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A response-adaptive design of initial therapy for emergency department patients with heart failure

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ABSTRACT

Finding safe and effective treatments for acute heart failure syndrome (AHFS) is a high priority. More than 80% of patients with AHFS who present to emergency departments are treated identically with intravenous diuretics, despite recognition of the syndrome's heterogeneity. We hypothesize that matching patient profiles with "personalized" AHFS treatments will improve outcomes. Matching multiple heterogeneous clinical profiles with a number of potentially effective treatments requires an adaptive trial design that can adjust for these complexities. We propose a Bayesian response-adaptive randomization trial design for AHFS patients. Baseline information collected for each patient with AHFS prior to randomization includes blood pressure, renal function, and dyspnea severity. The primary outcome is discharge readiness within 23h of presentation and no unplanned emergency visits or admissions for acute heart failure within 7days of discharge. We use a Bayesian logistic regression model to characterize the association between primary outcome and patient profile. We adaptively randomize patients to one of five treatments, basing the randomization probability on the cumulative data from the ongoing trial and fitting results from the regression model. Simulations show high probability of selecting the best treatment corresponding to the patient's profile while allocating more patients to the efficacious treatments within the trial.

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1. Introduction

Randomization ensures that the observed treatment effect is attributable to the treatment itself rather than to confounding elements, and is the hallmark of clinical trials assessing treatment effects. Recently, the response-adaptive (RA) randomization scheme has become popular in clinical research because of its flexibility and efficiency [1–7]. Based on the accruing history of patient responses to treatment, the RA randomization scheme adjusts the future allocation probabilities, thereby allowing more patients to be assigned to the superior treatment as the trial progresses. As a result, RA randomization can offer significant ethical and cost advantages over equal randomization. The Bayesian framework is particularly suitable for RA designs because it can incorporate historical information as a prior and allows for continually updating the model fitting based on cumulative data observed over time [8,9].

When we have more than one experimental treatment to test against the traditional therapy, testing each treatment in separate trials is inefficient and wasteful of limited resources. To address this issue, many phase II designs for multiple treatments or combinations have been proposed for oncology trials [7,10-12]. This paper is motivated by the challenge of designing a randomized trial with multiple treatment arms for patients with acute heart failure syndrome (AHFS). Heart failure affects nearly 6 million Americans and results in nearly one million annual hospital discharges [13]. It is estimated that by 2030, a 25% increase in the prevalence of AHFS will result in an additional 3 million people afflicted [13,14]. The in-hospital mortality reported in major registries ranges from 4–12%, and may increase to 20–25% in high-risk subgroups [15–20]. Finding safe and effective treatments for patients with AHFS is a critical unmet need identified as a high priority by investigators of heart failure [21,22]. Despite increasing recognition of disease heterogeneity and comorbidities in patients with AHFS, more than 80% are treated homogeneously – with intravenous diuretics [15,23]. An individualized approach that tailors therapy to improve symptoms, minimize adverse events, and promote earlier discharge has not been studied, largely due to significant limitations in current clinical trial

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design [24–27]. Such approaches study one therapy in a highly select group of patients, and have limited ability to test multiple treatment approaches within AHFS phenotypes, especially early in a patient's course when symptoms are maximal. It is critical to explore novel approaches to improve clinical trial design.

Bayesian adaptive trial design is ideally suited for complex diseases and allows for the study of multiple treatment options in diverse patient phenotypes. After a burn-in period of equal treatment assignment, the randomization scheme is continuously adapted such that treatment allocation is directed toward a responding phenotype. This approach has successfully answered complex hypotheses in cancer trials, but represents an innovative and promising methodology for other complex diseases such as AHFS [2,28]. Our design is further based on a significant body of research suggesting an association between initial AHFS therapy and near-term events [27,29,30]. This strongly suggests that AHFS patients with hypertension benefit from predominant vasodilator therapy, while those who are normotensive may improve with aggressive diuresis [31,32]. We hypothesize that "personalizing" AHFS treatments by matching patient profiles with targeted treatment options will more rapidly alleviate symptoms, improve outcomes and serve as a well-defined model for testing new therapies. We consider the following questions: For any treatment that does not work in all patients, is there a subset of patients in which it does work? Can we treat patients better during the trial based on each patient's profile? The Bayesian RA randomization design is ideally suited for facing these voluminous challenges. Bayesian RA designs use information existing at the initiation of the trial and combine it with data that accumulate during the trial to identify which treatments are most beneficial for which patients. Randomization is varied so that patients who are unlikely to benefit from a particular treatment are less likely to receive that treatment. Another benefit of this trial design is that ineffective treatments can be dropped and alternatives added as the trial is ongoing.

