ORIGINAL RESEARCH

Impact of Nitrate Use on Survival in Acute Heart Failure: A Propensity-Matched Analysis

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***Background*—**There is limited evidence that the use of nitrates in acute decompensated heart failure early after presentation to a hospital can improve clinical outcomes. We aimed to determine whether early nitrate exposure is associated with improved survival in a large retrospective cohort study.

***Methods and Results*—**We examined 11 078 acute decompensated heart failure patients who presented to emergency departments in Ontario, Canada, between 2004 and 2007, in the Enhanced Feedback For Effective Cardiac Treatment and the Emergency Heart failure Mortality Risk Grade studies. In propensity-matched analyses, we examined the effect of nitrate administration in the acute emergency department setting for its impact on death at 7, 30, and 365 days. In propensity-matched analyses, we found no difference in survival between those who received nitrates in the emergency department and the non-nitrate comparator group. Hazard ratios for mortality were 0.76 (95% CI; 0.51, 1.12) over 7 days, 0.97 (95% CI; 0.77, 1.21) over 30 days, and 0.91 (95% CI; 0.82, 1.02) over 1 year of follow-up. There was no significant difference in survival or hospital length of stay between nitrate and non-nitrate controls in extended follow-up. There was also no significant effect of nitrates in subgroups stratified by presence of chest pain, troponin elevation, chronic nitrate use, and known coronary artery disease.

***Conclusions*—**In acute decompensated heart failure, use of nitrates acutely in the emergency department setting was not associated with improvement in short-term or near-term survival. Our study does not support generalized use of nitrates when the primary goal of therapy is to reduce mortality. **(*J Am Heart Assoc*. 2016;5:e002531 doi: 10.1161/JAHA.115.002531)**

Key Words: angina • chronic ischemic heart disease • coronary artery disease • health services • heart failure • mortality/survival • myocardial infarction • quality and outcomes • statements and guidelines

Heart failure is a global public health problem, affecting ≈26 million people worldwide.[1] In North America, acute decompensated heart failure (ADHF) is the leading reason for hospitalization and readmissions, with a prevalence of over 6 million persons.[1,2] Despite the fact that the majority of patients with ADHF require care in the hospital, there is limited evidence evaluating the processes of care that are commonly provided in this setting. In some cases, therapies may be widely used despite limited evidence for effectiveness.

A class of agents that is widely used in HF is nitrates, which are believed to act by improving the abnormal hemodynamics of ADHF through vasodilation.[3–6] In the ADHERE registry, ≈10% of patients hospitalized with ADHF were treated with intravenous nitroglycerin during their admission.[7] When nonparenteral routes of administration are considered, the utilization rates of nitrates are higher. Indeed, the EuroHeart Failure Survey II reported that over 30% of all patients admitted with ADHF received nitrates, reflecting use of the drug in routine care.[8]

Guidelines recommend the use of nitrate therapy in ADHF, although the strength of the recommendation varies. The use of nitrates is strongly recommended by the Canadian Cardiovascular Society,[9] and it is a class IIa recommendation by the European Society of Cardiology.[10] The American Heart Association recommends nitrates least strongly, as a class IIb recommendation.[11] The evidence behind these recommendations is limited and based on small studies or consensus opinion of experts (moderate quality, level of evidence B and C). Indeed, most large studies of vasodilators in ADHF did not study nitrates, but instead, were randomized controlled trials

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that often evaluated the effect of nesiritide,[12] a recombinant brain natriuretic peptide.

Currently, the evidence supporting the use of nitrates in ADHF is limited. While a few studies have suggested that nitrates may provide potential benefits in ADHF, they were small and did not demonstrate an unequivocal impact on mortality.[13–15] This paucity of evidence may contribute to variability in the use of nitrate therapy for ADHF. The objective of this study was to investigate the effect of early nitrate therapy on clinical outcomes in ADHF. We hypothesized that early use of nitrates would significantly improve survival. As a secondary objective, we also aimed to determine the patterns of use of nitrate therapy in the emergency department (ED) for patients presenting with ADHF.

Methods

Study Sample

We examined patients aged ≥18 years who presented with ADHF to one of 86 EDs in the province of Ontario, Canada, who were included in either the Enhanced Feedback For Effective Cardiac Treatment HF (EFFECT-HF) or the Emergency Heart failure Mortality Risk Grade (EHMRG) studies. These population-based clinical studies, which included patients presenting to the ED (2004–2007), have been described previously.[16,17] The EFFECT-HF study entailed a retrospective review of over 16 000 charts of patients receiving care for ADHF between 2004 and 2005, collected by experienced, trained cardiology research nurses. Baseline characteristics, processes of care, clinical outcomes, and quality indicators were collected. The EHMRG study also employed highly trained research nurses to abstract data from ≈12 500 charts of ADHF patients who visited an ED and included patients who were admitted to a hospital or discharged home. A random sample of charts were reabstracted to verify data reliability. Using each patient's unique, encrypted health card number, the clinical data were linked with provincial administrative databases for vital statistics, including the Registered Persons Database (RPDB) for death events and the Ontario Registrar General Database (ORGD) for cardiovascular death. Institutional Review Board approval was obtained from the ethics review board of Sunnybrook Health Sciences Centre and all hospital sites prior to clinical chart abstraction. Consent was waived since this was a retrospective data collection and analysis.

