Study Protocol

ToRsemide compArisoN with furoSemide FOR Management of Heart Failure

SHORT TITLE: TRANSFORM-HF

ClinicalTrials.gov Identifier: NCT03296813

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PROTOCOL APPROVAL PAGE

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Date
Version 1.0	February 28, 2018
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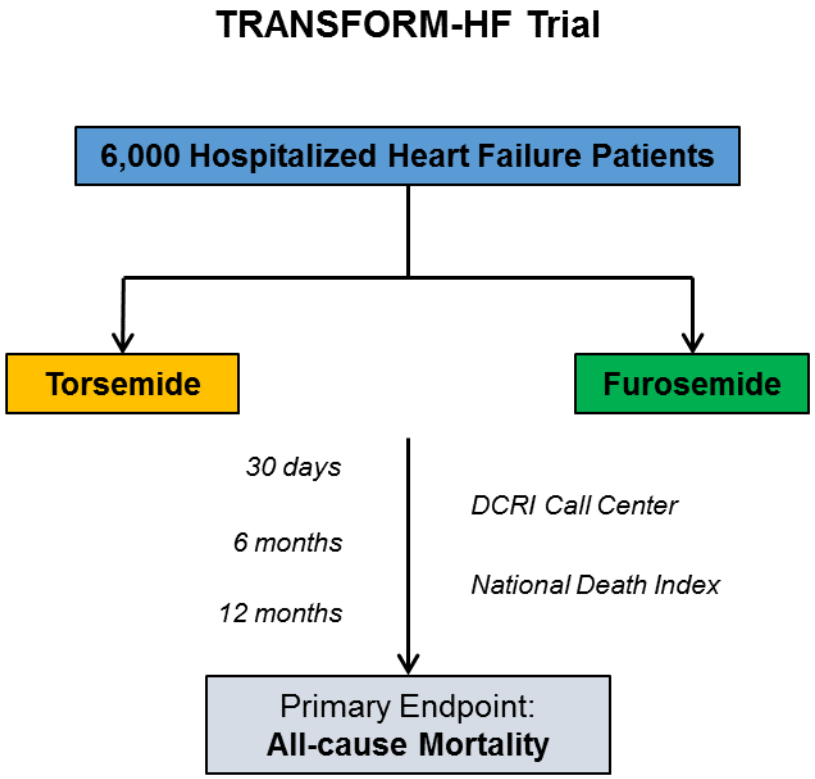
TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Title:	**ToRsemide compArisoN with furoSemide FOR Management of Heart Failure (TRANSFORM-HF)**
Location:	Approximately 50 clinical sites in the United States
Objectives:	To compare torsemide versus furosemide on long-term clinical outcomes among patients hospitalized for heart failure.
Study Design:	An approximately 6000-patient, randomized, unblinded, two-arm, multicenter clinical trial comparing torsemide with furosemide among patients hospitalized for heart failure.
Treatment Regimens:	1:1 randomization to either oral torsemide *OR* oral furosemide (dosing at discretion of local provider with dose equivalency guidance provided)
Primary Endpoint:	All-cause mortality
Secondary Endpoints:	• All-cause mortality or all-cause hospitalization over 12 months • Total hospitalizations over 12 months • All-cause mortality or all-cause hospitalization over 30 days • Health-related quality of life over 12 months • Symptoms of depression over 12 months

Study Flow Chart



2. HYPOTHESES AND OBJECTIVES

2.1 Primary Objectives and Hypothesis

The primary objective of the TRANSFORM-HF study is to compare the **treatment strategy** of torsemide versus furosemide on long-term clinical outcomes among patients hospitalized for heart failure. All patients will be followed for a minimum of 12 months.

Our ***primary hypothesis*** is that torsemide will reduce all-cause mortality by a relative 20% (i.e. a hazard ratio of 0.80) compared to furosemide. This is an event-driven trial that will require at least 721 primary endpoint events to have ≥ 85% power.

