (77.2%)
Race					
American Indian or Alaskan Native	0/13,238 (0.0%)	0/2,715 (0.0%)	0/782 (0.0%)	50/803 (6.2%)	2/586 (0.3%)
Asian	669/13,238 (5.1%)	73/2,715 (2.7%)	0/782 (0.0%)	0/803 (0.0%)	31/586 (5.3%)
Black	364/13,238 (2.7%)	122/2,715 (4.5%)	0/782 (0.0%)	0/803 (0.0%)	13/586 (2.2%)
Spanish descent	8/13,238 (0.1%)	1/2,715 (0.0%)	782/782 (100.0%)	0/803 (0.0%)	17/586 (2.9%)
Native Hawaiian or Pacific Islander	0/13,238 (0.0%)	0/2,715 (0.0%)	0/782 (0.0%)	19/803 (2.4%)	0/586 (0.0%)
White	12,188/13,238 (92.1%)	2,519/2,715 (92.8%)	0/782 (0.0%)	0/803 (0.0%)	494/586 (84.3%)
Other	9/13,238 (0.1%)	0/2,715 (0.0%)	0/782 (0.0%)	734/803 (91.4%)	29/586 (4.9%)
Collection prohibited	0/13,238 (0.0%)	0/2,715 (0.0%)	0/782 (0.0%)	0/803 (0.0%)	0/586 (0.0%)
Weight (kg)	13,205, 82 (72−93)	2,705, 82 (72−93)	780, 76 (66−85)	800, 75 (66−85)	585, 80 (69−92)
Body mass index (kg/m^2)	13,124, 27.5 (25−31)	2,688, 28.0 (25−31)	777, 27.3 (25−30)	798, 26.9 (24−30)	583, 27.4 (25−30)
Height (cm)	13,137, 172.7 (165−178)	2,690, 170.9 (164−177)	777, 167.0 (160−172)	799, 167.0 (160−173)	584, 172.0 (165−178)
Waist circumference (cm)	12,328, 99.0 (91−108)	2,550, 100.0 (93−109)	752, 97.0 (90−105)	764, 96.5 (90−104)	564, 97.0 (90−105)
Heart rate (beats/min)	13,193, 68 (60−76)	2,702, 67 (60−75)	779, 68 (62−75)	801, 68 (62−76)	586, 68 (60−76)
Systolic blood pressure (mm Hg)	13,210, 122 (110−135)	2,708, 128 (116−140)	779, 120 (110−130)	802, 122 (110−135)	587, 122 (110−135)
Diastolic blood pressure (mm Hg)	13,210, 72 (65−80)	2,708, 74 (67−80)	779, 70 (64−80)	802, 72 (68−80)	587, 72 (65−80)
Family history of coronary artery disease	3,712/13,207 (28.1%)	813/2,716 (29.9%)	170/781 (21.8%)	208/799 (26.0%)	163/587 (27.8%)
Region					
United States	4,575/13,252 (34.5%)	829/2,719 (30.5%)	221/782 (28.3%)	99/803 (12.3%)	142/587 (24.2%)
Canada	893/13,252 (6.7%)	135/2,719 (5.0%)	4/782 (0.5%)	40/803 (5.0%)	35/587 (6.0%)
Western Europe	5,649/13,252 (42.6%)	1,139/2,719 (41.9%)	33/782 (4.2%)	174/803 (21.7%)	278/587 (47.4%)
Eastern Europe	1,025/13,252 (7.7%)	327/2,719 (12.0%)	0/782 (0.0%)	20/803 (2.5%)	44/587 (7.5%)
Malaysia/Singapore/ Hong Kong	534/13,252 (4.0%)	55/2,719 (2.0%)	0/782 (0.0%)	0/803 (0.0%)	27/587 (4.6%)
South America	373/13,252 (2.8%)	188/2,719 (6.9%)	524/782 (67.0%)	451/803 (56.2%)	49/587 (8.3%)
Australia/New Zealand	203/13,252 (1.5%)	46/2,719 (1.7%)	0/782 (0.0%)	19/803 (2.4%)	12/587 (2.0%)
Smoker					
Never	4,568/13,244 (34.5%)	977/2,716 (36.0%)	293/782 (37.5%)	316/802 (39.4%)	191/587 (32.5%)
