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The Implications of Blood Transfusions for Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

Results From the CRUSADE National Quality Improvement Initiative

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OBJECTIVES In a large contemporary population of patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS), we sought to describe blood transfusion rates (overall and in patients who did not undergo coronary artery bypass grafting [CABG]), patient characteristics and practices associated with transfusion, variation among hospitals, and in-hospital outcomes in patients receiving transfusions.

BACKGROUND The use of antithrombotic agents and invasive procedures reduces ischemic complications but increases risks for bleeding and need for blood transfusion in patients with NSTE ACS.

METHODS We evaluated patient characteristics and transfusion rates in the overall population (n = 85,111) and determined outcomes and factors associated with need for transfusion in a subpopulation of patients who did not undergo CABG (n = 74,271) from 478 U.S. hospitals between January 1, 2001, and March 31, 2004.

RESULTS A total of 14.9% of the overall and 10.3% of the non-CABG population underwent transfusion during their hospitalization. Renal insufficiency and advanced age were strongly associated with the likelihood of transfusion. Interhospital transfusion rates varied significantly. Non-CABG patients who received transfusions had a greater risk of death (11.5% vs. 3.8%) and death or reinfarction (13.4% vs. 5.8%) than patients who did not undergo transfusion.

CONCLUSIONS Transfusion is common in the setting of NSTE ACS, and patients who undergo transfusion are sicker at baseline and experience a higher risk of adverse outcomes than their nontransfused counterparts. Given the wide variation in transfusion practice, further efforts to understand patient and process factors that result in bleeding and need for transfusion in NSTE ACS are needed. (J Am Coll Cardiol 2005;46:1490–5) © 2005 by the American College of Cardiology Foundation

In recent years, significant advances have been made in the diagnosis, risk stratification, and therapy of non–ST-segment elevation acute coronary syndromes (NSTE ACS) (1–3). A key part of this management strategy involves combining multiple antiplatelet and anticoagulation agents along with invasive therapy in high-risk patients with NSTE ACS (2,3). Although these therapeutic modalities have been shown to reduce recurrent ischemic events in patients with NSTE ACS (4–7), they also increase the risks for bleeding and need for blood transfusion (7,8). Reported rates of major bleeding and transfusion from NSTE ACS clinical trial populations range from 1% to 9% (9–12). However, extrapolation of these bleeding and transfusion rates from trial to community practice is challenging because trial populations tend to be younger and healthier (13). Additionally, patients within trials usually are treated according to rigorously defined protocols that influence drug dosing and combinations.

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 (CRUSADE) National Quality Improvement Initiative includes a broad sampling of U.S. practices, providing the ideal database in which to explore the use of blood transfusion in the community setting. The purpose of this analysis is to describe: 1) blood transfusion rates (both overall and those unrelated to coronary artery bypass grafting [CABG] surgery; 2) patient characteristics and care practices associated with transfusion; 3) variation in the use of transfusion across hospitals; and 4) in-hospital outcomes in patients receiving transfusions compared with those who do not during care for NSTE ACS in the community.

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CHF = congestive heart failure
CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines
MI = myocardial infarction
NSTE ACS = non–ST-segment elevation acute coronary syndromes

METHODS

The CRUSADE initiative is an ongoing database of patients with high-risk NSTE ACS that have been admitted to U.S. hospitals since November 2001. The hospitals participating in the CRUSADE initiative are diverse in their size, teaching status, capacity, and region. Relative to national averages, the CRUSADE hospitals are larger and more likely to have catheterization laboratories and surgical capabilities.

Inclusion criteria. Criteria for participation in the database include symptoms referable to myocardial ischemia lasting ≥10 min combined with positive cardiac biomarkers or ischemic ST-segment electrocardiograph changes (ST-segment depression or transient ST-segment elevation). Patients are ineligible if they transfer to a CRUSADE hospital >24 h after their last ischemic symptoms.

Patient population. The current population was derived from the 98,571 patients enrolled in CRUSADE initiative from January 1, 2001, to March 31, 2004. Patients were ineligible for this analysis if they were transferred to another hospital (n = 12,529) or had incomplete data on transfusion status (n = 931). Because of the different implications of transfusion in the setting of CABG, we excluded patients who underwent CABG during their hospitalization (n = 10,840) for analyses of factors associated with or outcomes related to use of transfusion. Thus, the overall sample included 85,111 patients, and the non-CABG sample included 74,271 patients enrolled in 478 hospitals.