Patients were included in the current study if they had both a primary discharge diagnosis of acute decompensated HF (International Classification of Diseases, Tenth Revision code I50), and also met the Framingham HF criteria, as described previously.[17] Patients were excluded if they were on dialysis, were transferred from another acute care hospital, had an active Do Not Resuscitate order on hospital presentation or admission, had known severe aortic stenosis, if key data were missing, or if they were non-Ontario residents. Conservatively, we also excluded those with systolic blood pressure <100 mm Hg or diastolic blood pressure <60 mm Hg on presentation to the hospital, since nitrates are cautioned in the presence of hypotension.[18] We excluded those who died prior to hospital admission since their foreshortened stay would limit the opportunity to administer nitrates in the hospital.

Data Collection and Variable Definitions

Baseline characteristics that were collected included demographic and clinical characteristics, presentation features, vital signs, cardiac and noncardiac comorbidities, and laboratory test results. We collected information on chronic medication use including nitrates and other cardiovascular medications (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-adrenoreceptor antagonist, loop diuretic, mineralocorticoid receptor antagonist, statin, and aspirin).

Acute nitrate exposure was defined as having received intravenous, oral, or transdermal nitroglycerin in the ED as part of initial management. Patients who were exposed to nitrates in the ED were assigned to the nitrate group and patients who were not exposed to nitrates formed the control group. Chronic nitrate use prior to ED presentation did not factor into group allocation. In a secondary analysis, we compared those who did or did not receive nonparenteral forms of nitrates in the ED as part of initial management.

Outcomes

The primary outcome of this study was all-cause mortality, which was examined over 7 days, 30 days, and 1 year, after presentation to the ED. We chose to examine survival to 1-year follow-up in our primary outcome analyses, because it has been previously demonstrated that acute HF processes of care can affect this outcome.[19] To determine whether there were any potential differences in long-term survival that might have been missed by limiting the primary analyses to 1 year, we extended the follow-up duration until March 31, 2011, examining events over 5 years after ED presentation. We also evaluated nonmortality care measures, including hospital admission, length of hospitalization (if admitted), and admission to an intensive care unit (ICU).

Statistical Analysis

Continuous variables are presented as medians (25th, 75th percentile) and were compared using the Wilcoxon rank-sum test. Categorical variables are presented as proportions, and

Table 1. Baseline Characteristics of Nitrate (Any Form) and Non-Nitrate Control Groups

	Nitrates	No Nitrates (Control)	
	N=3153	N=7925	*P* Value
Age, y	77 (69, 83)	77 (69, 84)	0.345
Male sex, n (%)	1617 (51.3)	4106 (51.8)	0.617
SES quintile			
1 (lowest)	838 (26.6)	1952 (24.6)	0.056
2	692 (21.9)	1701 (21.5)	
3	579 (18.4)	1538 (19.4)	
4	515 (16.3)	1455 (18.4)	
5 (highest)	516 (16.4)	1245 (15.7)	
Mode of transport to ED			
Ambulance	1717 (54.5)	2743 (34.6)	<0.001
Origin			
Home	2609 (82.7)	6176 (77.9)	<0.001
Long-term care	224 (7.1)	592 (7.5)	
Physician office	254 (8.1)	994 (12.5)	
Other	66 (2.1)	163 (2.1)	
Presenting vitals			
Heart rate, beats/min	92 (76, 110)	86 (72, 102)	<0.001
Systolic BP, mm Hg	157 (136, 181)	145 (128, 164)	<0.001
Diastolic BP, mm Hg	85 (73, 98)	80 (70, 90)	<0.001
Resp rate, breath/min	24 (20, 30)	20 (18, 24)	<0.001
Oxygen saturation, %	94 (89, 97)	96 (93, 98)	<0.001
HF etiology, n (%)			
Ischemic	2108 (66.9)	4345 (54.8)	<0.001
Valvular	96 (3.0)	326 (4.1)	
Hypertensive	346 (11.0)	1261 (15.9)	
Other	603 (19.1)	1993 (25.1)	
LVEF, n (%)			
≤45%	1683 (53.4)	3988 (50.3)	0.004
Medical history, n (%)			
Diabetes	1280 (40.6)	2889 (36.5)	<0.001
Hypertension	2223 (70.5)	4807 (60.7)	<0.001
Current smoking	119 (3.8)	363 (4.6)	0.061
Known CAD	1831 (58.1)	3774 (47.6)	<0.001
Previous PCI/CABG	668 (21.2)	1537 (19.4)	0.033
Prior MI	1366 (43.3)	2514 (31.7)	<0.001
Atrial fibrillation	635 (20.1)	1334 (16.8)	<0.001
Prior stroke/TIA	523 (16.6)	1224 (15.4)	0.137
Asthma	250 (7.9)	738 (9.3)	0.021
COPD	649 (20.6)	1654 (20.9)	0.737
Cancer	359 (11.4)	894 (11.3)	0.875
Dementia	182 (5.8)	507 (6.4)	0.219

