Clinical Investigations

Hypercholesterolemia Paradox in Relation to Mortality in Acute Coronary Syndrome

Address for correspondence:
Tracy Y. Wang, MD, MHS
Duke Clinical Research Institute
2400 Pratt Street, Room 0311
Terrace Level
Durham, NC 27705
wango085@mc.duke.edu

Tracy Y. Wang, MD, MHS; L. Kristin Newby, MD, MS; Anita Y. Chen, MS; Jyotsna Mulgund, MS; Matthew T. Roe, MD, MHS; Ali F. Sonel, MD; Deepak L. Bhatt, MD; Elizabeth R. DeLong, PhD; E. Magnus Ohman, MD; W. Brian Gibler, MD; Eric D. Peterson, MD, MPH

Division of Cardiology, Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina (Wang, Newby, Chen, Mulgund, Roe, DeLong, Ohman, and Peterson); Department of Cardiology, VA Pittsburgh Healthcare System, and the University of Pittsburgh, Pittsburgh, Pennsylvania (Sonel); Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio (Bhatt); Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio (Gibler)

ABSTRACT

Background: Hypercholesterolemia is a risk factor for coronary artery disease, yet is associated with lower risk of adverse outcomes in patients with acute coronary syndromes (ACS).

Hypothesis: We explored this paradox in 84 429 patients with non-ST-segment elevation ACS in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines registry.

Methods: We examined the association between a history of hypercholesterolemia and in-hospital mortality after adjusting for clinical covariates. After excluding patients with previously diagnosed hypercholesterolemia, we repeated the analysis, examining the association between newly diagnosed hypercholesterolemia (in-hospital low-density lipoprotein cholesterol [LDL-C] $\geq$100 mg/dL) and mortality.

Results: A history of hypercholesterolemia was associated with lower in-hospital mortality (unadjusted odds ratio [OR]: 0.58; 95% confidence interval [CI]: 0.55, 0.62). This protective association persisted after adjusting for baseline characteristics (OR: 0.71; 95% CI: 0.66, 0.76) and prior statin use (OR: 0.74; 95% CI: 0.68, 0.80). Among 22 711 patients with no history of hypercholesterolemia, 12 809 had a new in-hospital diagnosis of hypercholesterolemia. Unadjusted mortality in these patients was lower than among those with normal LDL levels (OR: 0.58; 95% CI: 0.50, 0.67); however, this difference was not significant after multivariable adjustment (OR: 0.86; 95% CI: 0.73, 1.01).

Conclusions: The association of hypercholesterolemia with better outcomes highlights a major challenge in observational analyses. Our results suggest this paradox may result from confounding due to other clinical characteristics, impact of statin treatment, and perhaps most importantly, the fact that previously diagnosed hypercholesterolemia is a marker for patients with more prior medical contact.

Introduction

Hypercholesterolemia is a well-known risk factor for the development of coronary artery disease.[1,2] Cholesterol-lowering therapies have been shown to significantly reduce downstream cardiovascular events;[3,4] however, in observational analyses of either acute coronary syndrome (ACS) clinical trials or registry databases, hypercholesterolemia has repeatedly been shown to be associated with a lower risk of adverse outcomes.[5–8]

The explanation for why hypercholesterolemia, unlike other cardiac risk factors, is paradoxically associated with better ACS outcomes remains elusive. Varying definitions of hypercholesterolemia (eg, patient-reported vs chart-documented) may have been applied over previous studies, thus confounding its association with outcomes. Furthermore, greater contact with the medical field increases the likelihood of a diagnosis of hypercholesterolemia, and, with better clinical optimization, may indirectly minimize adverse outcomes after ACS. We explored

The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines Quality Improvement Initiative (CRUSADE) is funded by the Schering-Plough Corporation (Kenilworth, NJ). Bristol-Myers Squibb/Sanofi Pharmaceuticals (New York, NY) Partnership provides additional funding support. Millennium Pharmaceuticals, Inc., (Cambridge, MA) also partly funded this work.