Data collection. Hospitals participating in the CRUSADE initiative collect detailed processes of care and in-hospital outcomes data through retrospective chart review using a standardized questionnaire. The institutional review board of each institution approves participation in the CRUSADE initiative. Data are collected anonymously during the initial hospitalization, and because no patient identifiers are collected, individual informed consent is not required. Data collected include demographic and clinical information, medical history, medical therapies and associated major contraindications, use of acute medications (within 24 h of presentation), use and timing of invasive cardiac procedures, laboratory results, in-hospital outcomes, physician and hospital characteristics, and discharge medications and interventions.

Data definitions. Blood transfusion is defined as any nonautologus transfusion of either whole blood or packed red blood cells. Renal insufficiency is defined by serum creatinine >2.0 mg/dl, creatinine clearance <30 ml/min, or the need for renal dialysis. Hypertension is defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg on repeated measurements, or hypertension chronically treated with antihypertensive medications. Signs of congestive heart failure (CHF) are indicated by exertional dyspnea, orthopnea, shortness of breath, labored breathing, fatigue at either rest or with exertion, rales greater than one-third of the lung fields, elevated jugular venous pressure, S_3 gallop, or pulmonary congestion on X-ray film believed to represent cardiac dysfunction. Additional clinical definitions are available on the CRUSADE web site (14).

Comparisons. Baseline patient characteristics were grouped according to the occurrence of in-hospital transfusion. Then, the proportion of patients undergoing transfusion was compared at the hospital level among the overall population (n = 85,111) and the non-CABG subpopulation (n = 74,271). In addition, the use of transfusion in the overall and non-CABG subpopulation by patient age groups was compared. Finally, the relationship between the number of antithrombotic agents used in the acute setting (e.g., heparin, glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel) and transfusion was determined by patient age group for the non-CABG subpopulation.

Statistical analysis. Continuous variables were reported as medians and 25th and 75th percentiles, and categorical variables were reported as percentages. To test for independence of transfusion status and in-hospital outcomes, Wilcoxon rank sum tests were used for continuous variables and chi-square tests were used for categorical variables. Multivariate models were used to determine the factors associated with transfusion, and relationship between transfusion and in-hospital outcomes. For the first analysis, a stepwise approach, including a list of variables, was used to establish the factors that were associated with blood transfusion. For the second analysis, the model controlled for a standard list of factors. Candidate variables included in the model included patient demographics, (such as age, gender, body mass index, race), cardiac risk factors (such as family history of coronary artery disease, hypertension, diabetes, current/recent smoker, hypercholesterolemia), medical comorbidities (such as renal insufficiency, previous myocardial infarction [MI], previous percutaneous coronary intervention, previous CABG, previous CHF, previous stroke), presenting characteristics (such as ST-segment depression, ST-segment elevation, positive cardiac marker, signs of CHF at presentation, heart rate, systolic blood pressure), and socioeconomic status (such as insurance status). Because patients within a hospital are more likely to be similar, generalized estimating equations were used to adjust for correlations among clustered responses (i.e., within hospital correlations) (15).

A p value of <0.05 was considered significant for all tests. All analyses were performed using SAS software (versions 8.2, SAS Institute, Cary, North Carolina).

RESULTS

Transfusion. Blood transfusion during NSTE ACS hospitalization occurred in 14.9% of the overall population and 10.3% of the non-CABG subpopulation (Fig. 1). The percentage of patients who received a transfusion across hospitals demonstrated a bell-shaped curve (Fig. 1). Although 30% of U.S. hospitals transfused more than 20% of their NSTE ACS population, 15% transfused less than 5%. Patients receiving transfusions were more likely to be admitted to larger hospitals (median 397 vs. 380 beds) and academic teaching hospitals (33.6% vs. 29.4%) and less likely to have a cardiologist as their attending physician (52.5% vs. 59.5%) compared with patients who did not undergo transfusion (Table 1). The median (25th, 75th percentile) number of units transfused per patient was 2.0 (2.0, 3.0) among non-CABG patients and 2.0 (2.0, 4.0) for the overall population.