2.2 Secondary Objectives

Other secondary objectives of this protocol will be to examine the effect of torsemide versus furosemide for the following endpoints:

- All-cause mortality or all-cause hospitalization over 12 months
- Total hospitalizations over 12 months
- All-cause mortality or all-cause hospitalization over 30 days
- Health-related quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), over 12 months

- Symptoms of depression, as measured by the Patient Health Questionnaire-2 (PHQ-2), over 12 months

3. BACKGROUND AND RATIONALE

Heart failure is a major and growing public health problem in the United States, affecting over 5 million Americans, causing over 1 million hospitalizations, and accounting for over $30 billion in total costs per annum.[1] Reduced cardiac output in heart failure patients activates the renin-angiotensin-aldosterone system (RAAS) which increases water and sodium retention with resultant edema and shortness of breath.[2] Loop diuretics including furosemide and torsemide (both of which are available as generic formulations) are commonly prescribed for the symptomatic treatment of heart failure—with use in >70% of patients.[3]

Furosemide is the most commonly used loop diuretic (approximately 90% use).[4] However, preclinical and clinical data support the benefits of torsemide over furosemide. Compared with furosemide, torsemide has increased bioavailability and a longer half-life with maintained absorption in the setting of oral intake (**Table 1**).[5] Torsemide also has beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular remodeling and natriuretic peptide levels.[6-10] Several small studies of torsemide vs. furosemide and two recent meta-analyses suggest a substantial decrease in heart failure morbidity and potentially mortality with torsemide compared to furosemide (**Figure 1**).[4,11-13]

Table 1. Pharmacokinetic properties of loop diuretics.

	Furosemide	**Torsemide**	**Bumetanide**
Relative potency	1x	2-4x	40x
Bioavailability, %	10-100 (avg 50)	80-100	80-100
Affected by food	Yes	No	Yes
Half-life, h			
Normal	1.5-2	3-4	1
Heart Failure	2.7	6	1.3
Renal Dysfunction	2.8	4-5	1.6
Liver Dysfunction	2.5	8	2.3
Average effect, h	6-8	6-8	4-6
Most Common Dosing Schedule	Once or Twice Daily	Once Daily	Once Daily

The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines indicate that the optimal use of diuretics is the cornerstone of any successful approach to the treatment of heart failure.[1] However, in light of the lack of an adequately powered study, there is insufficient evidence to conclude that torsemide should be recommended over furosemide in the management of heart failure. **Given this unmet clinical need, the TRANSFORM-HF trial was designed to be a prospective, randomized, comparative-effectiveness study to definitively compare torsemide with furosemide in heart failure patients.**

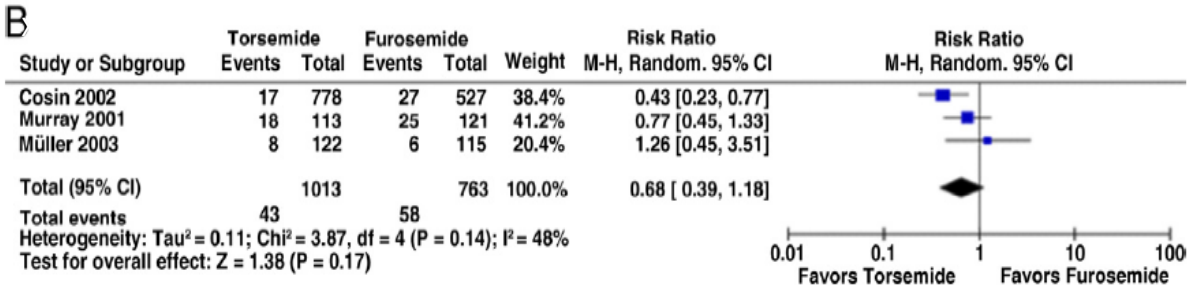


Figure 1. Mortality With Torsemide Compared With Furosemide. Modified from Bikdeli B, et al. J Am Coll Cardiol 2013.

4. BASIC STUDY DESIGN

This study will be a randomized, unblinded, two-arm, multi-center clinical trial of patients hospitalized for heart failure. Approximately 6,000 patients will be enrolled in the trial.

