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ORIGINAL RESEARCH

Contemporary Safety of Ultrasound Enhancing Agents in a Nationwide Analysis

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BACKGROUND: Ultrasound enhancing agents (UEAs) are an important diagnostic tool for transthoracic or stress echocardiography (TTE/SE) but recent concerns have been raised about their safety in reports from individual health systems. As such, we aimed to identify if UEAs for TTE/SE are associated with serious adverse events within 2 days of administration.

METHODS AND RESULTS: All-payor nationwide claims from 11.4 million insured individuals across the United States, 2018 to 2022 were used to evaluate rates of death, anaphylaxis, myocardial infarction, ventricular tachycardia, or cardiac arrest within 2 days of TTE/SE among adults receiving and not receiving UEAs. Of the 11 421 463 individuals included (mean age 57.5±16.2, 54.0% female, 46.2% White), a total of 500 073 (4.4%) received TTE/SE with UEAs. After propensity score matching, the odds of death were lower in those receiving UEAs (receipt versus nonreceipt, 0.02% versus 0.14%, odds ratio [OR], 0.23 [95% CI, 0.19–0.28], $P<0.001$) and were not different across agents (Definity: 0.02%, OR, 0.22 [95% CI, 0.18–0.28]; Lumason: 0.03%, OR, 0.33 [95% CI, 0.20-0.57]; Optison: 0.01%, OR, 0.17 [95% CI, 0.08–0.38]; all $P<0.001$). Rates of nondeath outcomes were similar to those observed in individuals not receiving UEAs, overall, and across specific agents. Rates of all outcomes were stable across years, including considering pre- and post-COVID periods.

CONCLUSIONS: In this large nationwide claims analysis from 2018 to 2022, serious adverse events associated with UEAs for TTE/SE were uncommon and overall consistent across agents and years of study. Compared with nonreceipt, receipt of UEAs was associated with a lower odds of death within 2 days of TTE/SE.

Key Words: adverse events ■ claims ■ echocardiography ■ safety ■ ultrasound enhancing agents

Approximately 10% to 15% of all ambulatory echocardiograms (TTEs) are estimated to have poor endocardial border definition.[1] Microbubble enhancing agents (UEAs), composed of lipid or albumin shells and high molecular weight gases that produce nonlinear acoustic signals and effective tissue contrast in the ultrasound field,[2,3] have substantial value in enhancing endocardial border delineation and influencing downstream clinical decision-making in diverse clinical circumstances.[4,5] Three commercially available agents (Optison, Definity, and Lumason) are currently approved by the US Food and Drug Administration for left ventricular opacification in the setting of poor endocardial border definition. In numerous small, single center studies,[4–7] UEAs have been shown to be cost effective, reducing downstream use, and may result in a change in clinical management in 1/3 of individuals who receive them.[4] Moreover, older safety data from over 2 million inpatients indicated a beneficial effect and no excess harm within 48 hours of UEA receipt, when comparing with those individuals who did not receive UEAs.[8,9] Moreover, additional meta-analyses including both inpatient and outpatients similarly indicated no safety signal.[10,11]

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CLINICAL PERSPECTIVE

What Is New?

- In this large, nationwide claims analysis evaluating 500 073 individuals who received ultrasound enhancing agents and 2 474 914 propensity-matched controls who did not receive ultrasound enhancing agents for transthoracic/stress echocardiography, 2018 to 2022, the odds of death within 2 days of transthoracic/stress echocardiography were lower in individuals receiving ultrasound enhancing agents, without significant differences across agents or study years.

What Are the Clinical Implications?

- These findings overall signify the continued safety of ultrasound enhancing agents in contemporary clinical practice.

Nonstandard Abbreviations and Acronyms

KH	Komodo Health
PS	propensity score
SE	stress echocardiography
SMD	standardized mean difference
TTE	transthoracic echocardiogram
UEAs	ultrasound enhancing agents

In the subsequent decade and a half, UEAs have been used globally according to professional society guidelines[2,3,12] and are an essential component of contemporary echocardiography laboratory practice with a recognized risk of severe allergic reaction rate of 1/10000. Pharmacovigilance reporting several years ago suggested that one possible explanation for these rare allergic reactions may be related to the polyethylene glycol component found in certain UEAs but did not find that the rate of reactions had increased.[13] However, a recent report described an increase in severe allergic reactions to UEAs, further suggesting that the risk of severe and critical adverse drug reactions may differ by agent and may be related to history of prior receipt of COVID-19 vaccination.[14] These observations were retrospectively compiled from a heterogeneous analysis of UEA administrations across 4 health systems, encompassing a total of 81 hospitals, of which only 12 (15%) were included in the analysis.[15] However, concurrent global pharmacovigilance data, now totaling over 13 million patients, have not suggested an increased safety risk.[16]

As such, we sought to investigate the acute severe adverse event rate associated with UEA administration in an unselected contemporary population in a nationwide health care claims database. We designed a large, retrospective propensity-score (PS) matched cohort study using all-payor nationwide claims from 11.4 million insured patients across the United States from 2018 to 2022 to identify in a modern cohort (1) if UEAs used for TTE or stress echocardiography (SE) are associated with a specific increase in risk for adverse events within 2 days of receipt, (2) whether this risk differs by agent, and (3) whether there has been a temporal change in the rate of severe adverse drug reactions.