Continued

Table 1. Continued

	Nitrates	No Nitrates (Control)	
	N=3153	N=7925	*P* Value
Pre-ED medications, n (%)			
Nitrates (any form)	962 (30.5)	1386 (17.5)	<0.001
ACEI or ARB	1894 (60.1)	4414 (55.7)	<0.001
β-Blocker	1586 (50.3)	3439 (43.4)	<0.001
Loop diuretic	1501 (47.6)	3957 (49.9)	0.027
Spironolactone	225 (7.1)	606 (7.6)	0.357
Statin	1407 (44.6)	3036 (38.3)	<0.001
Aspirin	1372 (43.5)	2878 (36.3)	<0.001
Laboratory			
Hgb, g/dL	12.7 (11.2, 14.0)	12.5 (11.2, 13.8)	0.004
WBC, $\times 10^9$/L	9.1 (7.3, 11.8)	8.3 (6.7, 10.3)	<0.001
Na+, mEq/L	139 (137, 142)	139 (137, 142)	0.203
Creatinine, μmol/L	104 (82, 136)	101 (81, 131)	<0.001
Creatinine, mg/dL	1.18 (0.93, 1.54)	1.14 (0.92, 1.48)	<0.001
Troponin >ULN, n (%)	658 (20.9)	809 (10.2)	<0.001
ECG abnormalities, n (%)			
ST-elevation	226 (7.2)	462 (5.8)	0.008
ST-depression	1237 (39.2)	2711 (34.2)	<0.001
Any Q-waves	530 (16.8)	1154 (14.6)	0.003
Medications in ED, n (%)			
ASA or clopidogrel	1081 (34.3)	890 (11.2)	<0.001
β-Blockers	566 (18.0)	611 (7.7)	<0.001
ACEI or ARB	628 (19.9)	595 (7.5)	<0.001
Furosemide	1675 (53.1)	4315 (54.4)	0.207
Metolazone	29 (0.9)	40 (0.5)	0.012
Digoxin	235 (7.5)	388 (4.9)	<0.001
Type of nitrates, n (%)			
Intravenous	388 (12.3)	0 (0.0)	<0.001
Nonintravenous	2765 (87.7)	0 (0.0)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ED, emergency department; HF, heart failure; Hgb, hemoglobin concentration; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Na, sodium concentration; PCI, percutaneous coronary intervention; SES, socioeconomic status; TIA, transient ischemic attack; ULN, upper limit of normal; WBC, white blood count.

compared using the χ^2 statistic. The primary analysis compared those who received nitrates via any route of administration versus controls using a propensity-matched analysis.[20] We examined those exposed to nitrates by nonintravenous routes of administration versus controls in a secondary propensity-matched analysis. We considered many covariates including those identified in previously published HF-specific mortality and morbidity risk adjustment models (as shown in Table 1),[19] and included the variables shown in Table 2 in our propensity-matched analyses. Greedy nearest neighbor matching was used to match subjects exposed to nitrates in the ED to control subjects on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score.[21] The balance of measured baseline covariates was assessed using standardized differences, and standardized differences less than 0.1 (10%) were deemed indicative of acceptable balance. The effect of nitrate exposure on the hazard of mortality was assessed using a Cox proportional hazards regression model in which the hazard of death was regressed on treatment status.[22] A robust variance estimator

Table 2. Propensity-Matched Hazard Ratios for Death Comparing Nitrate to Non-Nitrate Controls

	Hazard Ratio	95% CI	*P* Value
Any nitrate*			
7-day	0.76	0.51, 1.12	0.161
30-day	0.97	0.77, 1.21	0.781
1-year	0.91	0.82, 1.02	0.113
Nonintravenous nitrates*			
7-day	0.75	0.51, 1.12	0.158
30-day	0.90	0.71, 1.13	0.362
1-year	0.89	0.80, 1.00	0.056

*The following factors were included in the propensity-matched analysis: age, sex, socioeconomic status quintile, left ventricular systolic dysfunction, etiology of heart failure, mode of transportation to the emergency department (ED) and originating location, vital signs at presentation (systolic and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation on room air), presence of chest pain at presentation, initial blood test results (serum creatinine, hemoglobin, white blood cell count, sodium, troponin), abnormalities noted on the first ECG (ST-segment or T-wave abnormalities, and Q-waves), chronic use of nitrates prior to presentation, cardiovascular medications prior to ED presentation (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blockers [ARB], β-adrenoreceptor antagonist, loop diuretic, mineralocorticoid receptor antagonist, statin, or aspirin), atrial fibrillation, previous myocardial infarction, prior percutaneous coronary intervention or coronary artery bypass graft surgery, and past medical history (diabetes, hypertension, smoking, stroke or transient ischemic attack, asthma or chronic obstructive pulmonary disease, cancer, or dementia), medications used in the ED (aspirin, β-adrenoreceptor antagonist, ACE inhibitor or ARB, metolazone, or digoxin), and admission to ward or intensive care unit.

was used that accounted for the matched nature of the propensity-score matched sample.[22]

We planned sensitivity analyses for 8 subgroups of interest: (1) patients with a peak serum troponin above the upper limit of normal within the first day versus patients with peak serum troponin within normal limits, (2) patients with known versus unknown pre-existing coronary artery disease before ED presentation, (3) chronic nitrate users versus nonusers, and (4) patients with versus without chest pain on presentation.