Patients will be randomized 1:1 to either oral torsemide *OR* oral furosemide prior to hospital discharge. The initial and follow-up dosing of torsemide and furosemide will be at healthcare provider discretion, with the following conversion provided as a guide: 1 mg torsemide to 2-4 mg oral furosemide. For instance, a patient would receive torsemide 20 mg or furosemide 40-80 mg. Providers will be asked to document their planned initial dose and dosing frequency of torsemide and furosemide prior to patient randomization to assess the exact conversion factor being utilized.

Randomization can occur at any time before hospital discharge at the discretion of the healthcare provider. If patients receive intravenous diuretic therapy during the index hospitalization, it is expected that randomization will occur near the time of transition to oral loop diuretic therapy or after the patient has successfully transitioned to oral loop diuretic therapy. Following randomization, the study medication is expected to constitute the oral diuretic therapy for the remainder of the hospitalization, with the expectation for patients to receive at least 1 dose of study medication prior to discharge. Patients will be prescribed the randomized study medication at time of index hospital discharge.

Post-discharge dose adjustments will be at the discretion of the treating healthcare provider(s) with strategies in place to maintain prescription of and adherence to the randomized medication.

The primary endpoint will be all-cause mortality over the follow-up period.

Patients will receive follow-up per standard care without any additional study-specific visits.

All patients will have 30-day, 6-month, and 12-month post-randomization phone contacts performed by the Duke Clinical Research Institute (DCRI) Call Center for assessment of

vital status, interval hospitalizations, concomitant HF medications, adherence, quality of life, and symptoms of depression. As an additional mechanism to safeguard against hospitalization under-reporting, the DCRI Call Center will initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient. The National Death Index (NDI) will be searched during follow-up and prior to study close-out.

5. STUDY POPULATION AND ELIGIBILITY CRITERIA

5.1 Overview

The population will exclusively enroll patients while they are hospitalized. Eligible patients will have been hospitalized for worsening of chronic heart failure or hospitalized for management of a new diagnosis of heart failure. The diagnosis of heart failure utilized will be the responsibility of the treating clinician, with the exception that all patients must meet the ejection fraction and/or natriuretic peptide criteria outlined below. The selection criteria below were designed to be inclusive and representative of the broad heart failure population in routine clinical practice, including appropriate representation of women and minorities.

5.2 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

5.3 Exclusion Criteria

1) End-stage renal disease requiring dialysis 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 or women who are trying to conceive
6) Malignancy or other non-cardiac condition limiting life expectancy to <12 months
7) Known hypersensitivity to furosemide, torsemide, or related agents

6. TREATMENT INTERVENTIONS

6.1 Overview of Treatment Interventions

This will be an unblinded, two-arm randomized clinical trial comparing:

- Oral torsemide
- Oral furosemide

Prior studies have suggested oral torsemide has a relative potency 2-4 fold greater than oral furosemide per mg.[11,12,14-16] The initial and follow-up dosing of torsemide and furosemide will be at healthcare provider discretion, with the following conversions provided as a guide:

1 mg oral torsemide = 2-4 mg oral furosemide

1 mg oral or intravenous bumetanide = 40 mg oral furosemide

Prior to randomization, the starting dose of furosemide and torsemide will be documented by healthcare providers, with the intent that providers will initially order this dose of study medication after randomization. Patients will receive the randomized medication during the remainder of their hospitalization with continuation of the randomized therapy post-discharge. Post-discharge dose adjustments will be at the discretion of the treating healthcare provider(s) with strategies in place to maintain adherence (if possible) to the randomized medication.

6.2 Blinding

As this is a pragmatic trial with an objective primary endpoint, this study will be unblinded for patients, managing clinicians, and the study team.

6.3 Patient Safety and Concomitant Therapies

This study will evaluate and compare treatment strategies of loop diuretics in patients with heart failure. Although investigators are encouraged to follow the assigned treatment strategy until the end of the study (≥12 months for all patients), in all cases the patient's safety based on the clinical judgment of the treating physician will take priority over the specific treatment assignment.