Clin. Cardiol. 32, 9, E22–E28 (2009)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20518

Received: May 5, 2008
Accepted with revision: August 20, 2008

this "hypercholesterolemia paradox" among patients with non-ST-segment elevation (NSTE) ACS enrolled in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines Quality Improvement Initiative (CRUSADE). We hypothesize that if a prior history of hypercholesterolemia is associated with improved outcomes, then, all other things being equal, hypercholesterolemia that is newly diagnosed during ACS hospitalization should impart a similar protective effect.

Methods

Study Population

We explored the hypercholesterolemia paradox in 98 571 patients with NSTE ACS enrolled in the CRUSADE study from January 2001 through March 2004. CRUSADE is a national quality improvement initiative designed to promote evidence-based treatment of hospitalized patients with NSTE ACS. Patients included in CRUSADE have ischemic symptoms for at least 10 minutes within 24 hours prior to hospital presentation and at least 1 of the following high risk features designated by the ACC/AHA guidelines[9]: ST-segment depression $\geq$0.5 mm, transient ST-segment elevation 0.5–1.0 mm (lasting<10 min), and positive cardiac markers (troponin I or T and/or creatine kinase-MB>upper limit of normal). Participation in CRUSADE was voluntary and required approval by the Institutional Review Board of each hospital. Because data collection was anonymous, individual informed consent was not required.

Patients with a missing history of hypercholesterolemia (n = 1918) were excluded from the analysis. Patients who were transferred out from a CRUSADE hospital (n = 12 224) were excluded from the analysis, as outcomes data could not be collected after transfer due to U.S. privacy rules, yielding a final population of 84 429 patients treated at 478 U.S. hospitals.

Data Definitions

A prior history of hypercholesterolemia was defined as a known total cholesterol level>200 mg/dL or treatment with a lipid-lowering agent prior to hospital admission documented in the medical record. Newly diagnosed hypercholesterolemia was defined as a low-density lipoprotein cholesterol (LDL-C) level assessed during ACS hospitalization among patients without a prior history of hypercholesterolemia and found to be $\geq$100 mg/dL. Most in-hospital lipid measurements (91.3%) were obtained within the first 48 hours of hospitalization. The CRUSADE data collection form captures demographic and clinical characteristics at enrollment, preadmission medication use, use of acute evidence-based medical therapies (ie, within 24 hours of presentation), use and timing of coronary angiography and revascularization procedures, the presence or absence of contraindications to guideline-recommended therapies, and in-hospital clinical outcomes via retrospective chart review using standardized definitions.[10]

Statistical Analysis

Baseline characteristics, medication use, and outcomes are expressed as percentages for categorical variables and as medians (25th, 75th percentile) for continuous variables. In the full cohort of 84 429 patients, we used multivariable logistic generalized estimating equations models to explore the relation between a prior history of hypercholesterolemia and in-hospital mortality. The generalized estimating equations method was used to account for within-hospital clustering, whereby patients at the same hospital were more likely to have similar responses relative to patients in other hospitals (eg, within-center correlation for response).[11] We first adjusted for clinical covariates, and then further adjusted for home statin use prior to admission. Clinical covariates entered in the model were adapted from a validated mortality risk model for patients with NSTE ACS (c-index = 0.81)[3] and included age, race, sex, body mass index, family history of coronary artery disease, hypertension, diabetes mellitus, current/recent smoker, prior myocardial infarction (MI), prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG), prior heart failure, prior stroke, renal insufficiency, ST-segment depression, ST-segment elevation, positive cardiac markers, signs of heart failure, admission heart rate, admission systolic blood pressure, insurance status (Medicare, Medicaid, self/none vs HMO/private), total number of hospital beds, hospital geographic region (West, Northeast, Midwest vs South), facility type (no services, diagnostic catheterization only, PCI without on-site cardiac surgery vs PCI with on-site cardiac surgery), teaching/academic hospital status, and cardiologist care.

