# Supplemental Online Content

Mentz RJ, Anstrom KJ, Eisenstein EL, et al; TRANSFORM-HF Investigators. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA*. doi:10.1001/jama.2022.23924



This supplemental material has been provided by the authors to give readers additional information about their work.

**eMethods. Inclusion and Exclusion Criteria.**

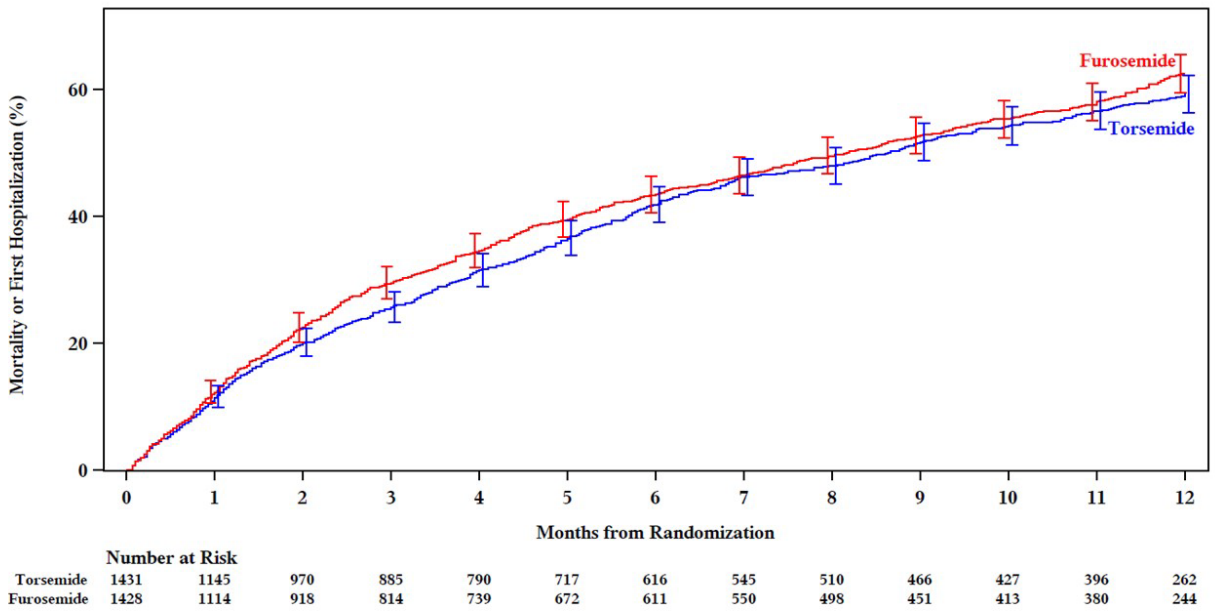
## Inclusion Criteria

1) Patient hospitalized (≥ 24 hours or over a change in calendar date) with worsening of chronic heart failure, or new diagnosis of heart failure **AND** meets 1 of the following criteria:
    a. Has a left ventricular ejection fraction (EF) ≤40% within 24 months prior to and including index hospitalization by any method (with most recent value used to determine eligibility)
    b. Has an elevated natriuretic peptide level (either NT-pro-B-type natriuretic peptide or B-type natriuretic peptide) during index hospitalization as measured by local laboratory
2) Plan for a daily outpatient oral loop diuretic regimen upon hospital discharge with anticipated need for long-term loop diuretic use
3) ≥ 18 years of age
4) Signed informed consent

## Exclusion Criteria

1) End-stage renal disease requiring renal replacement therapy
2) Inability or unwillingness to comply with the study requirements
3) History of heart transplant or actively listed for heart transplant
4) Implanted left ventricular assist device or implant anticipated <3 months
5) Pregnant or nursing women
6) Malignancy or other non-cardiac condition limiting life expectancy to <12 months
7) Known hypersensitivity to furosemide, torsemide, or related agents

## Online-Only Figure




**eFigure. All-cause mortality or all-cause hospitalization.**

Shown are the rates of the secondary outcome of all-cause mortality or all-cause hospitalization in the torsemide and furosemide groups. Whiskers represent 95% confidence intervals.