7. RECRUITMENT AND SCREENING PROCEDURES

7.1 Common Recruitment/Screening Procedures

All patients with a diagnosis of heart failure admitted to participating centers will be screened by study staff at the local sites. Patients meeting eligibility criteria will be approached regarding participation in this study.

7.2 Estimated Enrollment Period

This study will enroll approximately 6000 patients at approximately 50 U.S. study sites. The projected timeline for enrollment is approximately 36 months.

8. INITIAL STUDY EVALUATIONS AND RANDOMIZATION

A complete schedule of assessments throughout the study is given in Appendix A.

8.1 Screening/ Patient Enrollment

Potential trial patients believed to meet study selection criteria will be approached and willing patients will be consented for trial participation. After providing informed consent and signing the informed consent form (ICF), trial eligibility criteria will be formally confirmed. Patient contact information will be obtained for the post-randomization DCRI Call Center contacts. Patients will also designate and provide contact information for a person familiar with their medical care whom the DCRI Call Center may contact should the patient be unavailable.

8.2 Randomization/ Study Baseline

Among those meeting eligibility criteria, once the patient is on an oral loop diuretic regimen or the patient is near the time of transition from intravenous to oral loop diuretic therapy, patients will be randomized in a 1:1 fashion to one of two treatment groups prior to hospital discharge. Anticipated initial daily dosing regimens for oral torsemide and oral furosemide will be recorded by site investigators for each patient prior to randomization. Patient treatment assignment will be generated using a simple randomization scheme (i.e. no stratification) given the open-label nature of the intervention to limit the potential bias due to predictable treatment assignment.

At the time of randomization, the following baseline characteristics should be documented: age, sex, race, ethnicity, ejection fraction (most recent by any modality), concomitant HF medications and other key baseline variables. Baseline KCCQ and PHQ-2 data should be obtained and recorded on the same day of but prior to randomization.

Following randomization, site study staff will identify the treatment assignment and confirm inpatient oral loop diuretic use and outpatient loop diuretic prescription and accessibility. Patients will be provided medication adherence and educational materials to support adherence (see Adherence Section, 10). After this initial contact, no further study-specific patient contact will be required at the site level.

9. FOLLOW-UP EVALUATIONS

There will be no scheduled study-specific visits. All study patients will be followed on a usual care basis.

9.1 30 days

Patients will be contacted by the DCRI Call Center to document vital status, medication adherence, concomitant HF medications, KCCQ and PHQ-2 questionnaires, and to capture hospitalization information. The Call Center will obtain discharge summaries from hospitalizations as appropriate.

9.2 6 months

Patients will be contacted by the DCRI Call Center to document vital status, medication adherence, concomitant HF medications, KCCQ and PHQ-2 questionnaires, and to capture hospitalization information. The Call Center will obtain discharge summaries from hospitalizations as appropriate.

9.3 12 months

Patients will be contacted by the DCRI Call Center to document vital status, medication adherence, concomitant HF medications, KCCQ and PHQ-2 questionnaires, and to capture hospitalization information. The Call Center will obtain discharge summaries from hospitalizations as appropriate. As an additional mechanism to safeguard against hospitalization under-reporting, the DCRI Call Center will initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient.

9.4 National Death Index

NDI searches will be performed during follow-up and prior to study close-out. The DCRI will coordinate the NDI searches.

10. MEDICATION ADHERENCE

To adequately test the study's primary hypothesis, patient adherence with the randomized diuretic treatment is paramount. The approach to maintain study drug adherence in TRANSFORM-HF will involve study identification cards for patients, patient education materials, and validated adherence-assessment metrics. Since patients may receive care (including medication changes) from providers outside the enrolling institution, patients will be provided with a medication card for their wallet that identifies them as a trial patient randomized to a specific loop diuretic therapy. Patients will be asked to present this card to all care providers, including those who attempt to adjust their diuretic regimen. Patients will also receive educational information at baseline related to medication adherence. Recognizing that patients could mistake changes in medication dosage or appearance (e.g., pill color, size) with a change to the alternate study therapy, DCRI Call Center personnel will ask patients to specify the exact name of the therapy they are receiving and will encourage patient confirmation with pill bottles whenever a question.