When comparing secondary outcomes between nitrate-exposed patients and controls, McNemar's test was used for binary outcomes, while the Wilcoxon Signed Rank test was used for continuous outcomes.[23] Statistical significance was defined by a 2-tailed *P*-value <0.05. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Study Cohort

After applying the exclusion criteria to all 18 503 patients considered for study entry, the final study cohort was 11 078 patients, of whom 5948 were from the EFFECT-HF database and 5130 were from the EHMRG database (Figure 1). Death occurred in 2540 (22.9%) patients at 1 year and 7131 (64.4%) at the end of the study, and there were no losses to follow-up.

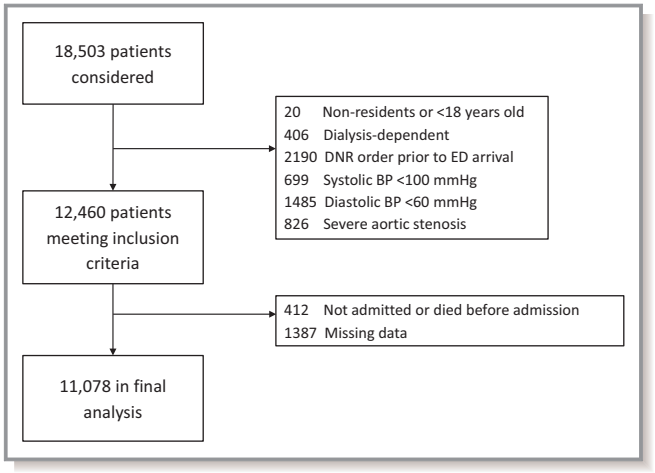

Figure 1. Patient flow diagram.

Of the study participants with ADHF, 28.5% received any form of nitrates in the ED.

Clinical Characteristics Associated With Early Nitrate Exposure

While there were no significant differences in age, sex, or socioeconomic status, nitrate recipients exhibited indicators of greater clinical severity, including higher presenting heart rate, respiratory rate, and a lower initial oxygen saturation. Patients who were prescribed nitrates in the ED were more likely to have arrived by ambulance and present with chest pain compared to non-nitrate recipients. More had a known history of coronary artery disease, systolic left ventricular dysfunction, troponin above the upper limit of normal, and ST- or T-wave abnormalities on the 12-lead ECG (Table 1).

Chest pain was more prevalent among patients administered nitrates (22.3%, n=702) than compared to those not receiving nitrates (16.5%, n=1310) in the ED (*P*<0.001). Pharmacologically, they were more likely to have used nitrates prior to hospital presentation and to have used other cardiac medications in the ED including anti-platelet agents, β-adrenoreceptor antagonists, renin–angiotensin–aldosterone system antagonists, and digoxin (Table 1). Using the EHMRG risk score,[17] the predicted probability of 7-day death was 0.7% (mean risk score −2.1±58.7) in the nitrate and 0.7% (mean risk score −12.0±54.5) in non-nitrate groups.

Clinical Outcomes

Comparing nitrate with non-nitrate groups, the unadjusted mortality rates did not differ at 7 days (1.8% versus 1.5%, *P*=0.151), 90 days (10.5% versus 10.1%, *P*=0.540), and 1 year (22.6% versus 23.2%, *P*=0.532) time points. The unadjusted 30-day mortality rate was higher among those who received nitrates in the ED: 5.9% versus 4.8% (*P*=0.016).

Propensity-Matched Analysis

In the analysis of nitrates versus controls, there were 2535 matched pairs consisting of one patient who received nitrates and one who did not. The matching rate was high in our analysis since 80% of nitrate users were successfully matched to a non-nitrate control. After propensity-matching, nitrate and non-nitrate groups were well matched with all standardized differences <0.10 (Figure 2). The risks of death over 7, 30, and 365 days of follow-up were not significantly different among nitrates versus control (Table 2), and there was no difference in survival in extended follow-up (Figure 3).

In the analysis of nonintravenous nitrates and non-nitrate controls, there were 2371 matched pairs consisting of one patient who received either oral or transdermal nitrates in the ED and one who did not. After propensity-matching, nonintravenous nitrate and non-nitrate groups were well matched with standardized differences <0.10 (Figure 4). The hazard ratios for mortality outcomes were not significantly different from unity at 7, 30, and 365 days (Table 2). There was again no difference in survival in extended follow-up (Figure 5).