Patients receiving transfusions. The likelihood of transfusion, overall and for non-CABG patients, increased linearly with patient age (Fig. 2). Although patients <55 years of age rarely required a transfusion (8% overall, 3% non-CABG), it was not at all uncommon for patients ≥75 years to receive transfusions (19% overall, 14% non-CABG). Patients who required a transfusion were older than those who did not (median age 73 vs. 67 years; Table 1). Along with being older, patients receiving transfusions also were more likely to be women (47% vs. 39%), have a smaller body mass index, and be more commonly covered by Medicare insurance (49% vs. 38%) than nontransfused patients. Transfused patients also had more comorbidity, including hypertension (75% vs. 68%), diabetes (41% vs. 31%), CHF (24% vs. 18%), and renal insufficiency (24% vs. 12%) than nontransfused patients (Table 1). Transfused patients also were sicker at presentation, with more frequent signs of CHF (33% vs. 21%), higher heart rates (86 vs. 82 beats/min), and lower systolic blood pressures (141 vs. 145 mm Hg) than nontransfused patients. Transfused patients were admitted with lower baseline hematocrit values than nontransfused patients (median hematocrit 35% vs. 41%) and had lower nadir hematocrit values as well (median hematocrit 26% vs. 36%). Treatment variables further interacted with patient factors like age to determine the risk of transfusion. As shown in Figure 3, patients age <75 years received multiple antiplatelet and antithrombin agents without increasing their risk of transfusion, whereas patients age

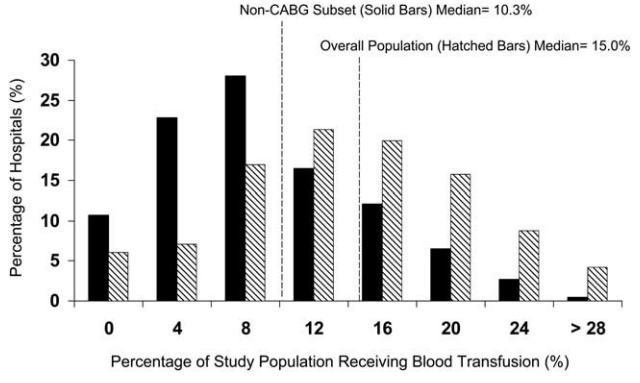

Figure 1. Transfusion by age group for non-coronary artery bypass grafting (CABG) and overall population. Use of transfusion by age group among the overall population **(hatched bars)** and the subset excluding patients who underwent coronary artery bypass grafting during hospitalization **(solid bars)**.

Table 1. Patient Characteristics by Blood Transfusion Status in Overall Population

Demographics	Blood Transfusion (n = 12,724)	No Blood Transfusion (n = 72,387)
Population	14.9	85.1
Age, yrs*	73 (63, 80)	67 (55, 78)
Age group, yrs		
<55	10.6	22.8
55–64	17.9	21.2
65–74	27.2	22.0
≥75	44.3	34.0
BMI, kg/m^2*	27.0 (23.7, 31.0)	27.7 (24.3, 31.9)
Female gender	47.1	39.2
White race	79.1	80.2
Insurance type		
HMO/private insurance	39.0	45.6
Medicare	48.7	38.2
Medicaid	7.0	8.2
Medical history		
Hypertension	74.6	68.4
Diabetes mellitus	41.1	31.3
Current/recent smoker	21.6	28.1
Dyslipidemia	47.6	47.2
Renal insufficiency†	23.9	12.3
Previous MI	30.7	30.8
Previous PCI	19.3	21.8
Previous CABG	17.2	21.0
Previous CHF	24.1	17.8
Previous stroke	13.5	10.5
Presenting characteristics		
Signs of CHF	32.6	21.1
Heart rate, beats/min*	86 (73, 103)	82 (69, 97)
Systolic blood pressure, mm Hg*	141 (119, 164)	145 (124, 165)
ST-segment depression	43.4	36.2
Troponin elevation	92.5	88.7
Baseline hematocrit*‡	35 (31, 39)	41 (37, 44)
Nadir hematocrit*‡	26 (24, 26)	35 (31, 39)
Hospital features		
Number of beds*	397 (281, 536)	380 (265, 524)
Academic teaching hospital	33.6	29.4
Cared for by cardiologist	52.5	59.5

Data are presented as percentages except as indicated. *Presented as median (25th, 75th percentiles); †renal insufficiency was defined by serum creatinine >2.0 mg/dl, creatinine clearance <30 ml/min, or need for renal dialysis; ‡hematocrit values from patients enrolled since November 2003 (n = 18,547). All p values are <0.0001, except for previous MI and dyslipidemia, where both are not significant.