The study will also utilize the Voils Medication Adherence Scale.[17] This simple questionnaire will be administered by the DCRI Call Center during phone contacts at 30 days, 6 months, and 12 months post-randomization, which will capture patient-reported adherence to the randomized study therapy.

11. COST CONSIDERATIONS

Furosemide is currently the most commonly used loop diuretic; however, torsemide represents a relatively inexpensive alternative therapy. Both furosemide and torsemide are generic medications. At the present time, costs vary modestly by region and pharmacy for these medications (e.g., medication tiers), but on average, the patient cost for a 30-day supply of torsemide is less than $3 more than furosemide and there is no difference for many patients. Clinicians currently prescribe these medications interchangeably in the context of routine HF management, and both are recommended by current ACC/AHA HF guidelines. Furthermore, this cost differential is less than that seen with other guideline-recommended and routinely used HF medications.

12. OUTCOME DETERMINATIONS

12.1 Primary Endpoint

The primary endpoint of this study will be all-cause mortality. Patients will receive a call from the DCRI Call Center at 30 days, 6 months, and 12 months post-randomization to document vital status. Subsets of patients enrolled early in the study will receive additional phone calls from the DCRI Call Center at 6 month intervals to document vital status. The NDI will be queried during follow-up and prior to study close-out. All patients will be followed for a minimum of 12 months.

12.2 Secondary Endpoints

- All-cause mortality or all-cause hospitalization over 12 months
    - Hospitalization data will be acquired via the DCRI Call Center with acquisition of hospital discharge summaries. The DCRI Call Center will initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient.
- Total hospitalizations over 12 months
    - Hospitalization data will be acquired via the DCRI Call Center with acquisition of hospital discharge summaries. The DCRI Call Center will initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient.
- All-cause mortality or all-cause hospitalization over 30 days
    - Hospitalization data will be acquired via the DCRI Call Center with acquisition of hospital discharge summaries.
- Health-related quality of life over 12 months
    - KCCQ
- Symptoms of depression over 12 months
    - PHQ-2

13. PARTICIPANT SAFETY AND ADVERSE EVENTS

13.1 Institutional Review Boards

All sites will submit the study protocol, informed consent form, and other relevant study documents to their Institutional Review Board (IRB) or the central IRB for approval.

13.2 Informed Consent

A signed ICF is a requirement for patient inclusion in the study. All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If patients consent to participation in this study, they will review and sign the ICF. The ICF will be administered by study staff at the enrolling site during the index hospitalization. At the time of ICF discussion, patients will receive study informational materials and the contact information for the site study staff at the enrolling site.

13.3 Voluntary Withdrawal from the Study

Patients may withdraw at any time during the study without giving reasons and will not suffer disadvantage as a result. In cases of study withdrawal, patient care will continue per the discretion of healthcare providers.

At the time of ICF discussion and signature, patients will have received the contact information for the study staff at the enrolling site and the DCRI Call Center. For patients electing to withdraw from the study prior to index hospitalization discharge, patients will alert site study staff at their enrolling site so that the site may notify the DCRI Call Center. For patients electing to withdraw from the study after index hospitalization discharge, patients may contact either study staff from the enrolling site or the DCRI Call Center.

Since both study therapies are standard of care and because the only study-specific patient follow-up requirement is participation in pre-specified DCRI Call Center calls, the impact of study withdrawal on patient activities will be cessation of study related phone calls. In cases of study withdrawal, individual patient care will continue per the discretion of local care providers.

13.4 Adherence Assessments and Discontinuation of Study Medications

The ongoing prescription of and adherence to randomized therapy during follow-up will be documented by the DCRI Call Center, as specified above. Since both study therapies are standard of care and because the only study-specific patient follow-up requirement is participation in pre-specified DCRI Call Center calls, the impact of study withdrawal on patient activities will be cessation of study related phone calls.