Past	3,973/13,244 (30.0%)	1,155/2,716 (42.5%)	244/782 (31.2%)	266/802 (33.2%)	171/587 (29.1%)
Current	4,703/13,244 (35.5%)	584/2,716 (21.5%)	245/782 (31.3%)	220/802 (27.4%)	225/587 (38.3%)
Co-morbidities					
Congestive heart failure	285/13,245 (2.2%)	405/2,718 (14.9%)	29/782 (3.7%)	46/802 (5.7%)	25/587 (4.3%)
Killip class >1	9,680/13,232 (73.2%)	1,830/2,697 (67.9%)	538/782 (68.8%)	585/794 (73.7%)	443/586 (75.6%)
Prior atrial fibrillation	511/13,245 (3.9%)	365/2,718 (13.4%)	18/782 (2.3%)	30/802 (3.7%)	24/586 (4.1%)
History of diabetes	3,138/13,245 (23.7%)	1,108/2,718 (40.8%)	263/782 (33.6%)	284/802 (35.4%)	140/587 (23.9%)
Hypertension	7,558/13,245 (57.1%)	2,175/2,718 (80.0%)	510/782 (65.2%)	554/802 (69.1%)	340/587 (57.9%)
Previous peripheral arterial disease	554/13,244 (4.2%)	335/2,718 (12.3%)	38/782 (4.9%)	41/802 (5.1%)	37/587 (6.3%)
History of stroke	374/13,244 (2.8%)	227/2,718 (8.4%)	21/782 (2.7%)	36/802 (4.5%)	24/587 (4.1%)
Previous myocardial infarction	2,004/13,235 (15.1%)	1,345/2,717 (49.5%)	165/781 (21.1%)	198/802 (24.7%)	94/585 (16.1%)
History of PCI	1,823/13,241 (13.8%)	1,374/2,718 (50.6%)	132/782 (16.9%)	156/802 (19.5%)	77/586 (13.1%)
Previous CABG (≥3 years prior to entry)	875/13,244 (6.6%)	627/2,718 (23.1%)	62/782 (7.9%)	80/802 (10.0%)	40/587 (6.8%)
History of angina	4,351/13,243 (32.9%)	2,177/2,718 (80.1%)	325/782 (41.6%)	385/802 (48.0%)	210/587 (35.8%)
PCI after index ACS*	10,089/13,244 (76.2%)	1,210/2,716 (44.6%)	534/782 (68.3%)	460/802 (57.4%)	413/587 (70.4%)
Catheterization after index ACS*	12,140/13,240 (91.7%)	1,975/2,717 (72.7%)	669/782 (85.5%)	615/801 (76.8%)	525/587 (89.4%)
Index ACS: non-ST elevation MI	7,253/13,242 (54.8%)	268/2,717 (9.9%)	275/782 (35.2%)	321/802 (40.0%)	438/587 (74.6%)
Index ACS: unstable angina	1,442/13,242 (10.9%)	2,263/2,717 (83.3%)	243/782 (31.1%)	288/802 (35.9%)	149/587 (25.4%)
Evidence of ST deviation ≥0.1 mV = 1 mm	5,401/13,242 (40.8%)	138/2,712 (5.1%)	273/782 (34.9%)	239/801 (29.8%)	587/587 (100.0%)
Transient ST elevation	6/13,242 (0.0%)	0/2,712 (0.0%)	0/782 (0.0%)	0/801 (0.0%)	587/587 (100.0%)
New ST depression	2,700/13,242 (20.4%)	64/2,712 (2.4%)	117/782 (15.0%)	124/801 (15.5%)	100/587 (17.0%)
T-wave changes	2,960/13,242 (22.4%)	681/2,712 (25.1%)	195/782 (24.9%)	240/801 (30.0%)	85/587 (14.5%)
Evidence of hyperlipidemia	9,328/13,252 (70.4%)	2,299/2,719 (84.6%)	536/782 (68.5%)	569/803 (70.9%)	418/587 (71.2%)

