SUBGROUP IDENTIFICATION AND VARIABLE SELECTION FOR TREATMENT DECISION MAKING

BY BAQUN ZHANG[1,a] AND MIN ZHANG[2,b]

[1]*School of Statistics and Management, Shanghai University of Finance and Economics,* [a]*zhang.baqun@mail.shufe.edu.cn*

[2]*Department of Biostatistics, University of Michigan,* [b]*mzhangst@umich.edu*

When treatment effect heterogeneity exists, identifying the subgroup of patients who would benefit from an active treatment relative to a control is an important question. This article focuses on subgroup identification in the presence of a large dimensional set of covariates, with the number of covariates possibly greater than the sample size. We approach this problem from the perspective of optimal treatment decision rules and propose methods that can simultaneously estimate the treatment decision rule and select prescriptive variables important for treatment decision making and subgroup identification. The proposed methods are built within a robust classification framework based on doubly robust augmented inverse probability weighted estimators (AIPWE), hence sharing the robustness property. An L_1 (lasso-type) penalty is used within the classification framework to target selection of prescriptive variables. We further propose a backward elimination process for fine-tuning selection. The methods can be conveniently implemented by taking advantage of standard software for logistic regression and lasso. The methods are evaluated by extensive simulation studies which demonstrated the superior and robust performance of the proposed methods relative to existing ones. In addition, the estimated decision rules from the proposed methods are considerably simpler than other methods. We applied various methods to identify the subgroup of patients suitable for each of the two commonly used anticoagulants in terms of bleeding risk for patients with acute myocardial infarction undergoing percutaneous coronary intervention.

1. Introduction. It has been increasingly recognized that patients may respond differently to treatments. A treatment that does not seem to be better on average may be quite effective for a subgroup of patients. In the presence of treatment effect heterogeneity, it is important to identify the subgroup of patients who could potentially benefit from a treatment, as opposed to finding the treatment option with a better average treatment effect. This study is motivated by the desire to understand the comparative effectiveness of bivalirudine vs. heparin in terms of bleeding risk for patients with acute myocardial infarction undergoing percutaneous coronary intervention (PCI). Anticoagulants, heparin or bivalirudine are routinely used for reducing the risk of thrombotic complications for PCI patients. Heparin is traditionally regarded as the standard strategy. Bivalirudine is newer and has shown superior safety in terms of bleeding risk by randomized clinical trials. However, with more evidences accumulated, whether bivalirudine leads to lower bleeding risk remains controversial, and the debate is not yet settled, despite many studies for more than two decades (e.g., Andreou, Maniotis and Koutouzis (2017), Cavender and Sabatine (2014), Elgendy and Capodanno (2017)). One possible explanation for the diverging results might be that studies differ in patient populations and the effect of bivalirudine varies, depending on patient characteristics and concomitant/prior medicine. The right question to ask might be that for what kinds of patients bivalirudine is better and should be preferred relative to heparin.

Traditionally, finding subgroups of patients who respond to treatments differently can be carried out by subgroup analysis where one evaluates treatment effects in predefined subgroups of patients separately. Alternatively, subgroup identification can be carried out by assessing interaction terms of the treatment with covariates. The last decade has seen many exciting advances in rigorous methodological developments for studying treatment effect modification and subgroup identification in a principled fashion. Foster, Taylor and Ruberg (2011) proposed a "Virtual Twins" method for subgroup identification from randomized clinical trial data. Tian et al. (2014) studied a simple and robust modified covariate approach for detecting treatment interactions with other covariates. Much of the new development on subgroup identification is studied from the perspective of causal inference and optimal treatment regimes, aiming to find the optimal treatment decision rule to classify patients to subgroups corresponding to the optimal treatment option. The literature on optimal treatment regimes has been enormous (e.g., Brinkley, Tsiatis and Anstrom (2010), Moodie, Richardson and Stephens (2007), Murphy (2003), Qian and Murphy (2011), Robins, Orellana and Rotnitzky (2008), Zhang et al. (2012a, 2012b), Barrett, Henderson and Rosthøj (2014), Chen et al. (2017), Zhao et al. (2012), Wang et al. (2018)). Instead of trying to be comprehensive, we refer readers to Chakraborty and Moodie (2013), Kosorok and Moodie (2016) and Tsiatis et al. (2019) for detailed reviews.

Relatively less attention has been given to variable selection among a large set of covariates, targeting subgroup identification and estimating the optimal treatment regimes. Variables that are important for treatment decision making and subgroup identification are those that interact qualitatively with treatment, referred to as prescriptive variables. Variable selection for prescriptive variables are important because, in practice, although many covariates are predictive of outcome, it is more plausible that only a subset of them interact qualitatively with treatment and are important for treatment decision making. In addition, in terms of interpretability and practical applicability it is obvious that one would favor simple treatment decision rules involving a smaller set of covariates. The recent work for variable selection targeting prescriptive variables includes the S-score ranking method of Gunter, Zhu and Murphy (2011) which is based on a measure that quantifies qualitative interaction. Biernot and Moodie (2010) studied the S-score method through simulations and found that it may identify too many variables, as this method considers each variable separately. The method of S-score was further studied by Gunter, Chernick and Sun (2011) and developed by Fan, Lu and Song (2016) into a sequential advantage selection (SAS) method, which leads to improved performance by accounting for variables selected in previous steps through sequential selection. Relative to the S-score method, it tends not to select variables that are only marginally important but not jointly important. Within a doubly robust classification framework for estimating the optimal treatment regime (Zhang et al. (2012b)), Zhang and Zhang (2018a) proposed a forward minimal misclassification error rate (ForMMER) method for selecting prescriptive variables simultaneously with estimation of the optimal treatment regime. Through comprehensive simulation studies, Zhang and Zhang (2018a) demonstrated that this method has considerable improvement over SAS in that it leads to more accurate treatment decisions with much smaller number of selected variables. Song et al. (2015) proposed a prescriptive variable selection method in the setting of randomized clinical trials within the framework of outcome weighted learning (Zhao et al. (2012)). A key difference between this method and other methods discussed above is that this method does not involve model building for the outcome. Other relevant work on this includes Qian and Murphy (2011), Lu, Zhang and Zeng (2013) and Shi, Song and Lu (2019). The first two methods, as commented by Fan, Lu and Song (2016), do not directly target selecting prescriptive variables, and the last one focuses on testing important qualitative interaction effects. More recently, there is a growing number of works on using machine learning methods to study heterogeneous treatment