METHODS

Data Source

We analyzed closed claims data from the Komodo Health (KH) Healthcare Map data source.[17] KH data include >65 billion deidentified clinical, pharmacy, and laboratory encounters for more than 320 million patients enrolled in health insurance (Commercial, Medicare, and Medicaid) in the United States from 2012 to present, >140 million of whom have closed claims from more than 150 payors.[17] Closed claims are health care encounters that came directly from the payor, which include full medical or prescription drug benefit information, insurance eligibility, and insurer reported costs. Nearly half of KH claims data are closed encounters, representing >140 million patients.[17] These encounters have census-level representation across patient populations and provide a representative cross-section of US health care activity.[18] The study was approved by the Beth Israel Deaconess Hospital Institutional Review Board with a waiver of informed consent. The data supporting this study are not available for review per KH data use agreements.

Study Population

Adult individuals (≥18 years old) in KH closed claims data were included if they (1) had at least 1 claim for a TTE or SE (Table S1) with or without UEAs (eg, the index TTE/SE) from January 1, 2018 to December 31, 2022, (2) had continuous enrollment in medical and pharmacy benefits during a 1-year baseline period preceding the date of the index TTE/SE, and (3) had continuous enrollment in medical and pharmacy benefits through 2 days following the index TTE/SE date (ie, the follow-up period). Patients with a Current Procedural Terminology (CPT) or Healthcare Common Procedural Coding System code for TTE/SE with UEA but without an accompanying CPT or National Drug Code for a specific agent (Lumason, Definity, or Optison) on the same day (Table S2) were excluded as it was not possible to identify if UEAs were used and the type of agent used. Furthermore, patients with claims for multiple UEAs on the same date as the index TTE/SE

were excluded as it is not possible to discern which UEA represented the appropriate exposure.

Covariates

To identify baseline covariates at the time of the index TTE/SE, a 1-year baseline period was used to observe patient-level characteristics including age, sex, race, ethnicity, census region for state of residence, insurance type, COVID-19 vaccination status, setting of care (inpatient, outpatient, versus emergency department), year of index TTE/SE, and comorbidities as determined by the Deyo-modified Charlson Comorbidity Index (Table S3).[19–24] Additional comorbidities not included in the Charlson Comorbidity Index were extracted from claims during the baseline period including recent acute coronary syndrome, presence of ventricular arrhythmias, receipt of coronary angiography or percutaneous coronary intervention (PCI), receipt of coronary artery bypass grafting, receipt of anticoagulant therapy, requirement for mechanical ventilation, and presence of COVID-19 vaccination in the 4 weeks before the index TTE/SE (Table S4).

Definition of Exposure

The primary exposure was administration of a UEA for TTE/SE, defined as the presence of a CPT code for a TTE/SE with UEA and a CPT or National Drug Code for a specific agent (Lumason, Definity, or Optison) on the same day as the index TTE/SE as per prior methods (Table S2).[25] Unexposed individuals were defined as having a CPT code for TTE/SE in the absence of a CPT or National Drug Code code for a specific agent on the same day. Only the first exposure to an agent during the study window was considered.

Definition of Outcomes

The primary outcome was all-cause death. KH data provide date of death at month-level granularity only; therefore, the following algorithm was used to estimate death date: insurance-enrolled individuals with a death occurring in the month of or following the date of the index TTE who had no claims for any medical care following 48 hours after the index TTE were determined to have died within the 2-day follow-up period. Secondary outcomes included anaphylaxis, myocardial infarction (MI), ventricular tachycardia, and cardiac arrest as ascertained using *International Classification of Diseases, Tenth Revision* (*ICD-10*) claims (Table S5). Additionally, given concerns about UEAs causing Kounis Syndrome,[26] we evaluated rates of coronary angiography, PCI, and coronary artery bypass grafting in the 2 days following TTE/SE receipt as exploratory end points (Table S5). Only outcomes within 2 days of the index TTE/SE were considered.

Statistical Analysis

Baseline characteristics are presented using means±SDs for continuous parameters and counts or percentages for categorical variables and compared across UEA groups (receipt versus nonreceipt) using SMDs, further stratifying by the specific agents received (Lumason, Definity, or Optison). Crude outcome rates were calculated for each outcome and presented in aggregate, by study group (receipt versus nonreceipt), by study year, and stratified by specific agent received. To account for confounding by indication (as individuals receiving UEAs are different than those not receiving), we employed a PS matching technique. Briefly, a PS was estimated using a separate multivariable logistic regression model containing all baseline variables (specifically, age, sex, race, ethnicity, insurance type, geographic region, COVID-19 vaccination status, setting of care, index TTE/SE year, Charlson Comorbidity Index, clinical comorbidities, and recent clinical events) as predictors to determine likelihood of UEA use using a single numerical estimate. Subsequently, PS values were used to match patients undergoing TTE/SE with UEAs versus those without receipt using 1:5 nearest neighbor matching with a caliper of 0.1. Standardized mean differences (SMDs) were calculated and presented to evaluate imbalance between the matched and unmatched cohorts, using a SMD ≤0.10 to indicate balance. To assess for the degree of residual imbalances after PS matching, a Love plot was generated. A separate multivariable logistic regression model using generalized estimating equations was used to estimate the risk of the primary outcome in the matched cohort for the receipt of UEA versus non-UEA as well as by specific agent received. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC) using a 2-tailed P value <0.05 to declare significance for logistic regression models and an SMD ≤0.10 to indicate significance when comparing baseline demographic and clinical characteristics by UEA receipt.