(*continued*)

Table 1 (***Continued***)

Characteristic	Cluster 1 (N = 13,252)	Cluster 2 (N = 2,719)	Cluster 3 (N = 782)	Cluster 4 (N = 803)	Cluster 5 (N = 587)
Laboratory values					
Hemoglobin (mg/dl)	12,444, 13.7 (12.6−14.7)	2,536, 13.8 (12.6−14.7)	715, 14.0 (12.8−15.2)	742, 13.8 (12.6−14.9)	547, 13.8 (12.8−14.8)
Creatinine (mg/dl)	12,954, 1.0 (0.9−1.2)	2,643, 1.0 (0.9−1.2)	772, 1.1 (0.9−1.2)	784, 1.1 (0.9−1.2)	570, 1.0 (0.9−1.1)
HDL cholesterol (mg/dl)	13,093, 40 (33−49)	2,655, 40 (33−49)	756, 37 (31−44)	783, 38 (32−47)	572, 40 (34−50)
LDL cholesterol (mg/dl)	13,146, 97 (81−112)	2,695, 83 (70−97)	778, 96 (81−109)	798, 93 (78−107)	581, 99 (84−112)
Total cholesterol (mg/dl) at qualifying event	13,152, 166 (147−182)	2,696, 151 (133−169)	778, 163 (144−181)	788, 162 (142−180)	583, 167 (147−183)
ALT (mU/ml)	13,252, 21 (15−32)	2,719, 17 (12−25)	782, 25 (17−37)	803, 22 (15−36)	587, 19 (14−28)
AST (mU/ml)	13,252, 21 (16−32)	2,719, 17 (13−23)	782, 22 (16−32)	803, 21 (15−31)	587, 19 (15−28)
CPK (mU/ml)	13,252, 56 (37−95)	2,719, 46 (31−68)	782, 51 (35−83)	803, 51 (34−77)	587, 49 (35−79)
Glucose (mg/dl)	13,252, 100 (89−122)	2,719, 105 (91−135)	782, 102 (90−136)	803, 102 (91−126)	587, 101 (90−126)
HCT (%)	13,252, 41 (37−44)	2,719, 41 (37−44)	782, 42 (39−46)	803, 41 (38−45)	587, 41 (38−44)
hs-CRP (mg/dl)	13,252, 11 (5−29)	2,719, 5 (2−13)	782, 10 (5−28)	803, 10 (4−27)	587, 10 (4−27)
Baseline medications					
Aspirin	13,112/13,244 (99.0%)	2,636/2,717 (97.0%)	772/782 (98.7%)	797/802 (99.4%)	580/587 (98.8%)
Beta-blocker	12,275/13,244 (92.7%)	2,435/2,718 (89.6%)	721/782 (92.2%)	720/802 (89.8%)	521/587 (88.8%)
Thienopyridine	12,382/13,241 (93.5%)	2,145/2,714 (79.0%)	687/782 (87.9%)	682/802 (85.0%)	559/587 (95.2%)
ACE inhibitor	9,356/13,240 (70.7%)	1,766/2,717 (65.0%)	606/782 (77.5%)	604/802 (75.3%)	411/587 (70.0%)
Statins	10,397/13,243 (78.5%)	2,384/2,717 (87.7%)	641/782 (82.0%)	685/802 (85.4%)	459/587 (78.2%)

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CABG = coronary artery bypass grafting; CPK = creatine phosphokinase; HDL = high-density lipoprotein; HCT = hematocrit; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Data displayed as n, median (25th to 75th percentiles) or n/N (%).

* Before randomization.

Kaplan-Meier event rates and risk of outcomes by cluster membership are presented in Tables 2 and 3. For the primary end point, cluster 2 had the highest rate of events (n = 940, 42.48%), whereas cluster 5 had the lowest rate of events (n = 143, 29.02%). Similar trends were seen with the outcome of cardiovascular death (Table 2).

Compared with cluster 1, cluster 2 consistently had an increased risk of the primary outcome (HR 1.33, 95% CI 1.24 to 1.43; Figure 1), cardiovascular death (HR 1.62, 95% CI 1.39 to 1.89; Figure 2), and all-cause death (HR 1.57, 95% CI 1.42 to 1.74; Figure 3). Compared with cluster 1, cluster 3 had a higher risk of cardiovascular death (HR 1.38, 95% CI 1.04 to 1.82), and cluster 4 had a higher risk of cardiovascular death (HR 1.63, 95% CI 1.25 to 2.11) and all-cause death (HR 1.52, 95% CI 1.27 to 1.81). Although cluster 5 had the lowest rates of events across the spectrum of events (Table 2), compared with cluster 1, the risk of outcomes was not significantly different (Table 3). We identified the following rates of PCI postrandomization: cluster 1 2,739/13,252 (20.7%); cluster 2 608/2,719 (22.4%); cluster 3 124/782