To discern the relation of hypercholesterolemia with risk in the absence of a previous diagnosis of or treatment for hypercholesterolemia (either of which may introduce multiple unmeasured confounders), we also identified a group of 22 711 patients without a prior history of hypercholesterolemia or home use of lipid-lowering agents who had lipid levels measured during the hospitalization (Figure 1). Of these, 12 809 patients had newly diagnosed hypercholesterolemia, defined as a LDL-C level $\geq$100 mg/dL. We then repeated the analysis to explore the relation between newly diagnosed hypercholesterolemia and in-hospital mortality in these 22 711 patients, adjusting for the same clinical covariates.

Results from multivariate models are expressed as odds ratios with 95% confidence intervals. A P value<0.05 was considered statistically significant for all tests. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20518

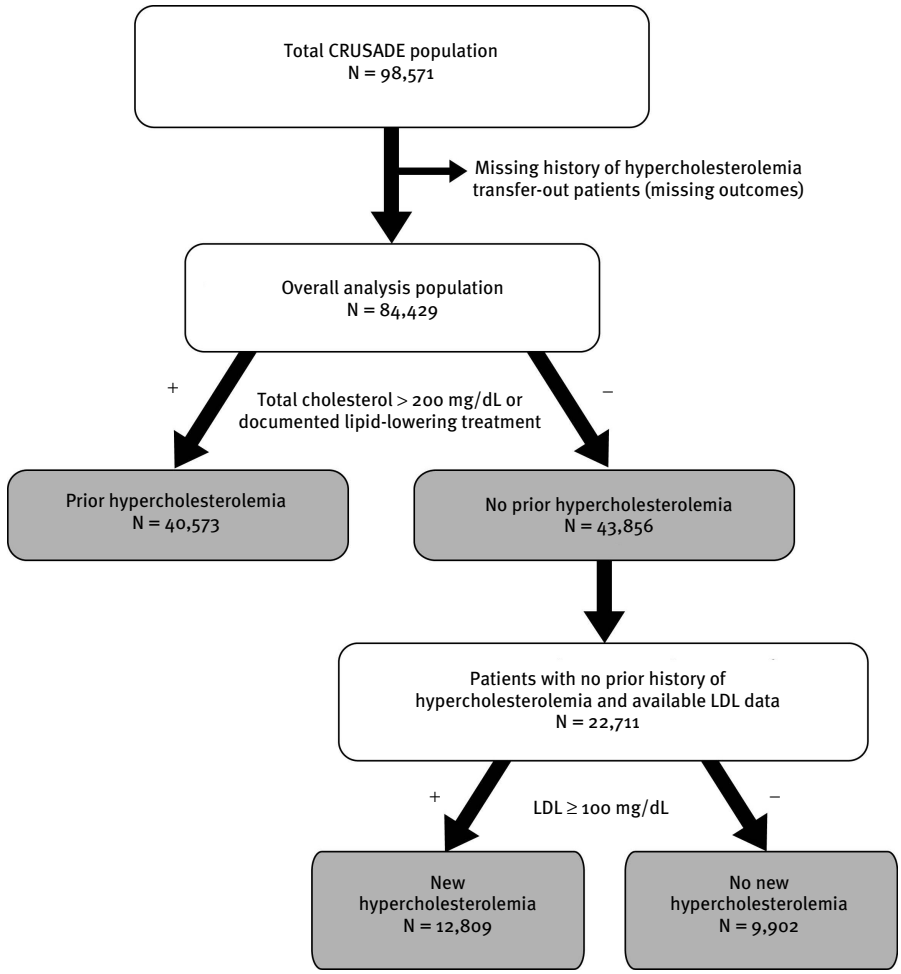

Figure 1. Flow diagram of analysis populations.