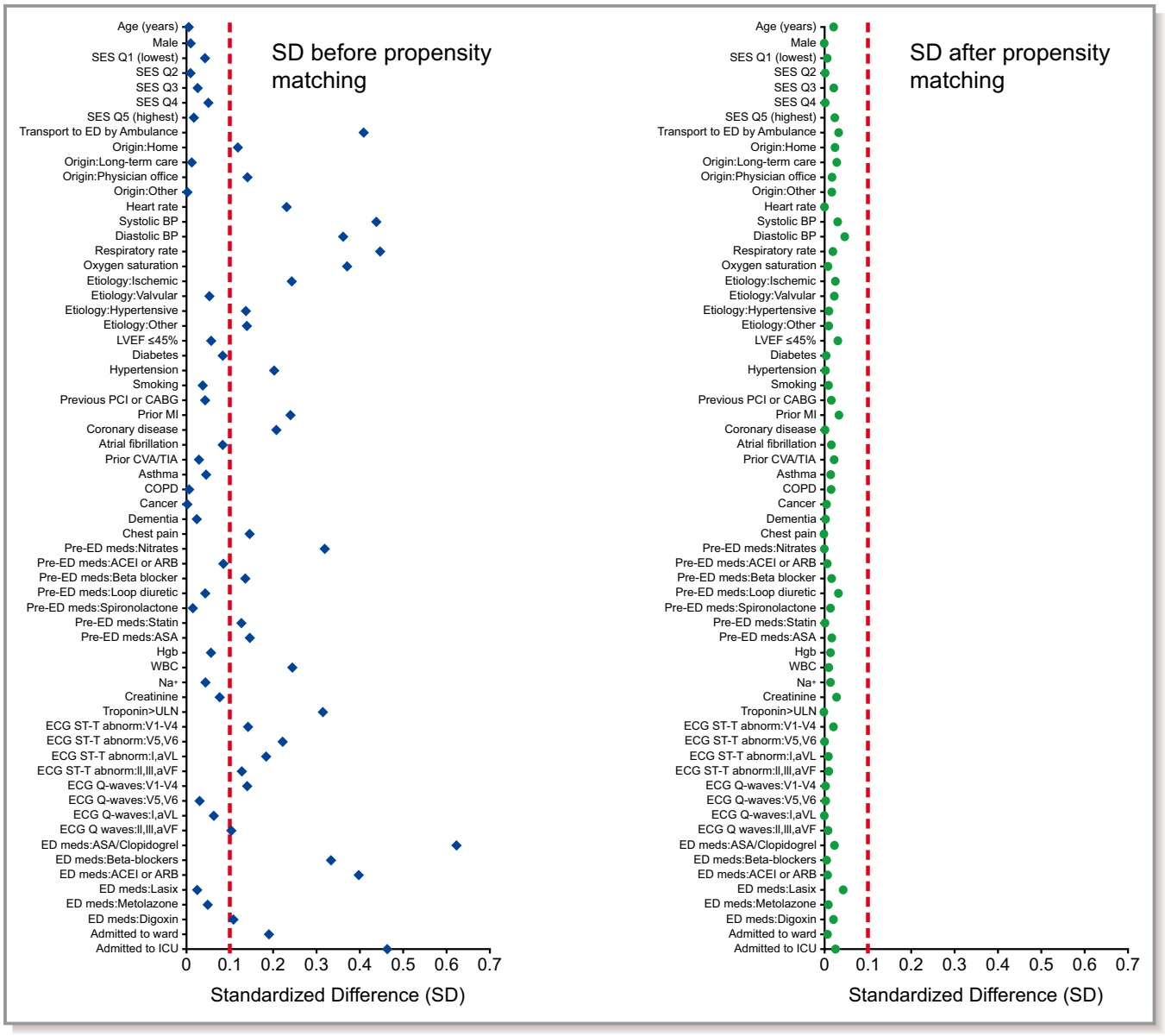

Figure 2. Standardized differences before (left) and after (right) propensity-matching in the nitrate cohort vs no nitrate use. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident (stroke)/transient ischemic attack; ED, emergency department; ICU, intensive care unit; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SES, socioeconomic status; ULN, upper limit of normal.

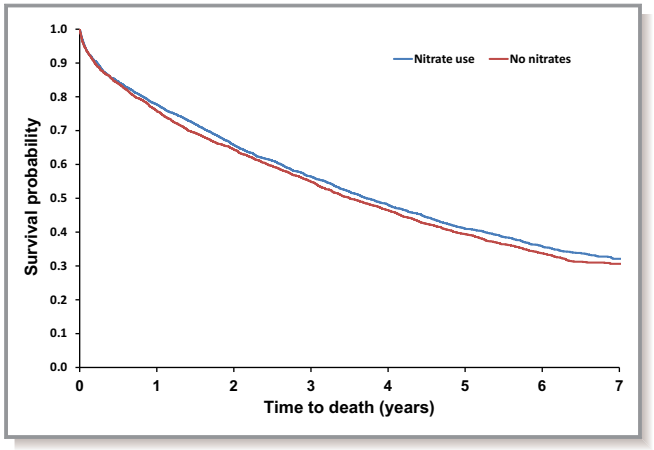

Figure 3. Long-term survival among patients prescribed nitrates vs no nitrate use.

Sensitivity analyses are shown in Table 3. In nearly all comparisons, there was no impact on mortality demonstrated between the nitrate and control groups, regardless of route of administration. The only comparison that was significant favored nitrate use in those without chest pain. However, given the number of comparisons it may be subject to type 1 error. The effect of nitrates on mortality was robust to inclusion of those with blood pressure <100/60 mm Hg (an exclusion criterion) in a sensitivity analysis where propensity-matching was repeated de novo. Finally, when we examined the outcome of cardiovascular death, there was no significant association with nitrate use, and results were similar to that for all-cause mortality (Table 4).