Table 2
Numbers, events, and Kaplan-Meier event rates at 7 years by cluster membership

Outcomes	Log-rank test p value	Cluster	Total	Event	Kaplan-Meier event rate, %
Primary outcome	<0.0001	1	13,252	3,803	32.54
		2	2,719	940	42.48
		3	782	205	30.30
		4	803	223	33.76
		5	587	143	29.02
		All	18,143	5,314	33.70
Cardiovascular death	<0.0001	1	13,252	712	6.17
		2	2,719	216	9.87
		3	782	54	7.92
		4	803	62	8.95
		5	587	31	6.45
		All	18,143	1,075	6.87
All-cause death	<0.0001	1	13,252	1,664	14.05
		2	2,719	478	21.37
		3	782	104	15.03
		4	803	131	19.28
		5	587	69	14.04
		All	18,143	2,446	15.32

Table 3
Association of cluster membership and risk of outcomes

	Hazard ratio (95% confidence interval)			
Endpoint	Cluster 2 vs 1	Cluster 3 vs 1	Cluster 4 vs 1	Cluster 5 vs 1
Primary outcome	1.33 (1.24−1.43)	0.93 (0.81−1.07)	1.01 (0.89−1.16)	0.86 (0.73−1.01)
Cardiovascular death	1.62 (1.39−1.89)	1.38 (1.04−1.81)	1.63 (1.25−2.11)	1.04 (0.72−1.48)
All-cause death	1.57 (1.42−1.74)	1.15 (0.94−1.40)	1.52 (1.27−1.81)	1.00 (0.79−1.28)

(15.9%); cluster 4 125/803 (15.6%); cluster 5 112/587 (19.1%).

Ezetimibe, on top of simvastatin, was associated with a consistent treatment effect across clusters for the primary outcome (interaction p value = 0.882), cardiovascular death (0.434), and all-cause death (0.388). In evaluating the risk of outcomes, there was no cluster that appeared to derive a significantly greater benefit with ezetimibe treatment (Figure 4).

Cluster membership, compared with the GRACE score, had an inferior ability to discriminate for the primary outcome (c-statistic = 0.52 vs 0.56), cardiovascular death (0.54 vs 0.74), and all-cause death (0.54 vs 0.72).

Discussion

We evaluated the approach of utilizing a data-driven machine-learning algorithm known as hierarchical cluster analysis to identify post-ACS patients who have different risks of outcomes. We also evaluated whether cluster analysis can identify patients that have a differential treatment effect of ezetimibe on top of simvastatin. We identified the following major findings: (1) hierarchical cluster analysis identified 5 patient clusters that have different phenotypes primarily centered around race, co-morbidities, and type of ACS; (2) the risk of outcomes appeared to be significantly different across clusters; (3) ezetimibe had a consistent treatment effect across clusters; and (4) cluster analysis did