13.5 Summary of the Risks and Benefits

This study will evaluate oral torsemide versus oral furosemide in patients with heart failure. Both torsemide and furosemide are currently used in routine clinical practice and are recommended by the current ACC/AHA heart failure guidelines. We therefore do not anticipate that participation in this study will be associated with increased risks beyond that of standard heart failure therapy. Potential benefits to study participants include the possibility of improvements in clinical congestion and associated symptoms and outcomes. Some patients may feel a sense of well-being due to their contribution to help their fellow heart failure patient by participating in this scientific research. In addition, there are several potential societal benefits to this study since determining the optimal loop diuretic care could impact the care of millions of patients with heart failure.

13.6 Adverse Events

Given that this is a study of 2 standard of care therapies, there will be no additional adverse event reporting beyond that of standard care.

14. STATISTICAL CONSIDERATIONS

14.1 Overview

Means, standard deviations, medians, 25^{th} and 75^{th} percentiles will be presented for continuous variables; the number and frequency of patients in each category will be presented for nominal variables. For the primary analysis, a two-sided p-value <0.05 will be considered statistically significant. For all other analyses, including secondary analyses and subgroup analyses, a p-value <0.005 will be considered statistically significant.[18] Analyses will be performed using SAS version 9.4 or higher software (SAS Institute, Inc., Cary, NC).

14.2 Analysis of Primary Endpoint

Detailed description of the plan for statistical analysis of each endpoint will be detailed in a Statistical Analysis Plan.

The primary analysis will be based on intention-to-treat. The data used for the primary analysis will be based on the DCRI Call Center data supplemented with the NDI search results.

The statistical comparison of the two randomized arms with respect to the primary endpoint will be a time-to-event analysis, and therefore will be based on the time from randomization to mortality. The Cox proportional hazards regression model will be the primary tool to analyze and assess outcome differences between the two treatment arms. A hazard ratio and 95% confidence interval for summarizing the difference in outcomes between the two treatment arms will be computed using the Cox proportional hazards regression model. Covariates in the primary model will include the randomized treatment,

age, sex, ejection fraction category, and loop diuretic treatment prior to index hospital admission.

14.3 Sample Size Justification

The planned study population for TRANSFORM-HF is broader than most prior HF clinical trials. As such, it is difficult to anticipate the expected event rates at 12 months. Additionally the planned statistical power is dependent on adherence to the assigned treatments. **Table 2** shows the required number of primary endpoint events (i.e. all-cause mortality) to obtain power ranging from 80% to 90% with hazard ratios ranging from 0.75 to 0.85. Ideally, the TRANSFORM-HF protocol will have 85+% power to detect a hazard ratio 0.80 for the primary endpoint. Therefore, TRANSFORM-HF will continue until at least 721 primary endpoint events have been observed. These power estimates are based on the following assumptions: 1:1 randomization, two-sided Type I error of 0.05, and a test statistic based on the log-rank test.

Table 2. Required number of primary endpoint events (two-sided Type I error of 0.05)

Power	**HR= 0.75**	**HR= 0.76**	**HR= 0.77**	**HR= 0.78**	**HR= 0.79**	**HR= 0.80**	**HR= 0.81**	**HR= 0.82**	**HR= 0.83**	**HR= 0.84**	**HR= 0.85**
80%	379	417	460	509	565	631	707	797	909	1033	1189
85%	434	477	526	582	646	**721**	809	912	1034	1181	1360
90%	508	558	615	681	756	844	947	1067	1211	1383	1591

HR – hazard ratio

In **Table 3**, the required number of events for the secondary time-to-event endpoints is provided to have power of 80% to 90%. The sample size assumptions are based on the log-rank test with a more conservative Type I error rate of 0.005.