Results

Association of Hypercholesterolemia with Outcomes

Between January 2001 and March 2004, 84 429 patients with NSTE ACS were enrolled in CRUSADE. Of those, 40 573 had a history of hypercholesterolemia at the time of admission. These patients were younger but were more likely to have hypertension, diabetes mellitus, prior coronary artery disease, prior revascularization (either PCI or CABG), and renal insufficiency (Table 1). They were more likely to be treated with guidelines-recommended primary or secondary prevention medications (aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, and statins). They were less likely to present with hemodynamic instability (hypotension, tachycardia), signs of heart failure, or positive cardiac biomarkers, and were more likely to be treated with guidelines-recommended ACS medications (including aspirin, clopidogrel, unfractionated or low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, β-blockers, and angiotensin-converting enzyme inhibitors) and invasive procedures (including diagnostic cardiac catheterization, PCI, and CABG; Table 2).

In the overall population, patients with a history of hypercholesterolemia had a lower risk of in-hospital mortality with an unadjusted odds ratio (OR) of 0.58 (95% confidence interval [CI]: 0.55–0.62). Lower mortality was still evident after adjustment for clinical variables (OR: 0.71; 95% CI: 0.66–0.76) and clinical variables plus prior statin use (OR: 0.74; 95% CI: 0.68–0.80).

Association of Hypercholesterolemia with Outcomes among Patients without Prior Diagnosis or Treatment

Among the total population, 22 711 patients (26.9%) had no prior history of hypercholesterolemia and were not receiving lipid-lowering therapy at the time of admission. In this subpopulation, newly diagnosed hypercholesterolemia, defined as an LDL-C level ≥100 mg/dL, was present in

DOI:10.1002/clc.20518

Table 1. Baseline Characteristics of Patients with and Without Prior Hypercholesterolemia

Variable (%)	Hyper-cholesterolemia (n = 40 573)	No Hyper-cholesterolemia (n = 43 856)
Demographics		
Age, y[a]	67 (57, 77)	70 (56, 81)
Female sex	38.0%	42.5%
Medical history		
Hypertension[b]	77.8%	61.6%
Diabetes mellitus	38.2%	27.7%
Prior MI	38.9%	23.3%
Prior PCI	30.3%	13.3%
Prior CABG	27.9%	13.4%
Prior heart failure	18.6%	18.9%
Renal insufficiency[c]	14.8%	13.3%
Home medication use		
Aspirin	54.5	35.6
Clopidogrel	14.6	7.9
β-blocker	46.2	29.2
ACE inhibitor	34.3	23.4
Presenting features		
Signs of heart failure	21.3%	24.4%
Systolic blood pressure ≤90 mm Hg	2.7%	3.7%
Heart rate ≥100 BPM	18.9%	24.0%
Positive cardiac necrosis markers	86.7%	89.0%

[a] Values are median (25th, 75th percentile).
[b] Hypertension defined as systolic blood pressure>140 mm Hg or diastolic blood pressure>90 mm Hg on repeated measurements or chronic treatment with antihypertensive medications.
[c] Renal insufficiency defined as known serum creatinine>2 mg/dL, calculated creatinine clearance<30 mL/min, or need for renal replacement therapy.
Abbreviations: BPM, beats per minute; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Treatment Patterns of Patients with and Without Prior Hypercholesterolemia

Variable (%)	Hyper-cholesterolemia (n = 40 573)	No Hyper-cholesterolemia (n = 43 856)
Medications within 24 h		
Aspirin	92.8%	91.3%
Heparin (UFH or LMWH)	84.8%	81.4%
Glycoprotein IIb/IIIa inhibitor	39.9%	34.7%
Clopidogrel	46.4%	39.5%
β-blocker	82.5%	77.9%
ACE inhibitor	48.6%	41.4%
Invasive procedures		
Diagnostic cardiac catheterization	75.1%	63.8%
PCI	42.9%	34.9%
CABG	12.8%	10.6%

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

12 809 patients (56.4%). Compared with patients who had an admission LDL level<100 mg/dL, these newly diagnosed hypercholesterolemic patients were younger and had fewer comorbidities (Table 3). Patients with newly diagnosed hypercholesterolemia were more likely to receive ACC/AHA guidelines-recommended medications and invasive therapies compared with patients without hypercholesterolemia (Table 4). Diagnostic cardiac catheterization and coronary revascularization procedures were also more frequently used among patients with newly diagnosed hypercholesterolemia.