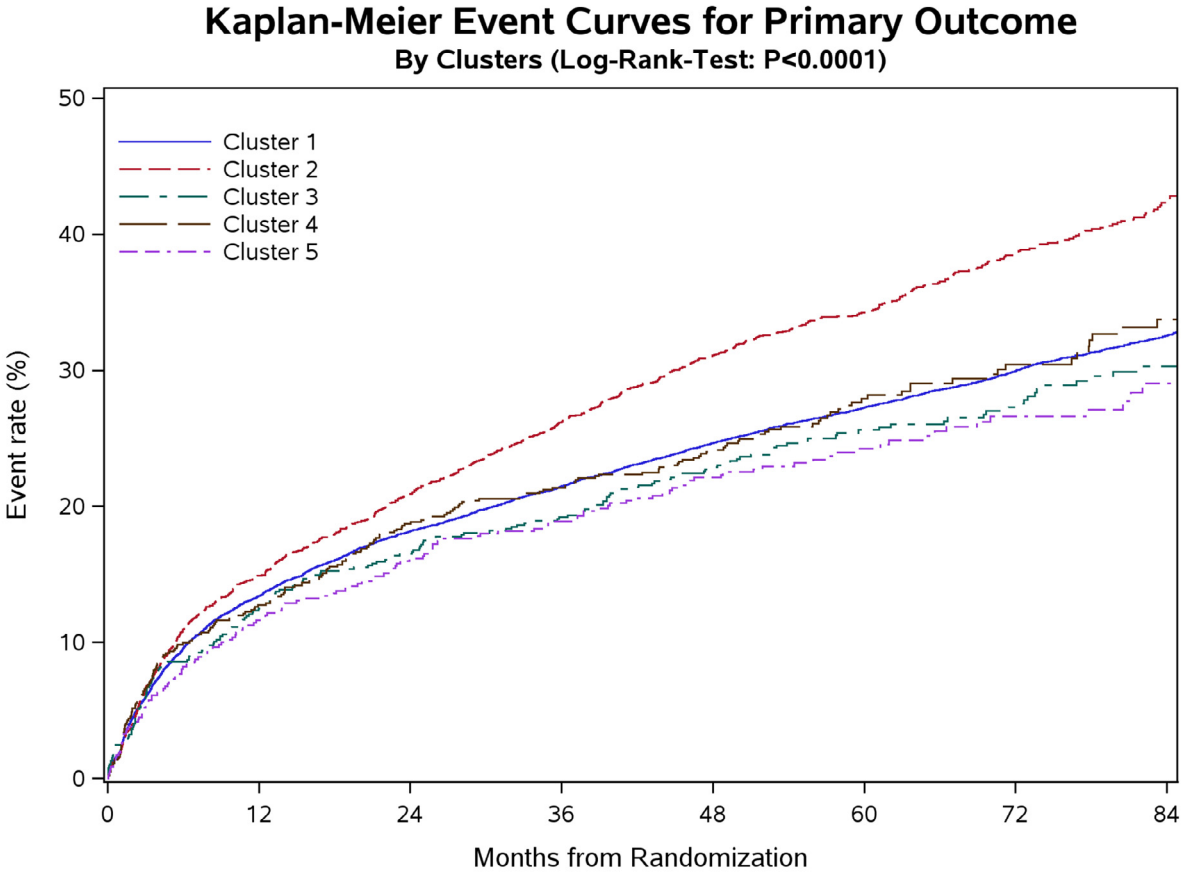

Figure 1. Kaplan-Meier event curves for the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or coronary revascularization ≥30 days after randomization.