Nonmortality Care Measures

As shown in Table 5, more patients who were prescribed nitrates were admitted to the hospital from the ED compared to controls (79.3% versus 76.1%, P=0.001). This difference was significant when comparing only those who received nonintravenous nitrates and controls. Additionally, in both comparisons of any nitrate versus control and nonintravenous nitrates versus control, there was no difference in the rate of admission to a hospital ward or to an ICU. There was also no clinically significant difference in length of stay comparing those who were or were not prescribed nitrates (median 6 days in both groups). The vast majority of patients (>95%) were not transferred out, and therefore length of stay metrics were largely attributable to the hospital where the initial presentation occurred.

Discussion

Nitrates are commonly used in ADHF, because of perceived benefits to the acutely ill patient presenting in the ED setting, and in our study ≈30% of all HF patients received this form of treatment. Nitrates were more likely prescribed when vital signs were abnormal or when there was a component of chest pain in the presentation. However, we found that the acute use of nitrates in the ED was not associated with improved or worsened short-term, near-term, or longer-term survival benefit when compared to no nitrate use. While nonparenteral forms of nitrates were more commonly used, there was also no difference in survival compared to non-nitrate users. In all subgroups examined, including those with or without chest pain, troponin elevation, chronic nitrate use, and known prior history of coronary disease, there was again no demonstrable benefit or harm when nitrates were used acutely in the ED setting.

Our findings expand on the findings of 3 previous, but much smaller, trials of nitrates in ADHF. In a randomized controlled trial of 110 patients comparing high- versus low-dose nitrates, Cotter et al reported that there was no difference in mortality rates, although there were only 4 deaths in total during the study.[24] Sharon and colleagues randomized 40 patients with severe pulmonary edema to either intravenous nitrates or noninvasive positive pressure ventilation and demonstrated a reduction in the composite end point of death, myocardial infarction, or mechanical ventilation in the intravenous nitrate group.[13] However, the study was terminated prematurely and a total of 2 deaths occurred during the study, limiting its inference in relation to survival benefit. Lastly, Breidthardt et al demonstrated in 128 patients that high-dose nitrates accelerated improvement in serial brain natriuretic peptide measurements, but they found no effect on clinical outcomes including mortality, length of stay, or 90-day rehospitalization rates.[25] The caveat in interpretation of the aforementioned trial is that there were only 20 deaths in the entire study.[25] While none of the above studies demonstrated a survival benefit of nitrates in ADHF, there were also too few events to draw meaningful conclusions on its mortality impact. In our study cohort, there were 3353 deaths, making this the largest mortality study of acute nitrate use in ADHF to date.

Our findings differ from prior studies that found nitrate use to be associated with decreased admissions to the ICU and reduction in use of mechanical ventilatory support. Levy et al found that patients who received high-dose nitroglycerin experienced decreased need for intubation, noninvasive mechanical ventilation, and ICU admission.[14] Reduced need for mechanical ventilation was also found by Cotter et al,[24] although this finding was not observed to be significant by Breidthardt et al.[25] However, despite the above, mortality is a clinically important outcome, which was not demonstrably improved in any of the aforementioned smaller studies and also in our present evaluation.