Among patients who were not previously hypercholesterolemic or treated with lipid-lowering therapy, a new diagnosis of hypercholesterolemia was associated with lower unadjusted mortality rates (OR: 0.58; 95% CI: 0.50–0.67). However, once adjusted for patient and hospital variables, in-hospital mortality was no longer significantly different from those without LDL elevation with an adjusted OR of 0.86 (95% CI: 0.73–1.01; Figure 2).

Discussion

Although baseline hypercholesterolemia was associated with lower mortality, our study shows that among patients with NSTE ACS, those with previously undiagnosed hypercholesterolemia did not have similarly lower risk. This dichotomy of findings highlights the challenges of observational analyses.

Plasma LDL-C level is an important risk factor for the development of coronary artery disease, including myocardial infarction. In both primary and secondary

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20518

Table 3. Baseline Characteristics of Patients with and Without Newly Diagnosed Hypercholesterolemia

Variable (%)	Newly Diagnosed Hypercholesterolemia (n = 12 809)	No Newly Diagnosed Hypercholesterolemia (n = 9902)
Demographics		
Age, y[a]	63 (52, 76)	70 (56, 80)
Female sex	39.4%	40.0%
Medical history		
Hypertension[b]	54.7%	62.2%
Diabetes mellitus	20.4%	27.6%
Prior MI	15.4%	20.6%
Prior PCI	8.2%	11.4%
Prior CABG	7.8%	11.2%
History of heart failure	10.0%	17.0%
Renal insufficiency[c]	6.4%	12.7%
Presenting features		
Signs of heart failure	17.1%	23.4%
Systolic BP ≤90 mm Hg	2.2%	3.6%
Heart rate ≥100 BPM	19.6%	24.6%
Positive cardiac necrosis markers	90.9%	91.7%

[a] Values are median (25th, 75th percentile).
[b] Hypertension defined as systolic blood pressure>140 mm Hg or diastolic blood pressure>90 mm Hg on repeated measurements or chronic treatment with antihypertensive medications.
[c] Renal insufficiency defined as known serum creatinine>2 mg/dL, calculated creatinine clearance<30 mL/min, or need for renal replacement therapy.
Abbreviations: BPM, beats per minute; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 4. Treatment Patterns of Patients with and Without Newly Diagnosed Hypercholesterolemia

Variable (%)	Newly Diagnosed Hypercholesterolemia (n = 12 809)	No Newly Diagnosed Hypercholesterolemia (n = 9902)
Medications within 24 h		
Aspirin	94.5	93.1
Heparin (UFH or LMWH)	87.2	85.5
Glycoprotein IIb/IIIa inhibitor	44.2	38.5
Clopidogrel	45.2	40.5
β-blocker	82.2	80.6
ACE inhibitor	40.9	43.5
Statin	35.1	26.9
Invasive procedures		
Diagnostic cardiac catheterization	80.3	71.1
PCI	50.2	42.3
CABG	15.7	13.0

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

prevention trials, the higher the baseline LDL-C level, the higher the placebo cardiovascular event rate.[4,12] Several landmark clinical trials have shown that use of LDL-lowering therapies significantly reduces the incidence of first or recurrent events.[3,12–15] However, once a patient has developed ACS, a history of hypercholesterolemia appears to be protective. In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy trial, examination of baseline characteristics associated with 30-day mortality showed hypercholesterolemia to be protective (OR: 0.80; 95% CI: 0.64–1.00) in patients with NSTE ACS.[5] Examination of registry databases has also revealed a protective association of hypercholesterolemia. In the Global Registry of Acute Coronary Events (GRACE) mortality model, a history of hypercholesterolemia was associated with lower in-hospital mortality (OR: 0.5; 95% CI: 0.40–0.58) for patients across the spectrum of ACS.[6] Prior statin use has also been associated with lower mortality among ACS patients. In a sub-analysis of the Platelet Receptor Inhibition for Ischemic Syndrome Management trial, patients with hypercholesterolemia receiving home statin therapy had a lower risk of death or nonfatal MI compared with those not on statin therapy at baseline.[7] This was also observed in the GRACE registry; patients with hypercholesterolemia who were on statin therapy at hospital admission had significantly lower mortality even after adjustment for comorbidities and in-hospital therapies (OR: 0.38; 95% CI: 0.28–0.52).[8] We explored this paradox in the current study and found that, despite an incremental narrowing of the difference in in-hospital mortality after adding clinical variables and clinical variables plus prior statin treatment to our model, prior treatment did not fully explain the apparent protective effect of a diagnosis of hypercholesterolemia prior to admission in patients with ACS.