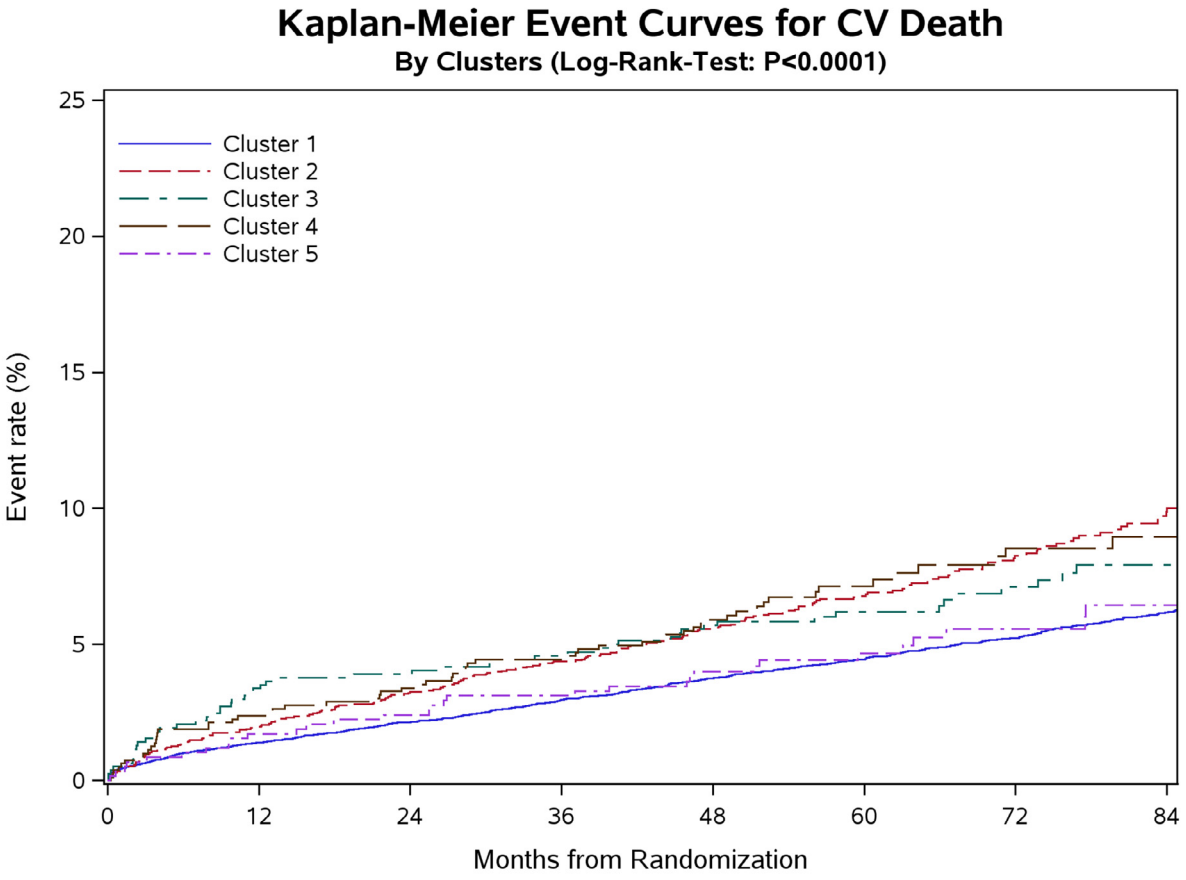

Figure 2. Kaplan-Meier event curves for cardiovascular death.

not provide superior discrimination compared with the GRACE score.

Previous cluster analyses among patients with ACS have been used to explore symptom correlation.[20,21] Our use of hierarchical cluster analysis focused on identifying high-risk patient phenotypes. Our data identified 5 distinct clusters primarily separated by race, region, co-morbidities, and type of ACS. Racial background and geographic location significantly influence treatment strategies, medication use, and processes of care in ACS and non-ACS populations[22–27] and may have contributed to the strong clustering by race and region seen in our analysis. The highest risk cluster (cluster 2) had the highest rate of postrandomization PCI. The lowest risk cluster for the primary end point (cluster 5) had an intermediate use of PCI compared with other clusters. As the majority of patients in cluster 5 had STEMI, the use of PCI here may reflect changes in treatment pattern based on the initial presentation.

Machine-learning algorithms to identify MI and aid in prognostication post-ACS have been previously explored.[6–8] However, these algorithms do not allow for the identification of specific high-risk patient phenotypes. In our analysis, there were significant differences among clusters regarding the risk of outcomes. Patients in cluster 2—who had a high burden of baseline angina and primarily presented with UA—had the highest risk of outcomes. Furthermore, we identified that cluster 5, with patients who had evidence of ST elevation, had the lowest risk of cardiovascular death and all-cause death. These results add to previous analyses suggesting improved outcomes in patients presenting with ST elevation MI compared with non-ST elevation MI.[28,29] Outcome differences based on these clusters may reflect differences in systems of care relating to the type of ACS, use of invasive coronary intervention, and associated co-morbidities.[28]

Machine-learning and data-driven algorithms represent an attractive approach to identifying patients who derive greater or less benefit, or even harm, from therapies; this stratification may ultimately allow for tailoring of therapies based on patient characteristics and risk profiles.[13,16] Our analysis demonstrated that ezetimibe had a consistent treatment effect on top of simvastatin across the cluster groups, even among the high-risk cluster 2 patients. Using data from the IMPROVE-IT trial, the TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2°P) was able to identify high-risk patients who derived the greatest benefit from the addition of ezetimibe to simvastatin therapy.[3] Although there is enthusiasm for utilizing machine-learning algorithms to identify patients