RESULTS

Overall Results

Of the 21 087 167 individuals who underwent TTE/SE during the study period, a total of 11 421 463 (54.2%) were ultimately included in the analysis (Figure 1; mean age 57.5±16.2, 54.0% female, 46.2% White). A total of 500 073 individuals (4.4%) received a TTE/SE with UEAs, of whom 404 858 (81.0%) received Definity, 52 023 (10.4%) received Lumason, and 43 192 (8.6%) received Optison. A total of 67.6% of index TTEs/SEs were performed in the pre-COVID-19-vaccine era and 32.5% in the postvaccine era and did not differ

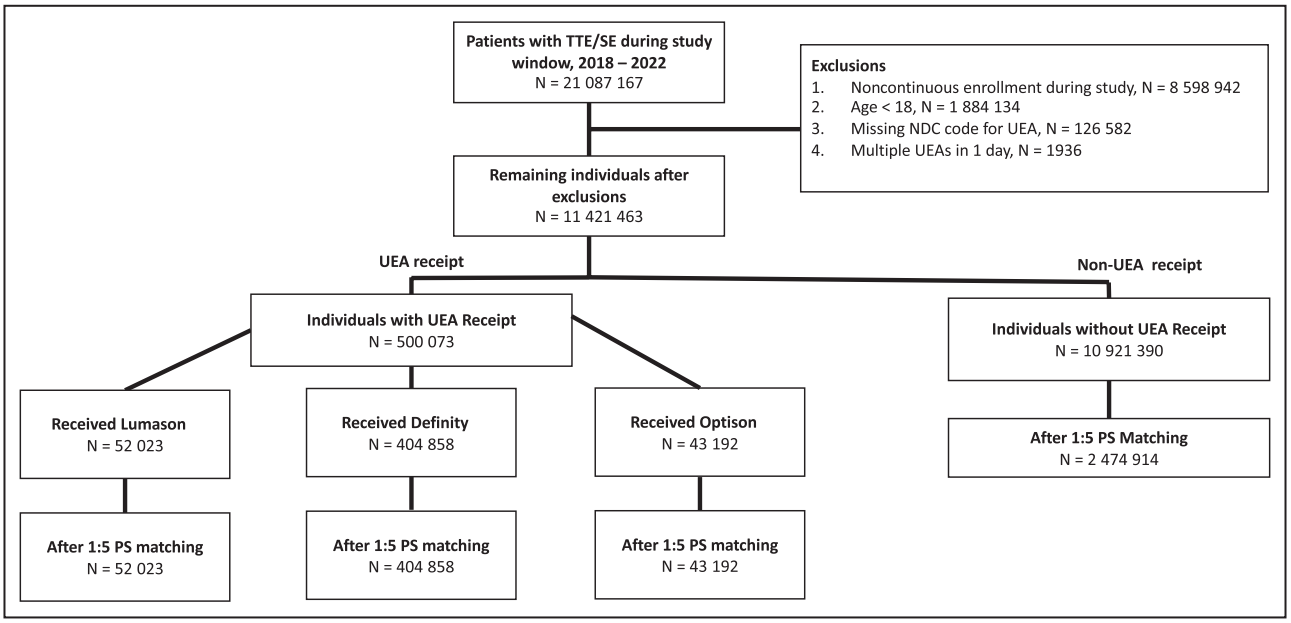

Figure 1. Study flow chart.
Shown is a flow chart demonstrating study inclusion and exclusion criteria. The numbers of individuals excluded for each reason are not mutually exclusive. NDC indicates National Drug Code; PS, propensity score; TTE/SE, transthoracic echocardiography or stress echocardiography; and UEA, ultrasound enhancing agents.

significantly by UEA receipt (SMD=0.07). Patients receiving UEAs were more frequently male (55.2% versus 45.6%, SMD=0.19), and non-Hispanic White (52.9% versus 45.9%; SMD=0.14) (Table 1). As a proportion of the overall number of TTEs/SEs with UEAs, use was highest in the Midwest (43.2%, SMD=0.54) and lowest in the West (9.9%; SMD=0.20). Patients receiving UEAs were more likely to have received their index TTE/SE in the emergency department (12.6% versus 4.5%, SMD=0.29). Individuals receiving UEAs more frequently received anticoagulation therapy during the 4 weeks before the index date (8.6% versus 5.8%, SMD=0.11) and less frequently had cerebrovascular disease (7.1% versus 10.2%, SMD=0.11), recent coronary angiography (0.6% versus 1.8%, SMD=0.11), or a recent acute MI (0.9% versus 2.7%, SMD=0.14).

Individuals receiving specific UEA brands were overall not statistically different across a broad range of baseline characteristics including age, sex, race, and number of comorbidities with a few notable differences (Table S6). The proportion of Lumason use was higher in the South (Lumason versus Optison, 32.2% versus 24.8%, SMD=0.16; Lumason versus Definity, 32.2% versus 21.7%, SMD=0.24) and lower in the Midwest (Lumason versus Optison, 37.9% versus 44.9%, SMD=0.14; Lumason versus Definity, 37.9% versus 43.8%, SMD=0.12). Definity use was higher in the West (Definity versus Optison, 11.1% versus 4.4%, SMD=0.25; Definity versus Lumason, 11.1% versus 5.1%, SMD=0.22). Additionally, Lumason use was proportionally lower than Definity in 2018 (20.3% versus 27.1%, SMD=0.16) and higher in 2022 (19.8% versus 15.1%, SMD=0.12).

Propensity Score Matching

All patients receiving UEAs were matched to a total of 2 474 914 individuals undergoing TTE/SE without contrast. After matching on age, sex, race, insurance, region, COVID-19 vaccination status, setting of care, year of study, number of comorbidities, recent acute coronary syndrome, presence of ventricular arrhythmias, receipt of coronary angiography or PCI, receipt of coronary artery bypass grafting, receipt of anticoagulant therapy, and requirement for mechanical ventilation, balance was achieved for all included covariates (Figure 2; Table S7).