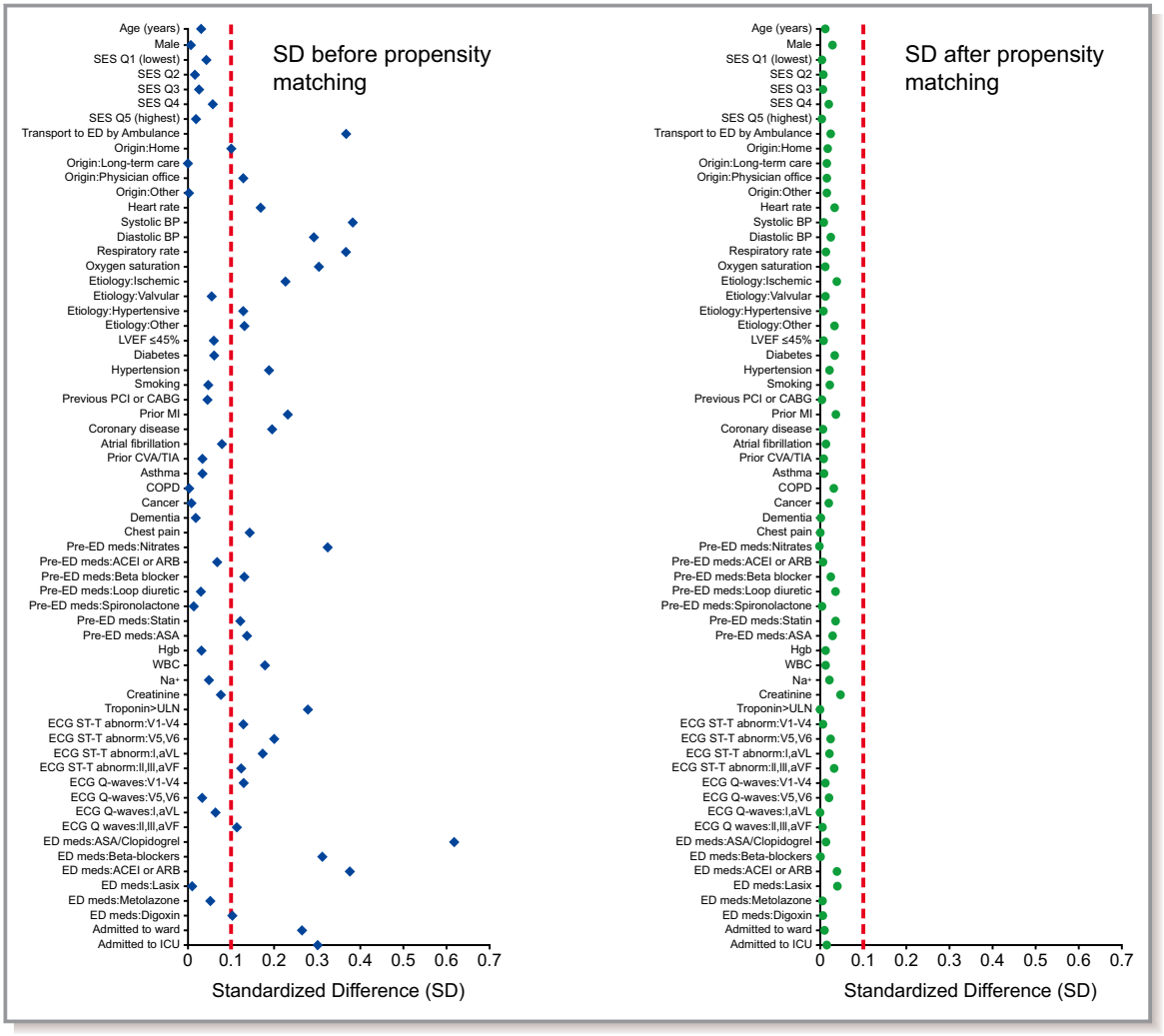

Figure 4. Standardized differences before (left) and after (right) propensity-matching in the cohort prescribed nonparenteral (nonintravenous) nitrates vs no nitrate use. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident (stroke)/transient ischemic attack; ED, emergency department; ICU, intensive care unit; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SES, socioeconomic status; ULN, upper limit of normal.

Several effects of nitrates have been demonstrated that may translate into symptom improvement. Nitrates may ameliorate the abnormal cardiovascular hemodynamics in ADHF by promoting vasodilation and consequently reducing ventricular filling pressure, systemic vascular resistance, pulmonary vascular resistance, and pulmonary capillary wedge pressure.[3,15] Additional benefits may be related to a reduction in subendocardial ischemia and mitral regurgitation.[6] However, tachyphylaxis may develop and a constant dose of nitrates may fail to have a persistent effect, depending on the duration of use. Lastly, because HF mortality is often secondary to arrhythmia or progressive pump failure, correction of hemodynamic parameters alone may not have a significant effect on mortality or other hard clinical outcomes.[26]

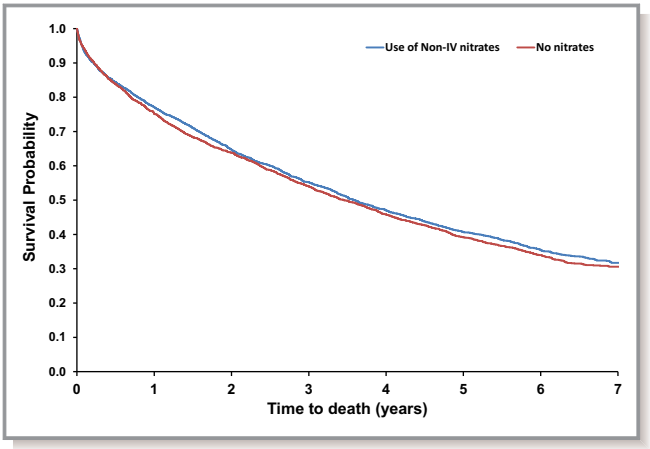

Figure 5. Long-term survival among patients prescribed nonparenteral (nonintravenous) nitrates vs no nitrate use.

The results of our study suggest that although nitrates have been shown to improve the abnormal hemodynamics associated with ADHF or ameliorate symptoms, it is doubtful there is any substantive effect on mortality. It is important to note that because there was no trend towards higher mortality observed in both the overall outcomes and sensitivity analyses, the use of nitrates appears to be safe in patients presenting with ADHF, provided that they have no contraindication to this class of medication. It is reassuring from a safety standpoint that there was no association between early nitrate use overall and admissions to ICU or prolongation of hospital length of stay. The broad, population-based nature of this study suggests that our findings are generalizable to most patients presenting to the ED with ADHF.

There are several notable limitations of our study. The propensity-matched analysis aims to control for confounding variables at baseline but does not account for unmeasured confounders.[27] However, we examined an extensive number of covariates including (but not limited to) those comprising validated models for ADHF mortality risk estimation, comorbidities, electrocardiographic features, and medications. We were also unable to determine any differences in the rapidity of symptomatic improvement. However, objective measures,