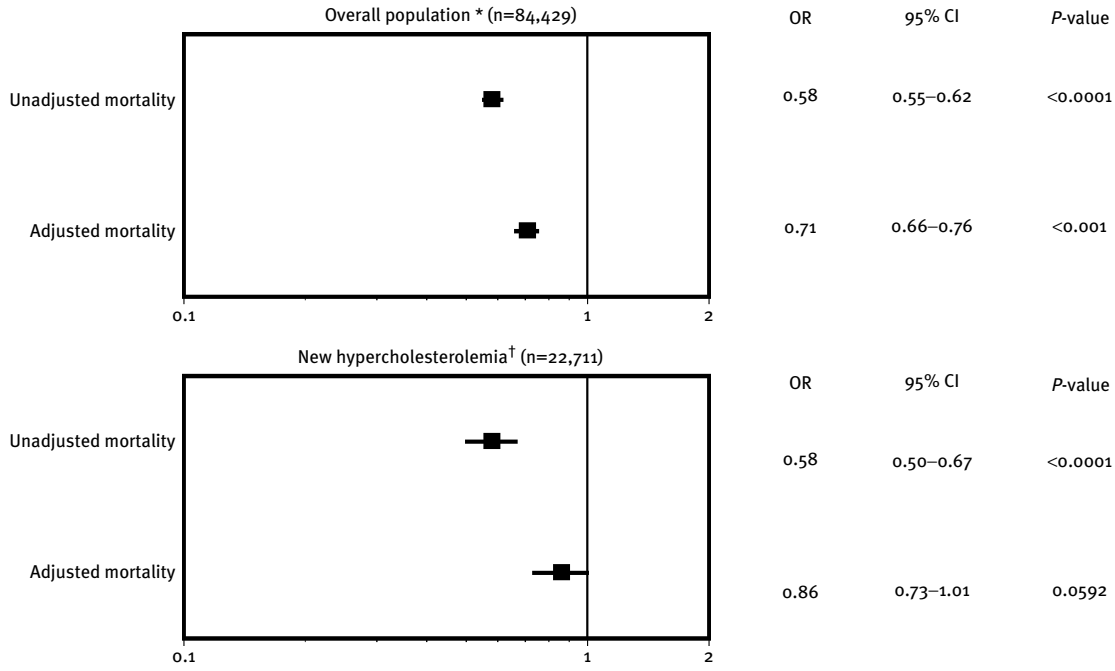

Figure 2. Association of hypercholesterolemia with mortality. Adjusted for age, race, sex, body mass index, family history of coronary artery disease, hypertension, diabetes mellitus, current/recent smoker, prior MI, prior PCI, prior CABG, prior HF, prior stroke, renal insufficiency, ST-segment depression, ST-segment elevation, positive cardiac markers, signs of CHF, heart rate, systolic blood pressure, insurance status, total number of hospital beds, hospital region, facility type, teaching/academic hospital status, and cardiologist care. [a] Mortality for patients with history of hypercholesterolemia on admission compared with patients without known history of hypercholesterolemia. [b] In the subpopulation of patients without known history of hypercholesterolemia or lipid-lowering therapy use, mortality for patients with LDL-C level ≥100 mg/dL (newly diagnosed hypercholesterolemia) compared with patients with LDL-C level<100 mg/dL.