Crude and Matched Outcome Rates

Overall, in the unmatched cohort, the primary outcome of all-cause death occurred in 93 (0.02%) of those receiving UEAs versus 15 289 (0.14%) of those not receiving UEAs. After matching, the primary outcome occurred in 93 (0.02%) of those receiving UEAs and 1992 (0.07%) of those not receiving UEAs (SMD=0.02; Table 2). In the matched cohort, rates of secondary outcomes were overall not significantly different between those receiving and not receiving UEAs (all SMDs ≤0.1) (Table 2). Rates of coronary angiography and PCI were numerically higher in those receiving

Table 1. Baseline Characteristics of Included Patients

Characteristic	All (N=11 421 463)	TTE/SE with UEA (N=500 073)	TTE/SE without UEA (N=10 921 390)	SMD
Age, y	57.5±16.2	58.1±13.4	57.5 ± 16.3	0.01
Age group in y				
18–34	1 166 822 (10.2%)	25 869 (5.2%)	1 140 953 (10.5%)	0.20
35–49	2 034 177 (17.8%)	94 010 (18.8%)	1 940 167 (17.8%)	0.03
50–64	4 432 313 (38.8%)	230 180 (46.0%)	4 202 133 (34.5%)	0.24
65+	3 788 151 (33.2%)	150 014 (30.0%)	3 638 137 (33.3%)	0.07
Female sex	6 164 282 (54.0%)	224 154 (44.8%)	5 940 128 (54.4%)	0.19
Race or ethnicity				
Non-Hispanic White	5 273 737 (46.2%)	264 331 (52.9%)	5 009 406 (45.9%)	0.14
Non-Hispanic Black	1 314 552 (11.5%)	42 408 (8.5%)	1 272 144 (11.7%)	0.11
Hispanic/Latino	1 348 008 (11.8%)	31 569 (6.3%)	1 316 439 (12.1%)	0.20
Other*	761 744 (6.7%)	22 081 (4.4%)	739 663 (6.8%)	0.10
Unknown/missing	2 723 422 (23.8%)	139 684 (27.9%)	2 583 738 (23.7%)	0.10
Insurance payor type				
Commercial	4 624 190 (40.5%)	219 457 (43.9%)	4 404 733 (40.3%)	0.07
Government-issued	4 969 109 (43.5%)	188 461 (37.7%)	4 780 648 (43.8%)	0.12
Other	1 650 094 (14.4%)	83 428 (16.7%)	1 566 666 (14.3%)	0.07
Unknown/missing	178 070 (1.6%)	8727 (1.8%)	169 343 (1.6%)	0.02
Geographic region				
Northeast	3 117 283 (27.3%)	118 642 (23.7%)	2 998 641 (27.5%)	0.09
South	4 089 150 (35.8%)	115 286 (23.1%)	3 973 864 (36.4%)	0.29
West	1 847 329 (16.2%)	49 617 (9.9%)	1 797 712 (16.5%)	0.20
Midwest	2 298 560 (20.1%)	216 255 (43.2%)	2 082 305 (19.1%)	0.54
Other	50 828 (0.5%)	11 (0.0%)	50 817 (0.5%)	0.10
Unknown	18 313 (0.2%)	262 (0.1%)	18 051 (0.2%)	0.03
COVID-19 vaccination status				
Vaccinated	503 911 (4.4%)	29 161 (5.8%)	474 750 (4.4%)	0.06
Unvaccinated/unknown	10 917 552 (95.6%)	470 912 (94.2%)	10 446 640 (95.7%)	0.07
Index TTE/SE setting of care				
Inpatient	2 790 625 (24.4%)	46 135 (9.2%)	2 744 490 (25.1%)	0.43
Outpatient	8 079 668 (70.7%)	390 778 (78.1%)	7 688 890 (70.4%)	0.18
Emergency department	551 170 (4.8%)	63 160 (12.6%)	488 010 (4.5%)	0.29
Index TTE/SE COVID-19 vaccine availability				
Prevaccine	7 714 699 (67.6%)	321 573 (64.3%)	7 393 126 (67.7%)	0.07
Postvaccine	3 706 764 (32.5%)	178 500 (35.7%)	3 528 264 (32.3%)	0.07
Index UEA				
Lumason	52 023 (0.5%)	52 023 (10.4%)	0 (0.0%)	0.48
Definity	404 858 (3.5%)	404 858 (81.0%)	0 (0.0%)	2.92
Optison	43 192 (0.4%)	43 192 (8.6%)	0 (0.0%)	0.43
None	10 921 390 (95.6%)	0 (0.0%)	10 921 390 (100.0%)	>9.85
Index year				
2018	3 493 321 (30.6%)	130 740 (26.1%)	3 362 581 (30.8%)	0.10
2019	2 418 034 (21.2%)	106 659 (21.3%)	2 311 375 (21.2%)	0.00
2020	1 803 344 (15.8%)	84 174 (16.8%)	1 719 170 (15.7%)	0.03
2021	2 062 369 (18.1%)	99 247 (19.9%)	1 963 122 (18.0%)	0.05
2022	1 644 395 (14.4%)	79 253 (15.9%)	1 565 142 (14.3%)	0.04

(*Continued*)