BMI = body mass index; CABG = coronary artery bypass grafting; CHF = congestive heart failure; HMO = health maintenance organization; MI = myocardial infarction; PCI = percutaneous coronary intervention.

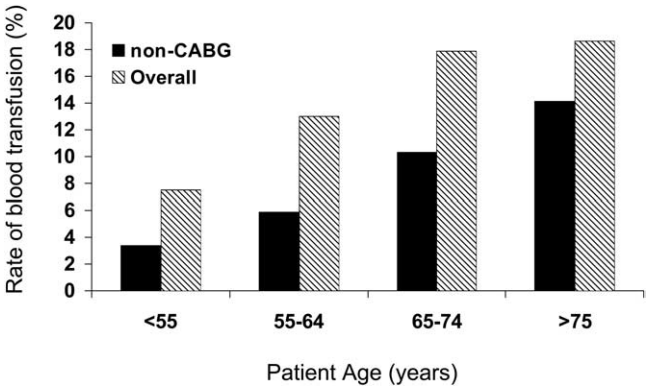

Figure 2. Transfusion practices across hospitals. Distribution of hospitals according to the percent of their overall **(hatched bars)** and non-coronary artery bypass grafting (CABG) population **(solid bars)** that underwent transfusion.

≥75 years experienced an increased risk in transfusion when given three or more antithrombotic agents.

Factors associated with transfusion. Renal insufficiency was the most powerful predictor of transfusion even after adjusting for factors known to affect renal function, such as age, body mass index, and female gender (Table 2). Advanced patient age remained strongly associated with an increasing likelihood for transfusion after accounting for other age-associated clinical factors in the model. The largest odds ratio for transfusion was in patients ≥75 year of age, who had a three-fold higher likelihood of transfusion than patients <55 years old, followed by patients age ≥65 years. Presenting characteristics, such as positive troponins, electrocardiogram changes, heart rate, and signs of CHF, also were explanatory in predicting the need for transfusion. After considering patient factors, the use of invasive care, either catheterization or percutaneous coronary intervention, did not contribute to the likelihood of transfusion.

Patient outcomes. Patients who received transfusions had longer hospital stays than those who did not (median [25th, 75th percentile] of 7 days [5.0, 11.0] vs. 4 days [2.0, 5.0],

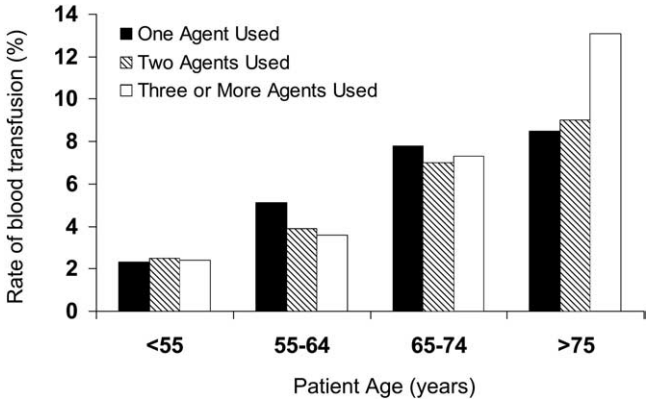

Figure 3. Age and transfusion as a function of the number of antithrombin and antiplatelet agents used. Acute (<24 h) agents considered include: 1) aspirin or clopidogrel, 2) unfractionated heparin, 3) low molecular weight heparin, and 4) glycoprotein IIb/IIIa inhibitors. Rate of transfusion displayed by patient age and number of agents delivered during hospital stay.