Table 3. Required number of events for secondary endpoints (2-sided α=0.005)

Power	**HR= 0.75**	**HR= 0.76**	**HR= 0.77**	**HR= 0.78**	**HR= 0.79**	**HR= 0.80**	**HR= 0.81**	**HR= 0.82**	**HR= 0.83**	**HR= 0.84**	**HR= 0.85**
80%	643	707	780	863	958	1069	1199	1352	1534	1752	2016
85%	714	785	865	957	1063	1187	1331	1500	1702	1944	2237
90%	808	888	979	1083	1203	1343	1506	1698	1926	2200	2532

HR – hazard ratio

Table 4 shows the sample sizes required to provide 80-90% power for key continuous endpoints, such as QOL. Differences are provided in terms of standardized differences. These calculations are based on the two-sample t-test and assume 1:1 randomization with a two-sided Type I error rate of 0.005. The planned sample size of approximately 6000 patients should provide >80% power to detect differences larger than 0.10 standard deviations. For the KCCQ overall summary and clinical summary scores that value equated to a treatment group difference of between 1.5 and 2.0 points. Generally, a

clinically meaningful difference, on a patient-level, is considered to be a 5 point difference.[19]

Table 4. Required Sample Sizes for Continuous Endpoints

Power	Std diff = 0.10	Std diff = 0.15	Std diff = 0.20	Std diff = 0.25	Std diff = 0.30
80%	5400	2400	1340	860	600
85%	6000	2700	1500	1000	700
90%	6700	3000	1700	1100	780

*values shown have been rounded up to the 10's digit. The total sample sizes shown do not allow for any missing data.

All enrolled patients will have DCRI Call Center interviews at 30 days, 6 months, and 12 months. We anticipate that the first cohort of 500 patients will have additional follow-up telephone calls at months 18, 24, and 30. Similarly, the second cohort of 500 patients will have two additional phone calls at months 18 and 24, and a third cohort of 500 patients will have a follow-up interview at 18 months. These data will be used to provide estimates on long-term treatment adherence data and to determine whether the study will provide the anticipated number of primary endpoint events. **Table 5** shows the expected half-width (i.e. distance from the point estimate to the confidence limit) for the 95% confidence interval for the pooled event rate.

Table 5. Expected Half-Width of 95% Confidence Intervals for Pooled Event Rate**s**

Expected proportion	N=500	N=1000	N=1500
0.10	0.026*	0.019	0.015
0.12	0.028	0.020	0.016
0.14	0.030	0.022	0.018
0.16	0.032	0.023	0.019
0.18	0.034	0.024	0.019
0.20	0.035	0.025	0.020

*Distance from the observed proportion to the 95% confidence interval limit based on a large-sample approximation.

14.4 Analysis of Secondary Endpoints

The analyses for the time-to-event secondary endpoints will be similar to those outlined for the primary endpoint using the time from randomization through the first occurrence of any component of a specific secondary endpoint (or censoring) as the response variable, and assessing group differences using the Cox proportional hazards model. Analyses of the longitudinal quality-of-life (QOL) data will be conducted using linear mixed models. A secondary analysis of the QOL data will apply the worst-rank approach of Lachin et al. to account for missing data related to deaths, and the test statistic will be based on a two-sample nonparametric test.[20] The total hospitalization endpoint will be

analyzed using the method of Bang and Tsiatis with partitions set at the planned interview dates.[21] The analyses of the remaining secondary endpoints will be detailed in the Statistical Analysis Plan.

14.5 Analyses of Patient Subgroups

Subgroup analyses will be conducted with the purpose of assessing consistency of treatment effects over subgroups. Subgroup analyses will be performed on the primary and secondary endpoints. Further details will be included in the Statistical Analysis Plan. The following pre-specified subgroup analyses are planned, with subgroups defined using data collected at study baseline (i.e., randomization):

- Age groups (<65, ≥65; <75, ≥75 years)
- Sex
- Race (Caucasian, Black, Asian, Other)
- Ejection Fraction (≤ 40%, 41-49%, ≥50%)
- Loop diuretic treatment prior to index hospitalization (furosemide, torsemide, bumetanide/ethacrynic acid, none)
- New York Heart Association class at randomization (I/II vs III/IV)
- Systolic blood pressure (</≥ median)
- eGFR categories (<30, ≥30 to <60, ≥60 mL/min/1.73m^2)
- Diabetes mellitus (yes/no, based on medical history)
- Mineralocorticoid receptor antagonist use at randomization (yes/no)
- Enrolling center an academic/teaching hospital (yes/no)
- Duration of heart failure prior to index hospitalization (worsening chronic heart failure, newly diagnosed heart failure during index hospitalization)