Table 1. Continued

Characteristic	All (N=11 421 463)	TTE/SE with UEA (N=500 073)	TTE/SE without UEA (N=10 921 390)	SMD
Number of Charlson Comorbidity Index comorbidities				
0	4 529 115 (39.7%)	187 069 (37.4%)	4 342 046 (39.8%)	0.04
1	2 473 112 (21.7%)	114 256 (22.9%)	2 358 856 (21.6%)	0.03
≥2	4 419 236 (38.7%)	198 748 (39.7%)	4 220 488 (38.6%)	0.02
Myocardial infarction	657 520 (5.8%)	29 136 (5.8%)	628 384 (5.8%)	0.00
Congestive heart failure	1 224 926 (10.7%)	60 763 (12.2%)	1 164 163 (10.7%)	0.05
Peripheral vascular disease	1 396 501 (12.2%)	54 460 (10.9%)	1 342 041 (12.3%)	0.04
Cerebrovascular disease	1 149 911 (10.1%)	35 443 (7.1%)	1 114 468 (10.2%)	0.11
Dementia	284 274 (2.5%)	6116 (1.2%)	278 158 (2.6%)	0.10
Pulmonary disease	2 311 727 (20.2%)	106 665 (21.3%)	2 205 062 (20.2%)	0.03
Connective tissue disease	424 532 (37.7%)	15 825 (3.2%)	408 707 (3.7%)	0.03
Peptic ulcer disease	142 646 (1.3%)	4992 (1.0%)	137 654 (1.3%)	0.03
Mild liver disease	801 509 (7.0%)	37 462 (7.5%)	764 047 (7.0%)	0.02
Diabetes (mild to moderate)	1 654 299 (14.5%)	84 949 (17.0%)	1 569 350 (14.4%)	0.07
Diabetes with complications	1 323 728 (11.6%)	66 173 (13.2%)	1 257 555 (11.5%)	0.05
Hemiplegia or paraplegia	155 940 (1.4%)	3590 (0.7%)	152 350 (1.4%)	0.07
Renal disease	1 197 997 (10.5%)	46 632 (9.3%)	1 151 365 (10.5%)	0.04
Cancer	793 677 (7.0%)	37 154 (7.4%)	756 523 (6.9%)	0.02
Metastatic cancer	234 846 (2.1%)	9337 (1.9%)	225 509 (2.1%)	0.01
Severe liver disease	87 271 (0.8%)	3202 (0.6%)	84 069 (0.8%)	0.02
AIDS	64 370 (0.6%)	2119 (0.4%)	62 251 (0.6%)	0.03
Acute coronary artery syndrome during baseline	400 209 (3.5%)	11 603 (2.3%)	388 606 (3.6%)	0.08
Serious ventricular arrhythmia during baseline	137 752 (1.2%)	8283 (1.7%)	129 469 (1.2%)	0.04
Anticoagulant therapy during 4 weeks before index date	678 540 (5.9%)	42 879 (8.6%)	635 661 (5.8%)	0.11
Mechanical ventilation during 4 weeks before index date	113 950 (1.0%)	182 (0.0%)	113 768 (1.0%)	0.14
Percutaneous coronary intervention during 4 weeks before index date	99 438 (0.9%)	893 (0.2%)	98 545 (0.9%)	0.09
Coronary angiography during 4 weeks before index date	198 805 (1.7%)	2785 (0.6%)	196 020 (1.8%)	0.11
Acute myocardial infarction during 4 weeks before index date	296 957 (2.6%)	4652 (0.9%)	292 305 (2.7%)	0.14
COVID-19 vaccination during 4 weeks before index date	68 950 (0.6%)	4176 (0.8%)	64 774 (0.6%)	0.02
Coronary artery bypass grafting during 4 weeks before index date	16 232 (0.1%)	85 (0.0%)	16 147 (0.2%)	0.06

SE indicates stress echocardiogram; SMD, standardized mean difference; TTE, transthoracic echocardiogram; and UEA, ultrasound enhancing agent.

Shown are baseline characteristics of included individuals at the time of index transthoracic echocardiogram or stress echocardiogram by receipt or nonreceipt of ultrasound enhancing agents. Estimates are shown as means±SDs or counts and percentages as appropriate. Absolute values for the standardized mean differences are provided for the comparisons of those receiving UEAs vs not receiving UEAs. SMDs ≤0.10 indicate balance between groups.

*"Other" race refers to those not designating as Non-Hispanic White, Non-Hispanic Black, or Hispanic or Latino.

UEAs, but this difference was not significant (all SMDs ≤0.1) (Table S8).

Outcome rates by the specific agent received are shown in Table S9. In the matched cohort, death rates were overall similar (Definity, 0.02%; Lumason, 0.03%, Optison, 0.01%) and not statistically different to the noncontrast group (0.07%) (all SMDs compared with no contrast ≤0.1). Similarly, in the matched cohort, rates of secondary outcomes were overall similar across agents (all SMDs compared with no contrast