## Online-Only Tables

**eTable 1.** Pre-specified on-treatment sensitivity analyses assessing the primary endpoint and all-cause mortality or all-cause hospitalization*.

| | ITT Analysis | On-treatment at Discharge | On-treatment at 30-Days |
|---|---|---|---|
| All-cause mortality | 1.02 (0.89, 1.18), P=0.76 | 0.99 (0.85, 1.15), P=0.86 | 0.96 (0.78, 1.18), P=0.69 |
| All-cause mortality or all-cause hospitalization | 0.92 (0.83, 1.02), P=0.11 | 0.91 (0.81, 1.01), P=0.082 | 0.89 (0.78, 1.02), P=0.10 |

*Presented as HR and 95% CI with p-value based on a Cox proportional hazards regression model including the assigned treatment (torsemide vs. furosemide as the reference group) as well as age, sex, baseline ejection fraction (<40%, 41-49%, >50%, unknown), and loop diuretic treatment prior to index hospital admission as covariates.

**eTable 2**. Baseline Characteristics of TRANSFORM-HF Participants by on-treatment status at 30 days.

| Characteristics | On-treatment (N=1703) | Not on-treatment (N=1156) |
|---|---|---|
| Age | | |
| Mean (SD) y | 64.5 (13.7) | 64.5 (14.4) |
| Median [IQR], y | 65.0 (56, 74) | 66.0 (56, 75) |
| Sex, No. (%) | | |
| Female | 629 / 1703 (36.9%) | 426 / 1156 (36.9%) |
| Male | 1074 / 1703 (63.1%) | 730 / 1156 (63.1%) |
| Race, No. (%) | | |
| American Indian or Alaska Native | 5 / 1701 (0.3%) | 7 / 1153 (0.6%) |
| Asian | 36 / 1701 (2.1%) | 27 / 1153 (2.3%) |
| Black or African American | 568 / 1701 (33.4%) | 400 / 1153 (34.7%) |
| Native Hawaiian or Pacific Islander | 8 / 1701 (0.5%) | 12 / 1153 (1.0%) |
| White | 1024 / 1701 (60.2%) | 644 / 1153 (55.9%) |
| Other | 36 / 1701 (2.1%) | 43 / 1153 (3.7%) |
| Multiple | 24 / 1701 (1.4%) | 20 / 1153 (1.7%) |
| Not reported | 2 / 1793 (0.1%) | 3 / 1156 (0.3%) |
| Hispanic ethnicity—no. (%) | 71 / 1699 (4.2%) | 84 / 1156 (7.3%) |
| Vital Signs | | |
| Systolic blood pressure—mmHg | 118.8 (19.3) | 118.8 (20.6) |
| Heart rate—beat/min | 79.8 (15.5) | 81.7 (16.3) |
| Body mass index—kg/m$^2$ | 32.35 (9.47) | 31.92 (9.52) |
| Baseline Laboratories | | |
| Median NT-proBNP (IQR)—pg/mL | 3721 (1904, 7611) [N=850] | 4202 (2127, 9404) [N=526] |
| Median BNP (IQR)—pg/dL | 855 (438, 1693) [N=787] | 1064 (531, 1935) [N=594] |
| Estimated GFR—ml/min/1.73 m$^2$ | 59.9 (25.3) [N=1701] | 58.7 (25.8) [N=1153] |

Values shown as n / N provided (%) or mean (SD), unless otherwise specified.
Abbreviations: BNP denotes B-type natriuretic peptide, GFR glomerular filtration rate.

**eTable 3**. Additional post-hoc Cox Proportional Hazards Models of the Time to Event Endpoints.

| Endpoint | Model | Hazard ratio (95% CI) |
|---|---|---|
| All-cause mortality | Pre-specified adjustment model* | 1.02 (0.89, 1.18) |
| | Adjusted model plus site as a random effect | 1.02 (0.89, 1.18) |
| | Treatment only with robust variance estimate | 1.00 (0.87, 1.15) |
| All-cause mortality or all-cause hospitalization through 12 months | Pre-specified adjustment model* | 0.92 (0.83, 1.02) |
| | Adjusted model plus site as a random effect | 0.92 (0.83, 1.02) |
| | Treatment only with robust variance estimate | 0.92 (0.83, 1.03) |
| All-cause mortality or all-cause hospitalization through 30 days | Pre-specified adjustment model* | 0.94 (0.75, 1.18) |
| | Adjusted model plus site as a random effect | 0.94 (0.75, 1.18) |
| | Treatment only with robust variance estimate | 0.94 (0.75, 1.17) |

*Hazard ratio (HR), 95% confidence interval (CI) and p-value are based on a Cox proportional hazards regression model including the assigned treatment (torsemide vs. furosemide as the reference group) as well as age, sex, baseline ejection fraction (<40%, 41-49%, >50%, unknown), and loop diuretic treatment prior to index hospital admission as covariates.