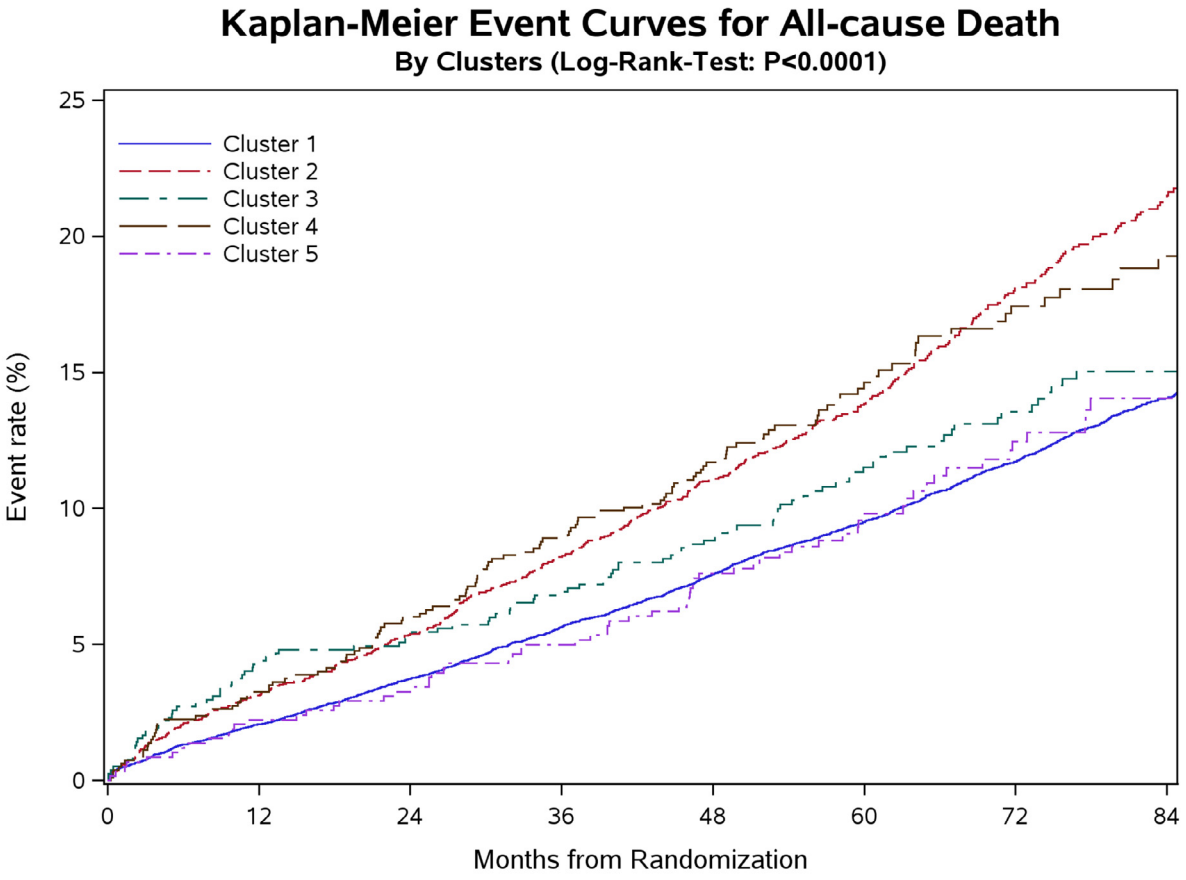

Figure 3. Kaplan-Meier event curves for all-cause death.

with differential responses to therapies, utilizing cluster analysis to identify phenotypes of patients that have differential response to therapies post-ACS would require further evaluation.

Traditional risk models such as the TIMI and GRACE risk scores identify risk of events at discreet time points. Cluster analysis represents a tool that may complement traditional risk models and allow for a continuous assessment of longitudinal risk. Such tools can be embedded within electronic health system databases and can be incorporated into shared decision-making models.[30] As we move toward personalized medicine, such algorithms may represent an avenue to improve the health outcomes of patients while minimizing cost and burden to health care systems.[31] Our results suggest that the use of other data-driven approaches to risk stratification must be carefully evaluated before implementing in routine clinical care.

These results are subject to the limitations of a post hoc analysis. The use of a selected clinical trial population with narrow inclusion criteria may have not resulted in the development of more phenotypically distinct clusters. Furthermore, these results may not be generalizable to a nontrial population. The phenotypes ascribed to different clusters are primarily descriptive; however, similar approaches have been used in previous analyses.[13,14] The clustering algorithms may have different results depending on the variables utilized and the quality of the available data. Cluster 1 included a majority of the overall patients, which may have influenced the ability to find treatment differences among other clusters. The decision to limit the number of clusters to 5 was influenced by the investigators' discretion, which may have influenced cluster composition. Fewer clusters would not have allowed for the identification of phenotypically meaningful groups of patients; more clusters would have significantly reduced the size of each cluster, resulting in a decreased ability to identify treatment differences in groups. Further validation of these findings in another independent dataset is required.