Table 2. Factors Associated with Blood Transfusion

Variable	Adjusted OR (95% CI)	Chi Square
Renal insufficiency*	2.43 (2.29–2.58)	835.5
Systolic BP (per 10 mm Hg drop)	1.08 (1.07–1.09)	288.1
Female gender	1.51 (1.43–1.60)	202.2
Diabetes mellitus	1.42 (1.35–1.50)	175.8
Patient age (vs. <55 yrs)		
≥75 yrs	2.98 (2.62–3.39)	102.9
65–75 yrs	2.58 (2.28–2.91)	
55–64 yrs	1.52 (1.37–1.68)	
Signs of CHF	1.43 (1.34–1.53)	109.1
Heart rate (per 10 beats/min increase)	1.05 (1.04–1.07)	94.2
Positive cardiac markers	1.73 (1.55–1.94)	91.1
ST-segment depression (vs. neither)	1.46 (1.37–1.55)	84.1
Transient ST-segment elevation (vs. neither)	1.22 (1.10–1.37)	
BMI (per 5-U reduction)	1.08 (1.05–1.10)	36.2
Insurance type (vs. HMO/private)		
Medicaid	1.55 (1.37–1.75)	33.8
Medicare	1.07 (1.00–1.15)	
Self/none	0.98 (0.86–1.12)	
No family history of CAD	1.14 (1.07–1.21)	18.8
Hypertension	1.13 (1.07–1.21)	16.6
Absence of dyslipidemia	1.07 (1.02–1.13)	7.1
Nonwhite versus white	1.10 (1.02–1.19)	6.6
Previous stroke	1.08 (1.01–1.15)	5.3

Determined using non-CABG subpopulation. All p values are <0.0001 except for absence of dyslipidemia ($p < 0.008$), nonwhite versus white ($p < 0.01$), and previous stroke ($p < 0.02$). *Serum creatinine <2.0 mg/dl.

BP = blood pressure; CAD = coronary artery disease; CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

respectively). Transfused patients also had a higher absolute rate of death (11.5% vs. 3.8%) and of death or MI combined (13.4% vs. 5.8%) compared with nontransfused patients (Table 3). The higher rate of death and MI among patients receiving blood transfusions remained significant after adjustment for a comprehensive list of patient and hospital characteristics. After adjustment, patients undergoing transfusion remained 67% more likely to die and 44% more likely to experience either death or MI than those who did not undergo transfusion during their care.

DISCUSSION

In the community setting, blood transfusions frequently are given during the care of patients with NSTE ACS. Patients with advanced age or renal dysfunction are at greatest risk, particularly when treated simultaneously with multiple antithrombotic agents. Although cause and effect cannot be established in an observational analysis, our study demonstrates an adverse association between transfusion and outcomes that persists after adjusting for clinical characteristics. The wide variation in transfusion rates across hospitals suggests that clarification is needed regarding the causes of bleeding, as well as the appropriate triggers and beneficial uses of transfusion in the setting of NSTE ACS.

Transfusion comparisons. The transfusion rates reported in the CRUSADE initiative are higher than from published NSTE ACS trial populations (12). Trials of antithrombin

Table 3. In-Hospital Death and Myocardial Infarction by Transfusion Status

Outcomes	Blood Transfusion (%)	No Blood Transfusion (%)	Unadjusted Risk OR (95% CI)	Adjusted Risk OR (95% CI)*
Death	11.5	3.8	2.96 (2.62–3.35)	1.67 (1.48–1.88)
Death or MI	13.4	5.8	2.27 (2.06–2.51)	1.44 (1.30–1.60)

Determined using non-CABG subpopulation. *Adjusted using the CRUSADE clinical model.
Abbreviations as in Tables 1 and 2.

therapy for NSTE ACS report transfusion rates of 1% to 5% (16–19), trials of glycoprotein IIb/IIIa inhibitors report transfusion rates of 4% to 9% (20,21), and a pooled NSTE ACS trial population reported a transfusion rate of 2.7% (12). Higher transfusion rates in the CRUSADE initiative may be due to a greater incidence of patient comorbidities compared with trial populations. For example, older age, renal dysfunction, and presenting CHF are known to be more common in community populations than in trial populations because of trial exclusions and lower elderly representation in trials (22). Accordingly, each of these factors was found in our study to be a major predictor of the need for transfusion (Table 2). The overlap between predictors of transfusion and predictors of major bleeding validate the association of transfusion as a marker of preceding bleeding events (9,11). In the Global Registry of Acute Coronary Events (GRACE) population, the predictors of bleeding in NSTE ACS also were found to be age, female gender, renal insufficiency, blood pressure, and treatments for heart failure (9), which are similar to the risk factors for transfusion identified in our population. In addition to higher comorbidity-related risks for bleeding in a community population, these risks overlap with treatment factors. For example, although younger patients can receive multiple antithrombotic agents without increasing their overall risk of transfusion, the risks increase substantially when three or more agents are given to elderly patients (age ≥75 years). Thus, patient and treatment factors both contribute to observed risk of bleeding and transfusion.