**eTable 4**. Additional post-hoc sensitivity analysis for COVID-19 pandemic*.

| Endpoint | Time-Dependent COVID-19 Covariate | Treatment HR (95% CI) | COVID-19 Time-Dependent Covariate P-value | Interaction P-value |
|---|---|---|---|---|
| | | | | |
| **All-cause mortality** | | | | |
| Pre-specified adjustment model | | 1.02 (0.89, 1.18) | | |
| | | | | |
| | Prior to the US COVID-19 National Emergency Date of March 13, 2020 | 0.99 (0.77, 1.28) | 0.80 | 0.77 |
| | | | | |
| | On/After US COVID-19 National Emergency Date of March 13, 2020 | 1.04 (0.87, 1.23) | | |
| | | | | |
| **All-cause mortality or all-cause hospitalization through month 12** | | | | |
| Pre-specified adjustment model | | 0.92 (0.83, 1.02) | | |
| | Prior to the US COVID-19 National Emergency Date of March 13, 2020 | 0.89 (0.77, 1.03) | 0.85 | 0.56 |
| | | | | |
| | On/After US COVID-19 National Emergency Date of March 13, 2020 | 0.95 (0.82, 1.10) | | |
| | | | | |

* Adjusted Cox model including a time dependent covariate based on a date of 3/13/2020 (time dependent covariate COVID status = no prior to this date, COVID status = yes on/after this date) and time dependent covariate*treatment interaction. The treatment HRs, (95% CI) within each time dependent COVID status are provided as well as the p-values for the time dependent covariate and the interaction.

**eTable 5**. Additional post-hoc analysis of all-cause hospitalizations through 12 months with a competing risk model.

| | ***First* event rate per 100 pt-years** | | |
|---|---|---|---|
| **Endpoint** | **Torsemide** | **Furosemide** | **HR (95% CI)*** |
| All-cause hospitalization through 12 months | | | |
| Primary ITT Analysis | 82.5 | 92.2 | 0.88 (0.78, 0.99) |
| On-treatment at discharge | 81.1 | 91.3 | 0.87 (0.77, 0.99) |
| On-treatment at 30 days | 75.3 | 82.8 | 0.88 (0.77, 1.02) |

Hazard ratio (HR), 95% confidence interval (CI) are based on a Fine and Gray competing risk model including the assigned treatment (torsemide vs. furosemide as the reference group) as well as age, sex, baseline ejection fraction (≤ 40%, 41-49%, ≥50%, unknown), and loop diuretic treatment prior to index hospital admission as covariates. In the competing risk model, subjects who did not have an event and died were considering competing risks (i.e., precludes the occurrence of the event of interest) and have a different censoring code from those who were alive at censoring.