In our study, a data-driven machine-learning algorithm among stable post-ACS patients identified 5 different clusters with unique phenotypes and different risks of outcomes. Our results demonstrate clustering primarily around race, region, and type of ACS. Our approach demonstrated that ezetimibe on top of simvastatin had a consistent treatment effect across clusters. Cluster analysis may represent an avenue to complement traditional risk models in identifying continuous longitudinal risk of events. Future research will have to explore different machine-learning algorithms and their role in risk stratification and identifying strategies to tailor therapies post-ACS.

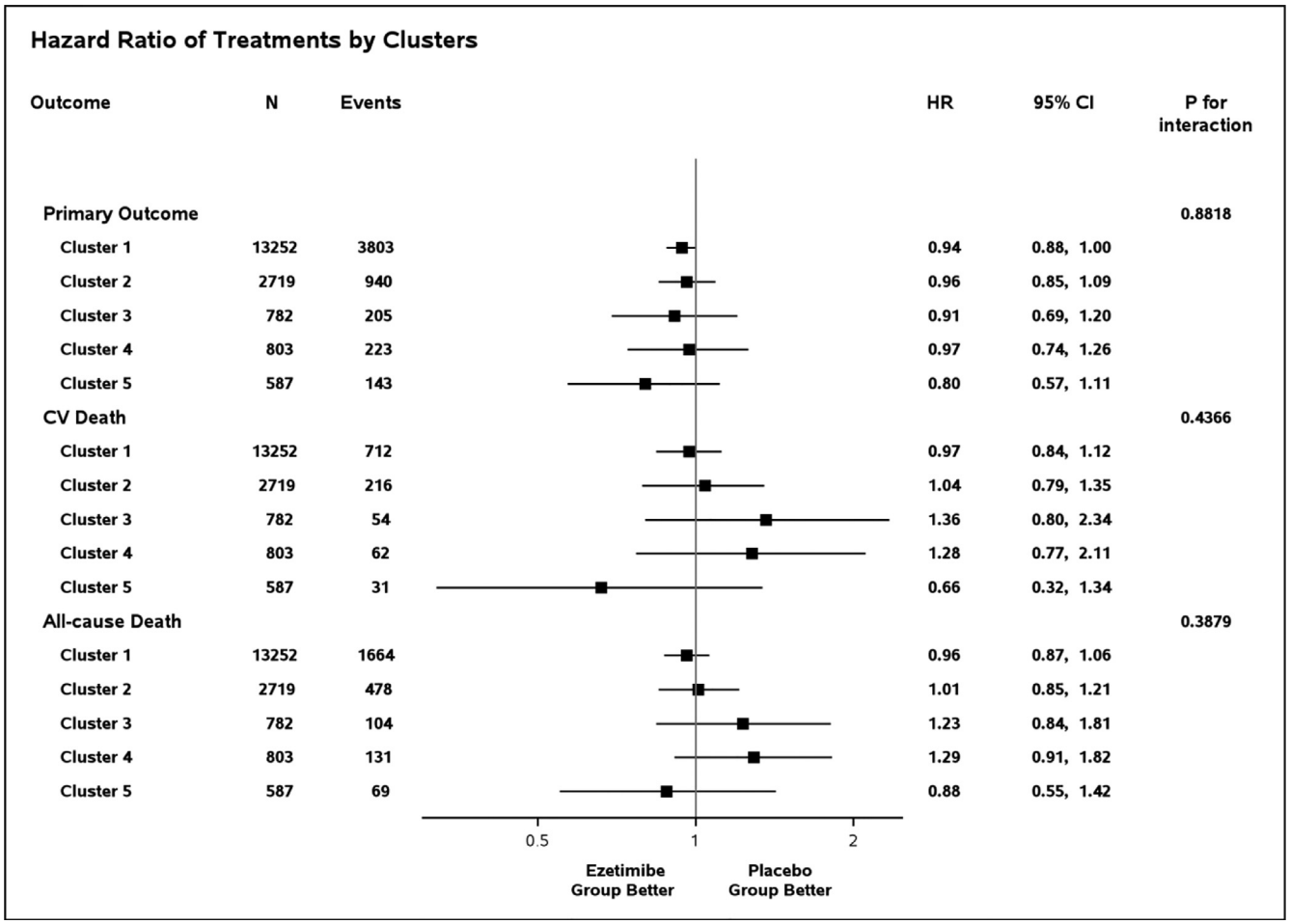

Figure 4. Hazard ratio of treatment effects on outcomes by each cluster.

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Supplementary materials

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