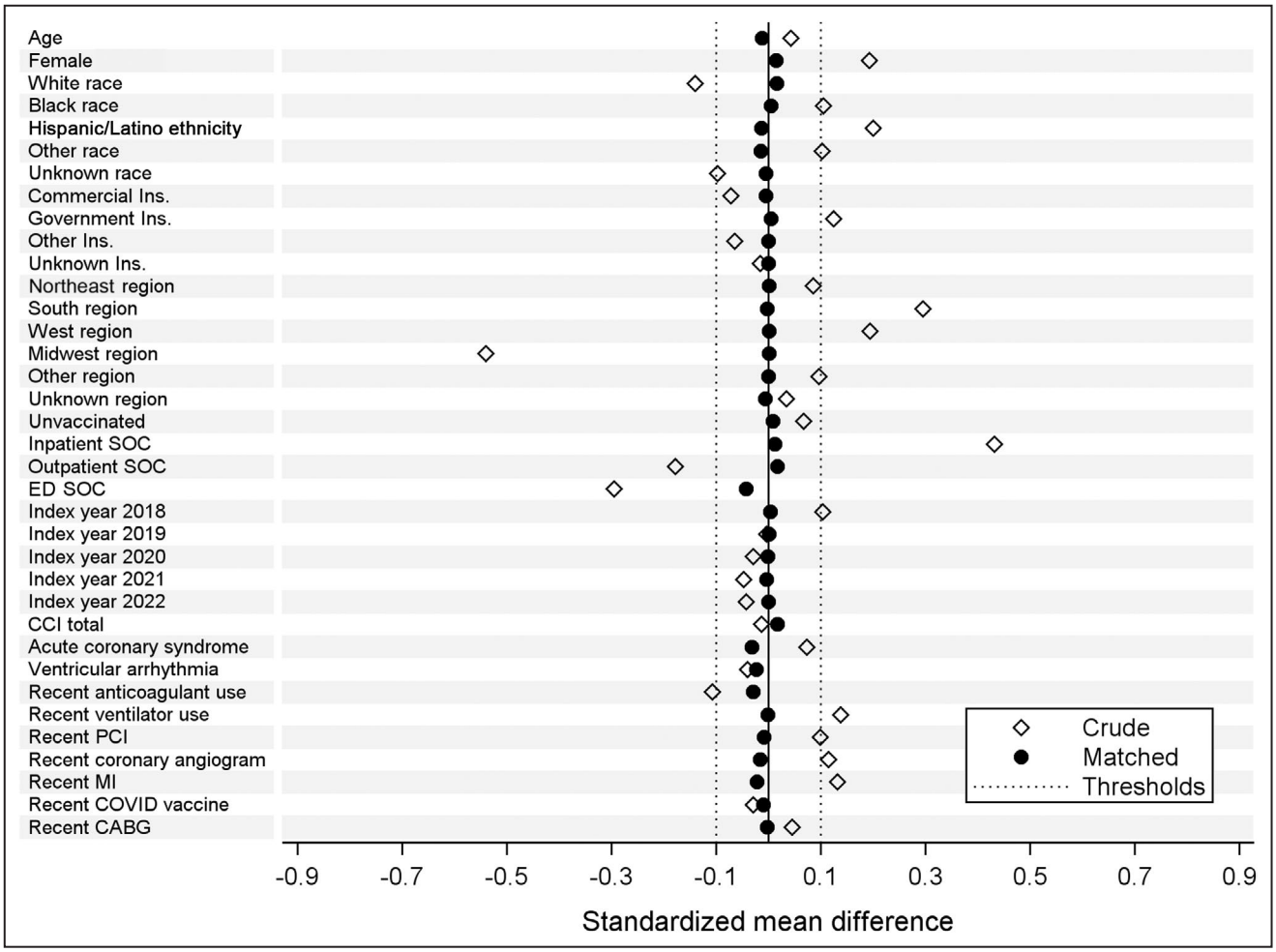

Figure 2. Love plot demonstrating imbalances between groups before and after propensity score matching.
Shown are the standardized mean differences in baseline covariates between groups receiving and not receiving ultrasound enhancing agents both before propensity score matching (crude; white diamond) and after (matched; black circle). Vertical hashed lines indicate the standardized mean difference thresholds above and below which a group is considered to be imbalanced. In general, the plot results indicate that the groups are well balanced after matching. CABG indicates coronary artery bypass grafting; CCI, Charlson Comorbidity Index; ED, emergency department; Ins., insurance; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SOC, setting of care.

≤0.1; Table S9). Coronary angiography and PCI were numerically more frequent among those receiving UEAs, regardless of specific agent, but this difference was not significant (all SMDs compared with no contrast ≤0.1; Table S10).

Crude death rates by specific agent and year of study are shown in Table S11. Crude death rates did not significantly change from the pre-COVID (2018–2019) to the post-COVID period (2020–2022) (Definity, +0.004%, SMD=0.06; Lumason, +0.006%, SMD=0.01; Optison, +0.007%, SMD=0.003) and not different than the noncontrast group (+0.009%, SMD=0.002).

Results of Modeling

In the PS-matched cohort, the odds of death within 2 days of the index TTE/SE were lower among individuals who received UEAs (UEA receipt versus nonreceipt, odds ratio [OR], 0.23 [95% CI, 0.19–0.28], P<0.001) (Table 3). This relationship was consistent across agents (UEA receipt versus nonreceipt, Definity: OR, 0.22 [95% CI, 0.18–0.28], P<0.001; Lumason: OR, 0.33 [95% CI, 0.20–0.57], P<0.001; Optison: OR, 0.17 [95% CI, 0.08–0.38], P<0.001).