**eTable 6**. Details of loop diuretic status at study follow-up as acquired via the DCRI Call Center.

| Timepoint | Torsemide (N=1431) | Furosemide (N=1428) | All Patients (N=2859) |
|---|---|---|---|
| ***Discharge*** | | | |
| Known loop diuretic status | 1371 (95.8%) | 1384 (96.9%) | 2755 (96.4%) |
| Prescribed assigned loop diuretic^ | 1223 (89.2%) | 1268 (91.6%) | 2491 (90.4%) |
| Total daily dose prescribed (furosemide-equivalents), mg | 79.5 (69.8) | 79.1 (56.4) | 79.3 (63.3) |
| Total daily dose prescribed (reported), mg | 39.7 (34.9) | 79.1 (56.4) | 59.8 (51.0) |
| Prescribed a different loop diuretic^ | 112 (8.2%) | 75 (5.4%) | 187 (6.8%) |
| Crossover (between arms)^ | 96 (7.0%) | 53 (3.8%) | 149 (5.4%) |
| No loop diuretic^ | 36 (2.6%) | 41 (3.0%) | 77 (2.8%) |
| Death as reason for not on assigned loop | 3 (0.2%) | 4 (0.3%) | 7 (0.2%) |
| Unknown loop diuretic status | 57 (4.0%) | 40 (2.8%) | 97 (3.4%) |
| ***Month 1*** | | | |
| Month 1 visit record | 1423 (99.4%) | 1419 (99.4%) | 2842 (99.4%) |
| Known loop diuretic status* | 1016 (71.4%) | 1031 (72.7%) | 2047 (72.0%) |
| Prescribed assigned loop diuretic^ | 848 (83.5%) | 862 (83.6%) | 1710 (83.5%) |
| Total daily dose prescribed (furosemide-equivalents), mg | 77.8 (74.5) | 68.4 (50.2) | 73.1 (63.4) |
| Total daily dose prescribed (reported), mg | 38.9 (37.2) | 68.4 (50.2) | 53.9 (46.7) |
| Prescribed a different loop diuretic^ | 92 (9.1%) | 102 (9.9%) | 194 (9.5%) |
| Crossover (between arms)^ | 81 (8.0%) | 57 (5.5%) | 138 (6.7%) |
| No loop diuretic^ | 76 (7.5%) | 67 (6.5%) | 143 (7.0%) |
| Unknown loop diuretic status at conducted visit* | 52 (3.7%) | 46 (3.2%) | 98 (3.4%) |
| Death as reason for not on assigned loop* | 56 (3.9%) | 63 (4.4%) | 119 (4.2%) |
| Unknown status due to visit not done* | 299 (21.0%) | 279 (9.7%) | 578 (20.3%) |
| ***Month 6*** | | | |
| Month 6 visit record | 1290 (90.1%) | 1267 (88.7%) | 2557 (89.4%) |
| Known loop diuretic status* | 826 (64.0%) | 855 (67.5%) | 1681 (65.7%) |
| Prescribed assigned loop diuretic^ | 672 (81.4%) | 633 (74.0%) | 1305 (77.6%) |
| Total daily dose prescribed (furosemide-equivalents), mg | 78.3 (83.4) | 66.2 (52.0) | 72.3 (69.9) |
| Total daily dose prescribed (reported), mg | 39.1 (41.7) | 66.2 (52.0) | 52.5 (49.0) |
| Prescribed a different loop diuretic^ | 88 (10.7%) | 129 (15.1%) | 217 (12.9%) |
| Crossover (between arms)^ | 74 (9.0%) | 82 (9.6%) | 156 (9.3%) |
| No loop diuretic^ | 66 (8.0%) | 93 (10.9%) | 159 (9.5%) |
| Unknown loop diuretic status at conducted visit* | 36 (2.8%) | 28 (2.2%) | 64 (2.5%) |
| Death as reason for not on assigned loop* | 100 (7.8%) | 81 (6.4%) | 181 (7.1%) |
| Unknown status due to visit not done* | 328 (25.4%) | 303 (23.9%) | 631 (24.7%) |
| ***Month 12*** | | | |
| Month 12 visit record | 1062 (74.2%) | 1069 (74.9%) | 2131(74.5%) |
| Known loop diuretic status* | 690 (65.0%) | 673 (63.0%) | 1363 (64.0%) |
| Prescribed assigned loop diuretic^ | 510 (73.9%) | 477 (70.9%) | 987 (72.4%) |
| Total daily dose prescribed (furosemide-equivalents), mg | 83.0 (93.1) | 61.6 (45.7) | 72.6 (74.7) |
| Total daily dose prescribed (reported), mg | 41.5 (46.6) | 61.6 (45.7) | 51.3 (47.2) |
| Prescribed a different loop diuretic^ | 92 (13.3%) | 104 (15.5%) | 196 (14.4%) |
| Crossover (between arms)^ | 67 (9.7%) | 71 (10.5%) | 138 (10.1%) |
| No loop diuretic^ | 88 (12.8%) | 92 (13.7%) | 180 (13.2%) |
| Unknown loop diuretic status at conducted visit* | 20 (1.9%) | 27 (2.5%) | 47 (2.2%) |
| Death as reason for not on assigned loop* | 72 (6.8%) | 84 (7.9%) | 156 (7.3%) |
| Unknown status due to visit not done* | 280 (26.4%) | 285 (26.7%) | 565 (26.5%) |

Denominators: * = patients with a monthly visit record; ^ = patients with a known loop diuretic status; otherwise column header N