The common feature of these overlapping major predictors of bleeding and transfusion is their association with the pharmacokinetics and pharmacodynamics of antithrombotic therapy. Older, smaller patients with renal insufficiency have lower creatinine clearance. Antithrombotic therapy is dose-adjusted on the basis of patient weight and renal function. The relationship among patients age ≥75 years, the use of three or more antithrombotic agents, and an increased transfusion rate also supports the association between transfusion need and patient factors related to antithrombotic therapy. Although drug dosing data are not available in this population, this association raises the possibility that a failure to adjust dosing may be a causative and potentially modifiable factor.

Interhospital variation in the use of transfusion in this study was greater in magnitude than any differences observed between transfusion in community and trial populations. Although some CRUSADE hospitals have low transfusion rates (<5%), one-quarter of the hospitals in our study transfused more than 20% of their NSTE ACS population. Some potential explanations include local differences in the use of drugs and interventions, differences in patient populations at the site level, or differing local transfusion practice. However, clustering of patient characteristics at the hospital level was considered in the adjustment, and variation in transfusion rates was observed even among centers with similar use of revascularization and antithrombotic agents (data not shown). Thus, in the absence of clear guidelines on transfusion thresholds in NSTE ACS, local transfusion practice remains a potential contributor to this observed variation. Further exploration into practice patterns that influence bleeding and transfusion thresholds during NSTE ACS is warranted.

Transfusion and outcomes. Our study demonstrates an association between transfusion and adverse outcomes in an NSTE ACS population. The unadjusted rates of death and a composite of death and MI among transfused patients are three-fold higher and persist after adjustment. In large part, this rate may be because patients who receive transfusions are at higher risk and sicker at baseline. We controlled for identifiable clinical factors with use of adjustment, yet patients who undergo transfusion continued to have a higher likelihood of dying. Transfusions often are in response to bleeding events, which themselves add risk. In the GRACE population, patients who experienced a major bleeding event had three times higher rate of mortality than those without bleeding events (18.6% vs. 5.1%) (9). Thus, bleeding events may further explain excess mortality in the transfused population. Finally, the safety of transfusion itself in NSTE ACS is increasingly controversial. Rao et al. (11) demonstrated in trial populations that blood transfusion was associated with worse survival when given to patients with nadir hematocrits >25%. Sabatine et al. (12) further demonstrated in NSTE ACS trial populations that transfusions were associated with more recurrent ischemia and worse survival across all hemoglobin levels.

For comparison, the median nadir hematocrit value in our population of those who received a transfusion was 26%. In contrast, Wu et al. (10) demonstrated in a community population with acute MI that blood transfusion had a beneficial effect on survival when hematocrit was <30%. Although blood transfusions increase oxygen-carrying capacity and restore plasma volume, adverse consequences include exposure to viral pathogens, immune reactions, expansion of blood volume, and increased blood viscosity (23). Stored blood also may promote vasoconstriction and trigger ischemic events (24). Thus, the use of transfusions

above some threshold in local practice may contribute to adverse outcomes among transfused patients. Although only a randomized trial of transfusion in a NSTE ACS population would clarify the independent effect of transfusion on outcomes, or its applicable thresholds, observational data such as those in this analysis help identify concerns related to transfusion in community practice.

Study limitations. We collected transfusion, rather than actual bleeding events, because these events are poorly reported in medical records and difficult to capture via chart review in an observational study. The timing of transfusion in relation to therapeutic interventions and bleeding events thus could not be determined. As is the case in any observational study, the influence of confounding factors on outcomes between groups is likely to persist despite adjustment. However, these limitations did not devalue our primary goal of demonstrating variation in use of transfusion across community practice and its associated risk in community NSTE ACS populations.

Conclusions. Our study highlights that blood transfusion is common during management of NSTE ACS. Patients who undergo a transfusion are at high baseline risk and experience worse outcomes after adjustment compared with nontransfused patients. With increasing use of antithrombotic therapy and an aging population, the potential for an increase in transfusion over time is substantial. Although cause and effect between transfusion and outcomes could not be determined in our study, every effort should be made to minimize the likelihood of transfusion through careful dosing of adjustable anticoagulants and management of patients during invasive procedures. Furthermore, the wide variation found in transfusion practice across centers emphasizes that indications for its use in the care of NSTE ACS patients need further clarification.

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