DISCUSSION

In this large, nationwide study evaluating individuals who received UEAs for TTE/SE from 2018 to 2022, serious adverse events within 2 days of UEA receipt were overall uncommon and confirmed the stated estimated rate of anaphylaxis from UEAs for approximately 1:10000. Individuals receiving UEAs were more

Table 2. Crude Adverse Events Rates in the Overall and Matched Cohort

Outcome	Overall cohort		Matched cohort		Standardized mean difference
	TTE/SE with UEA	TTE/SE without UEA	TTE/SE with UEA	TTE/SE without UEA	
	No.=500 073	No.=10 921 390	No.=500 073	No.=2 474 914	
Crude adverse event rates					
Death	93 (0.02%)	15 289 (0.14%)	93 (0.02%)	1992 (0.07%)	0.02
Anaphylaxis	72 (0.01%)	2263 (0.02%)	72 (0.01%)	356 (0.01%)	0.00
Myocardial infarction	9844 (1.97%)	426 620 (3.91%)	9844 (1.97%)	41 226 (1.67%)	0.02
Ventricular tachycardia	4935 (0.99%)	100 369 (0.92%)	4935 (0.99%)	19 789 (0.8%)	0.02
Cardiac arrest	606 (0.12%)	60 387 (0.55%)	606 (0.12%)	6417 (0.26%)	0.03

Shown are the crude numbers and rates (in parentheses) of the primary outcome of all-cause mortality as well as secondary outcomes of anaphylaxis, myocardial infarction, ventricular tachycardia, and cardiac arrest among those who received a transthoracic echocardiogram or stress echocardiogram with and without ultrasound enhancing agents. Shown are results in the overall cohort (left) as well as the propensity-score matched cohort (right). Absolute values for the standardized mean differences are provided for the comparisons of those receiving UEAs vs not receiving UEAs in the matched cohort. SMDs ≤0.10 indicate balance between groups. SE indicates stress echocardiogram; SMD, standardized mean difference; TTE, transthoracic echocardiogram; and UEA, ultrasound enhancing agent.

frequently male, non-Hispanic White, and located in the Midwest. Accounting for likelihood of receipt of UEAs using PS matching, individuals who received UEAs versus those who did not had a lower odds of death within 2 days of receipt without differences across agents. Crude rates of secondary outcomes of anaphylaxis, MI, ventricular tachycardia, or cardiac arrest were not different across groups. Overall, crude rates of adverse events did not change substantially across the years of the study including from the pre-COVID (2018–2019) period to the post-COVID (2020–2022) period. These results overall underscore the continued safety of UEAs in nationwide practice and suggest observed differences across agents may be due in part to the settings in which these agents are used and patient comorbidities.

UEAs are an essential element of the diagnostic armamentarium available for use in cardiovascular ultrasound. UEAs have been previously associated with a reduced need for additional downstream testing, may improve time to diagnosis, lower overall imaging costs, and potentially improve workflows.[1,4,5,27,28] UEAs have demonstrated utility in TTE/SE through improving endocardial border resolution, assessment of myocardial masses, and assessment of blood volume and myocardial perfusion,[1,3,12,29] with additional applications being explored including molecular imaging and sonothrombolysis.[30,31] Although UEAs are among the safest of all contrast media in part due to lack of effect on thyroid or renal function,[32] a small but fixed rate of serious adverse reactions has been described, predominantly felt to be due to complement activation-related pseudoallergy reactions resulting from interaction of the complement system with the UEA shell.[32] These reactions may be present with anaphylactoid symptoms and may be fatal unless recognized and treated promptly. Since the Food and Drug Administration issued a boxed warning on UEAs in 2007,[33] multiple large safety studies have been published documenting the overwhelming safety of these agents with a serious adverse event rate of approximately 1:10000 UEA administrations.[8–10,34–38]

Despite these reassuring data, recent reports have called into question the modern safety profile of these agents. In 2021, the Food and Drug Administration product safety reporting system issued a *MedWatch* report on presumed Type I hypersensitivity reactions to polyethylene glycol, an excipient used to stabilize the microbubble shell, based on case reports of allergy to polyethylene glycol[13,39] and 11 cases of anaphylaxis including 2 deaths presumed related to UEAs over 2 decades of use in patients with polyethylene glycol allergy.[13] Furthermore, rare cases of Kounis Syndrome, causing allergic coronary vasoconstriction, have been described with receipt of UEAs,[26,40,41] likely occurring at a rate of <1/20000 according to Food and Drug

Table 3. Results of Multivariable Logistic Regression Evaluating Odds of Each Outcome Within 2 Days of the Index Echocardiogram in the Matched Cohort

	Death	
	OR (95% CI)	*P* value
TTE with UEAs (vs without as ref)	0.23 (0.19–0.28)	<0.001
Index UEA		
Lumason	0.33 (0.20–0.57)	<0.001
Definity	0.22 (0.18–0.28)	<0.001
Optison	0.17 (0.08–0.38)	<0.001
No contrast	Ref	Ref

Shown are the results of a multivariable logistic regression model evaluating the likelihood of the primary outcome. Displayed are the odds ratio, 95% CI, and *P* value for the likelihood of each outcome comparing those who received a TTE or stress echocardiogram with UEAs vs without (reference; ref) (top) and by brand of UEA received (bottom). All analyses were conducted in the propensity score matched cohort. OR indicates odds ratio; TTE, transthoracic echocardiogram; and UEA, ultrasound enhancing agent.

Administration Adverse Event Reporting System data.[42] More recently, a multicenter retrospective study suggested that severe adverse events, although rare, had increased in frequency with differential effects seen across brands, possibly related to the population-wide COVID-19 vaccination efforts.[14] However, these conclusions were based on analysis of data from 4 health systems encompassing a total of 81 hospitals, of which only 12 hospitals (15%) were included in the study,[15] leading to concerns about whether the results observed could be related to the selection of sites with clusters of reactions to UEAs. Moreover, across and within sites of this study, individual agents were used in different clinical settings (ie, SE versus TTE, inpatient versus outpatient), making it challenging to identify if the differential frequency of adverse events across agents observed in this study could be related to differences in the acuity of the patients receiving these agents.