Table 3. Propensity-Matched Sensitivity Analyses*

Subgroup	7-Day Mortality HR (95% CI)	30-Day Mortality HR (95% CI)	1-Year Mortality HR (95% CI)
Any nitrate vs control†			
Chest pain			
Present	1.41 (0.44, 4.45)	1.42 (0.77, 2.64)	1.06 (0.81, 1.38)
Absent	0.69 (0.46, 1.05)	0.91 (0.71, 1.16)	0.89 (0.78, 1.00)
Coronary disease or prior MI			
Present	0.77 (0.45, 1.31)	0.97 (0.72, 1.31)	0.94 (0.82, 1.08)
Absent	0.74 (0.42, 1.32)	0.96 (0.68, 1.36)	0.87 (0.72, 1.05)
Nitrate use prior to ED visit			
Yes	0.71 (0.31, 1.62)	1.17 (0.77, 1.78)	0.95 (0.78, 1.16)
No	0.77 (0.49, 1.20)	0.90 (0.69, 1.17)	0.90 (0.79, 1.03)
Troponin elevated >ULN			
Yes	0.69 (0.35, 1.39)	0.83 (0.55, 1.25)	0.93 (0.74, 1.17)
No	0.79 (0.49, 1.27)	1.04 (0.79, 1.36)	0.90 (0.79, 1.03)
Nonintravenous nitrate vs control†			
Chest pain			
Present	1.00 (0.35, 2.87)	1.00 (0.54, 1.85)	1.08 (0.80, 1.45)
Absent	0.72 (0.47, 1.10)	0.88 (0.69, 1.13)	0.86 (0.76, 0.98)
Coronary disease or prior MI			
Present	0.75 (0.44, 1.28)	0.85 (0.63, 1.14)	0.91 (0.79, 1.06)
Absent	0.76 (0.42, 1.36)	0.98 (0.68, 1.41)	0.86 (0.71, 1.04)
Nitrate use prior to ED visit			
Yes	1.17 (0.54, 2.55)	1.10 (0.72, 1.67)	0.92 (0.75, 1.13)
No	0.64 (0.40, 1.02)	0.82 (0.63, 1.09)	0.88 (0.77, 1.01)
Troponin elevated >ULN			
Yes	0.59 (0.31, 1.13)	0.71 (0.48, 1.05)	0.86 (0.68, 1.08)
No	0.88 (0.53, 1.45)	1.01 (0.76, 1.34)	0.90 (0.79, 1.03)

*Prespecified subgroup analyses comparing the effect of nitrate administration vs non-nitrate controls (reference) showing hazards ratios (HR) for death at 3 time points after emergency department (ED) arrival.

†Propensity matching in subgroups stratified by presence or absence of chest pain, history or no history of coronary disease or myocardial infarction (MI), chronic nitrate use prior to the ED visit or nitrate naive, and serum troponin above the upper limit of normal (ULN) or nondetectable.

Table 4. Effect of Nitrates on Cardiovascular Death

	Hazard Ratio	95% CI	*P* Value
Any nitrate			
7-day	0.67	0.42, 1.08	0.100
30-day	0.85	0.64, 1.14	0.283
1-year	0.90	0.77, 1.04	0.157
Nonintravenous nitrates			
7-day	0.75	0.51, 1.12	0.158
30-day	0.90	0.71, 1.13	0.362
1-year	0.89	0.80, 1.00	0.056

such as length of hospital stay, were not significantly different, suggesting that there were no major differences in time-to-symptom relief. Details about the timing and dosing of nitrates were not available, limiting the ability to comment on specific doses or nitrate treatment protocols. We studied a large sample of HF patients, likely mitigating the effects of underpowered analyses. However, small magnitude differences that might be detectable with far larger sample sizes cannot be excluded. Finally, our study does not rule out a potential benefit of nitrates when used for patients with primary acute myocardial ischemia or valvular heart disease with secondary HF.

In conclusion, among patients with ADHF presenting to the ED, nitrate therapy was not associated with a significant improvement in survival. Similarly, there was no survival benefit in clinical subgroups, including presence or absence of an abnormal serum troponin, known history of coronary artery disease, chronic nitrate use prior to ED presentation, or chest pain symptoms on presentation. Our study does not support the use of nitrates as a generic form of therapy for ADHF in the early ED setting, when the specific aim of its use is to reduce risk of mortality. However, the administration of nitrates acutely in the ED appeared to be safe, with no undue increase in mortality risk. Therefore, its use to improve symptoms and clinical status in ADHF is reasonable. Further prospective studies with specific nitrate protocols are needed to further clarify the efficacy and safety of this medication.

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Table 5. Secondary Outcomes

	Nitrate	No Nitrates (Control)	*P* Value
Any nitrate			
N	N=2535	N=2535	
Admitted to hospital, n (%)	2010 (79.3)	1928 (76.1)	0.001
Admission location, n (%)			
ICU/CCU	394 (15.5)	386 (15.2)	0.735
Hospital ward	1386 (54.7)	1401 (55.3)	0.649
Length of stay, days			
Median*	6 (3–9)	6 (3–10)	0.006
Nonintravenous nitrate			
N	N=2371	N=2371	
Admitted to hospital, n (%)	1857 (78.3)	1798 (75.8)	0.017
Admission location, n (%)			
ICU/CCU	308 (13.0)	306 (12.9)	0.927
Hospital ward	1348 (56.9)	1360 (57.4)	0.700
Length of stay, days			
Median	6 (3–9)	6 (3–10)	0.213

ICU/CCU indicates intensive care unit or coronary care unit.
*The Wilcoxon rank sum test is not a formal test comparing medians; it tests the null hypothesis that the distribution of length of stay is the same in the 2 groups.

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None.

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