The remainder of this article is organized as follows. In Section 2, we specify our models and describe the proposed trial design. In Section 3, we evaluate the operating characteristics of the proposed design through simulation studies. We conclude with a brief discussion and comments in Section 4.

2. Methods

We implement a Bayesian RA randomization scheme in a clinical trial design to screen for effective treatments and identify which patient groups will and will not benefit from the treatments. To illustrate this design, we use a trial of initial therapy in patients who present to emergency departments with heart failure. The first line of emergency treatment for these patients consists of a diuretic (furosemide) and a vasodilator (nitroglycerin). The five targeted treatments (Fig. 1) are low-dose diuretics plus intravenous (IV) vasodilator boluses (treatment 1), low-dose diuretics plus IV vasodilator infusion (treatment 2), daily-dose diuretics plus topical vasodilator (treatment 3), high-dose diuretics plus topical vasodilator (treatment 4), and daily-dose diuretics plus IV vasodilator infusion (treatment 5). A total of 1000 patients will be enrolled in the study. All enrolled and eligible patients are required to undergo baseline phenotype profile assessment before randomization. Specifically, three phenotypes are assessed before randomization for all enrolled patients: blood pressure (¿160 mm Hg vs ¡160 mm Hg), renal function (glomerular filtration rate [GFR] ¡ 60 ml/min/1.73 m^2 vs ¿60 ml/min/1.73 m^2) and dyspnea severity (initial respiration rate [RR] ¿ 24 breaths/min vs ¡24 breaths/min). Thus, this trial will sequentially enroll patients and assign each patient to receive one of five competing treatments based on his/her phenotype profile. Given

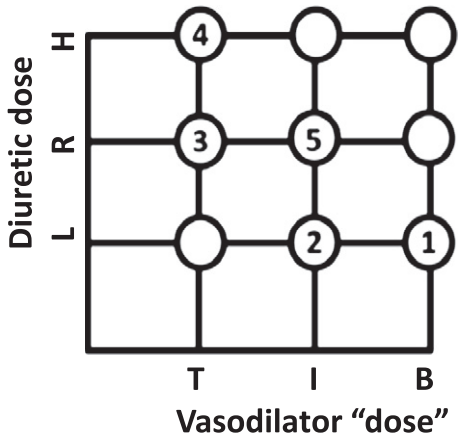

Fig. 1. Schematic of treatment combinations of nitroglycerin and furosemide dosing and route (B=intravenous vasodilator bolus; I=intravenous vasodilator infusion; T=topical vasodilator; R=regular/daily-dose diuretic; L=low-dose diuretic; H=high-dose diuretic). The open circles are potential combinations not considered in this trial.

five treatments and eight subgroups defined by patient phenotypes, there are forty subgroups in this trial.

2.1. Probability model

The limited sample size and low prevalence of some phenotype subgroups make it difficult to draw inferences for the low prevalence subgroups when considered separately. We address this challenge by using covariate analysis to borrow information across subgroups to enhance the precision of the inference. We use a logistic regression model to evaluate the main effects of the five treatments and eight patient phenotypes (covariates) and their interactions. Our formulation of the model, which includes the treatment effects (β^T), covariate effects (β^Z), and treatment-covariate interactions (β^I), is shown hereafter. For patient i,

$$logit\,(\Pr(Y_i = 1)) = \beta_0 + \sum_{j=1}^{3}\beta_j^Z Z_{ij} + \sum_{k=1}^{5}\beta_k^T T_{ik} + \sum_{j=1}^{3}\sum_{k=1}^{5}\beta_{jk}^I Z_{ij} T_{ik}, \quad (1)$$

where Y_i is the response indicator that takes a value of 1 if the ith patient is discharged within 23 h of presentation and has no unplanned emergency visits or admissions for acute heart failure within 7 days of discharge, Z_{ij} is the phenotype covariate j, and T_{ik} is the indicator for the kth treatment. To complete the Bayesian model formulation, we assume that the parameters follow a multivariate normal distribution with independent components. Historical data or elicited information may be used to construct informative priors on non-treatment parameters, such as the effects of phenotype covariates in the present setting. However, to ensure that the trial design is both ethical and widely acceptable, we take the prior of each component to be $Normal(\hat{\beta}_{MLE}, \sigma^2)$, where $\hat{\beta}_{MLE}$ is the maximum likelihood estimators of the regression coefficients from the run-in phase in this study (the first 200 patients) and $\sigma^{-2} \sim Gamma(0.001, 0.001)$. This Bayesian structure via logistic regression in the RA randomization design allows for borrowing strength of information across patients who are receiving the same treatment but have different phenotypes. Hence, the information obtained in one subset of patients provides some information that is useful for patients with similar phenotype profiles.

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