As such, in this study, we sought to evaluate the contemporary safety of UEAs in a large, multicenter, nationwide analysis using claims from 2018 to 2022 in the KH data set. This data set represents an aggregation of claims from all payors across the United States and is broadly representative of US health care activity.[18] As the sites included are not selected for the occurrence or nonoccurrence of adverse reactions, the results represent an unbiased assessment of the occurrence of adverse events. Among individuals receiving UEAs for TTE or SE, serious adverse events occurring within 2 days of UEA receipt were uncommon with death occurring in 0.02% of uses. Use of UEAs was less frequent among women, a finding additionally noted in several prior studies.[27,43,44] Notably, the geographic setting in which UEAs were used differed by agent with those receiving Lumason for TTE/SE more frequently in the South those receiving Definity more frequently in the West. Accounting for baseline differences through PS matching, individuals receiving UEAs were less likely to die within 2 days of the index TTE/SE than those not receiving UEAs. Moreover, this association was consistent across agents, with all 3 commercially available UEAs being similarly associated with a reduction in death within 2 days of the index TTE/SE. These results mirror results published a decade prior by Main et al.[8] and reassuringly suggest the continued safety of UEAs in practice.

After matching, crude rates of anaphylaxis, MI, ventricular tachycardia, or cardiac arrest were not different in those receiving UEAs versus not receiving UEAs and across specific agents. Although rates of coronary angiography, PCI, and coronary artery bypass grafting were numerically higher in those who received UEAs, this difference was not statistically significant. This finding may reflect the predominant use of UEAs for SE[27] where abnormal findings may prompt urgent angiography within short duration. They may also reflect the improved resolution for detection of wall motion abnormalities using UEAs.[12] Reassuringly, however, crude rates of anaphylaxis, MI, cardiac arrest, and ventricular tachycardia were not significantly different between those receiving and not receiving UEAs, suggesting that UEAs are broadly safe in contemporary practice. Anaphylaxis rates in the non-UEA group were not different than those who received UEAs, suggesting that medications received in the 2-day period following the TTE/SE may also influence anaphylaxis risks, regardless of UEA receipt. Moreover, similar adverse event rates between Lumason and Definity argue that prior findings suggesting an increased risk attributable to Lumason[14] may be related to selection bias. Importantly, and suggesting against impact of the COVID-19 vaccination on predisposition to serious adverse events to UEAs, there was no notable increase in adverse events to UEAs when comparing the pre-COVID period to the post-COVID period, both overall and by agent evaluated.

Overall, these findings suggest the continued safety profile of UEAs in contemporary practice. Moreover, they suggest that safety differences between agents should be contextualized by the setting of administration, the comorbidities of those receiving UEAs, and the route/manner of administration. Given the plurality of benefits associated with UEA receipt and underuse relative to need,[1,27,43] these data support the continued use of UEAs for diagnostic evaluation. However, the persistent small but fixed rate of serious adverse events associated with UEA use suggest the need for vigilance and preparedness among echocardiography laboratories using UEAs. Although this risk should be interpreted in the context of higher risks posed by other contrast media[32] and thus should not preclude use, appropriate processes should be in place within echocardiography laboratories to mitigate risk and respond urgently to potential anaphylactoid reactions, to ensure the highest standards of quality are employed with all patients.

Although strengths of this nationwide multicenter analysis include size and unselected population, several limitations must be recognized. First, as a retrospective study, causality should be not be inferred with the current methods[45]; pharmacovigilance and prospective monitoring assures continuous rigorous evaluation of UEA safety. Second, although PS matching accounts for measured variables, there may be imbalances across groups among unmeasured variables that are not fully accounted for during the matching process. For this reason, comparisons between agents should be interpreted with caution and are intended to be hypothesis-generating. Third, as death date was not available in the KH data set, death within the month of or following the TTE/SE and absence of claims beyond the 2-day follow-up period were used to define death. Although this algorithm may tend to overestimate rather than underestimate the rate of death, death rates from this study should not be directly compared with other

studies of UEAs. Although most serious adverse reactions to UEAs occur within an hour of receipt,[2,3] it remains possible that some individuals who experienced a serious adverse event could die >2 days after their receipt of UEAs. Fourth, although validated claims algorithms[25] were used to identify receipt of TTE/SE and UEAs, as administrative codes are designed for billing, some misspecification of exposures and outcomes is possible. Fifth, although large and broadly representative of patients receiving health care, the KH data set does not encompass all of the US population, nor does it generalize to patients receiving UEAs for noncardiac applications or international settings. Sixth, claims data on COVID-19 vaccine receipt were available in only <6% of individuals, consistent with prior reports of undercapture of COVID-19 vaccination using claims.[46] Nevertheless, the absence of an increase in event rates in the pre- and post-COVID-19 periods suggests against a possible association with vaccination and serious adverse reactions to UEAs. Sixth, as only an individual's first UEA exposure during the time period was considered for this analysis, the impact of serial exposures on risk remains uncertain and should be a topic of future investigation. Seventh, the current article does not evaluate predictors of UEA use that are better described in a separate study.[27]

CONCLUSIONS

In a large nationwide claims analysis evaluating individuals who received UEAs for TTE/SE from 2018 to 2022, serious adverse events within 2 days of UEA administration were uncommon. Accounting for imbalances between baseline covariates, individuals who received UEAs had a lower odds of death within 2 days of the index TTE/SE compared with those who did not receive UEAs, without differences noted across individual agents or years of study. These results overall underscore the continued safety of UEAs in contemporary clinical practice.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S11

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