In contrast to prior studies, we also analyzed a subpopulation of patients without a prior history of hypercholesterolemia who were not already receiving home lipid-lowering therapy. In this cohort, newly diagnosed hypercholesterolemia was not associated with a similar lowering of mortality risk after adjustment. Thus, the observed association of preexisting hypercholesterolemia with better clinical outcomes must be attributed to other factors beyond comorbid disease and in-hospital therapies that may not be captured by an observational database. One possible explanation is that previously documented hypercholesterolemia is a general marker for patients who have had more contact with the medical field prior to admission, such that when admitted for their ACS event, they are healthier or better treated overall and thus less likely to suffer adverse outcomes. While patients with prior hypercholesterolemia have greater atherosclerotic burden and inflammatory levels, these effects may be mitigated by the pleiotropic properties of preadmission statin therapy either directly through LDL-C reduction or via an indirect effect on vasomotor function, coagulation, or inflammatory modulation.[16] The fact that patients with prior hypercholesterolemia are more likely to be taking medications such as aspirin, clopidogrel, β-blockers, statins, and angiotensin-converting enzyme inhibitors prior to their ACS admission further supports this explanation; these medications may individually or synergistically contribute to the paradoxically lower risk of these diagnosed patients. While insurance status also correlates with health care use, the association between hypercholesterolemia and mortality that we observed persisted even after adjusting for insurance status and hospital factors. These results underscore the potential for confounding of associations in observational analyses.

Limitations

As with any retrospective analysis, we cannot account for the influence of perceived severity of illness on clinical decisions made by treating physicians. We believe the results of our study highlight the problem of unmeasured confounders that arises when using an observational database to explore the associations of clinical factors and interventions with outcomes. In this case, we do not have information detailing medical care received by patients prior to hospitalization. It is clear that patients with newly diagnosed hypercholesterolemia do not first develop this risk factor on admission

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20518

with NSTE ACS; it is simply the point of its first measurement or recognition. Once prehospital recognition of the illness and treatment are removed from the equation, there is no longer a significant association of hypercholesterolemia with short-term outcomes. In this retrospective study, timing of lipid measurement could not be specified. Thus, while most lipid measurements were made within the first 48 hours of ACS hospitalization, varying time points of lipid measurement, whether lipids were measured under fasting conditions, and inter-hospital laboratory variability in lipid measurements may contribute to the misclassification of hypercholesterolemia. Finally, the CRUSADE database only reports in-hospital outcomes, so conclusions about associations with long-term mortality and morbidity cannot be drawn.

Conclusion

The well documented association of hypercholesterolemia with better outcomes among ACS patients highlights one of the principal challenges when performing observational analyses. In this study, we confirm this association and further demonstrate that patients with newly diagnosed hypercholesterolemia do not have similarly demonstrated protective associations. Our results suggest that this paradoxical association results from a combination of factors outside of routinely documented risk factors, prior statin treatment, and differential in-hospital therapies. Perhaps most importantly, hypercholesterolemia is a marker for patients who have had more contact with the medical field before admission for ACS.

Acknowledgments

The authors would like to thank David Bynum for his editorial assistance.

References

1. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361 662 men. *Lancet*. 1986;2(8513):933–936.
2. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322(24):1700–1707.
3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383–1389.
4. 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(9326):7–22.
5. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*. 2000;101(22):2557–2567.
6. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345–2353.
7. Heeschen C, Hamm CW, Laufs U, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation*. 2002;105(12):1446–1452.
8. Spencer FA, Allegrone J, Goldberg RJ, et al. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. *Ann Intern Med*. 2004;140(11):857–866.
9. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. 2002;106(14):1893–1900.
10. CRUSADE National Quality Initiative Web Site. Available at: www.crusadeqi.com. Accessed November 14, 2007.
11. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121–130.
12. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615–1622.
13. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495–1504.
14. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001–1009.
15. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301–1307.
16. Pucci A, Sheiban I, Formato L, et al. In vivo coronary plaque histology in patients with stable and acute coronary syndromes: relationships with hyperlipidemic status and statin treatment. *Atherosclerosis*. 2007;194(1):189–195.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20518