14.6 Statistical Monitoring Plan

Interim data analysis for efficacy will be conducted due to the large sample size. The DSMB will meet approximately every 6 months to review study progress. The data presented at these meetings will include information regarding clinical outcomes, enrollment, patient characteristics, and trial processes. All-cause mortality is primary endpoint in the TRANSFORM-HF study. The study investigators are suggesting that the DSMB use a Haybittle-Peto-type boundary using p=0.005 as a guideline for stopping the study due to differences in all-cause mortality. Given the importance of this endpoint, the investigators recommend that the guideline is applied in a two-sided symmetric fashion.

Additionally, the DCRI Coordinating Center will monitor treatment adherence by enrolling site using one-sided 90% confidence intervals based on the exact binomial distribution. Enrolling sites with poor adherence (e.g. <90%) will review their study practices with the DCRI study monitors and the TRANSFORM-HF coordinating center. Crossovers will be tracked by the DCRI Call Center at 30 days, 6 months, and 12 months post-randomization. A set of sensitivity analyses will be conducted on the subset of patients

with documented adherence to the assigned therapy at 30-days. Details of the planned DSMB reviews will be described in the DSMB Charter.

15. STUDY ADMINISTRATION

15.1 Executive and Steering Committees

An Executive Committee comprised of NHLBI representatives, the CCC and DCC investigators and the Study Chair will be the primary decision making body of the study and is responsible for its successful completion. A Steering Committee will meet regularly (no less than once, yearly) and will include site investigators and other investigators with specific expertise in heart failure and clinical trials to advise the Executive Committee on the operational conduct of the trial and with primary responsibility to approve and amend the protocol.

15.2 DSMB

A DSMB will be appointed by the NHLBI for the TRANSFORM-HF trial, which will include individuals with pertinent expertise in heart failure, clinical trials, research ethics, and biostatistics. The DSMB will make recommendations to the Steering Committee and NHLBI regarding the continuing safety of current participants and those yet to be recruited.

16. ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1) ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6) 1996.

2) US 21 Code of Federal Regulations Title 45 Part 46 Protection of Human Subjects dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Participating investigators agree to adhere to the instructions and procedures described in the protocol. This protocol was designed to conform to principles of Good Clinical Practice and investigators agree to adhere to these principles.

17. REFERENCES

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18. APPENDICES

18.1 Appendix A. Schedule of Assessments*

	Screening/ Enrollment	Randomization/ Baseline	30 days	6 months	12 months	18 months^	24 months^	30 months^
Informed Consent (Site study staff)	**X**							
Inclusion/exclusion criteria confirmed	**X**	**X**						
Age, sex, race, ethnicity, most recent ejection fraction by any modality, past medical history, routine vital signs/ laboratories, and randomized study therapy		**X**						
Anticipated initial dosing regimen for oral torsemide and oral furosemide		**X (completed prior to randomization on the same day)**						

Concomitant heart failure medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adherence wallet card and education materials		**X**						
Vital status			**X**	**X**	**X**	**X**	**X**	**X**
Interval rehospitalizations			**X**	**X**	**X**			
KCCQ and PHQ-2 Assessment		**X (completed prior to randomization on the same day)**	**X**	**X**	**X**			
Medication Adherence			**X**	**X**	**X**	**X**	**X**	**X**

* NDI queries will be conducted by the DCRI Call Center during follow-up and prior to study close-out.

^The first cohort of 500 patients enrolled will have additional follow-up telephone calls at 18, 24, and 30 months. The second cohort of 500 patients will have additional follow-up telephone calls at 18 and 24 months. The third cohort of 500 patients will have an additional follow-up telephone call at 18 months.