effects and optimal decision rules in the presence of high-dimensional data (Athey and Imbens (2015), Bargagli Stoffi, Tortú and Forastiere (2021), Wager and Athey (2018), Athey and Wager (2021)). In particular, the method of Wager and Athey (2018) is based on doubly robust estimators, similar in spirit to Zhang et al. (2012b) and Zhang and Zhang (2018a). However, Wager and Athey (2018) focuses on theoretical properties and does not consider variable selection.

In this article we study a new and much improved method for simultaneous prescriptive variable selection and subgroup identification in the presence of a large set of covariates. The method is built upon the doubly robust classification framework of Zhang et al. (2012b). It takes advantage of the convenient weighted logistic regression for optimizing decision rules to improve computation. It features a lasso selection for handling high dimensionality of covariates, targeting selecting only prescriptive variables while incorporating information from all predictive variables. It is further coupled with a backward elimination process for fine-tuning the selection to achieve simplicity and easy interpretation of the identified subgroups.

2. Methods.

2.1. *Notation and assumptions.* Consider an observational or randomized study with n subjects. We let Y_i denote a continuous outcome for subject i, and, without loss of generality, we assume a larger value indicates a better outcome. For subject i, we let A_i (0 or 1) be the treatment indicator and X_i denote a vector of baseline variables measured before treatment. To facilitate causal treatment effect comparison and estimation, we use the potential outcomes framework. Specifically, we let $Y_i^*(0)$ and $Y_i^*(1)$ be the potential (or counterfactual) outcomes for subject i if he/she, possibly contrary to fact, received treatment 0 and 1, respectively. We assume that the measured covariates are sufficient to account for confounding; that is, the so-called no unmeasured confounders assumption holds, denoted by $\{Y_i^*(0), Y_i^*(1)\} \perp\!\!\!\perp A_i \mid X_i$. Note this assumption holds automatically for a randomized study by design since treatment is randomized. We also make the standard stable unit treatment value assumption (SUTVA), which states that there is no interference among subjects and $Y_i = Y_i^*(1)A_i + Y_i^*(0)(1 - A_i)$, meaning that the observed outcome for subject i is equal to the potential outcome corresponding to the actually received treatment A_i.

In contrast to estimating the average treatment effect of $A = 1$ vs. $A = 0$ for the whole study population, this article focuses on the situation where there might be heterogeneous treatment effect. That is, while treatment 1 (or 0) is possibly beneficial to some subjects with certain characteristics, it is not effective or even harmful for other subjects. Based on the observed data on n subjects, we aim to identify the defining characteristics of the subgroup that can potentially benefit from treatment 1 relative to 0 and, therefore, should be treated with treatment 1. This can be formalized using the framework of treatment regimes, which are treatment decision rules $g(x)$, taking value 0 or 1 each corresponding to a treatment decision based on a patient's characteristics x. The goal is to estimate the optimal treatment regime $g^{\text{opt}}(x)$ that will lead to the optimal (equivalently maximum) average potential outcomes if followed by the entire intended population among all treatment decision rules $g(x) \in \mathcal{G}$. That is, denoting the potential outcome of a subject if he/she follows the regime $g(x)$ by $Y^*(g)$, then $E\{Y^*(g^{\text{opt}})\} \geq E\{Y^*(g)\}$ for any $g(x) \in \mathcal{G}$. The expectation, $E\{Y^*(g)\}$, is referred as the value of regime g. This statement is equivalent to $E[Y^*(1)g^{\text{opt}}(X) + Y^*(0)\{1 - g^{\text{opt}}(X)\}] \geq E[Y^*(1)g(X) + Y^*(0)\{1 - g(X)\}]$ because $Y^*(g) = Y^*(1)g(X) + Y^*(0)\{1 - g(X)\}$.

To see the connection of subgroup identification with optimal treatment regime, we note

$$E\{Y^*(g)\} = E\{E[Y^*(1)g(X) + Y^*(0)\{1 - g(X)\} \mid X]\}$$

(1)
$$= E[\{\mu(1, X) - \mu(0, X)\}g(X) + \mu(0, X)]$$

$$\equiv E\{C(X)g(X) + \mu(0, X)\},$$

where $\mu(a, X) = E(Y \mid A = a, X) = E\{Y^*(a) \mid X\}$ for $a = 0$ and 1 and $C(X) = \mu(1, X) - \mu(0, X)$ is the contrast in expected outcomes between treatments. It is straightforward to see from (1) that $E\{Y^*(g)\}$ is maximized when $g(X) = I\{C(X) > 0\}$, that is, $g^{\text{opt}}(X) = I\{C(X) > 0\}$. Then, the subgroup of patients who could potentially benefit from treatment 1, that is, subjects with $C(X) > 0$, are subjects with characteristics X such that $g^{\text{opt}}(X) = 1$. To summarize, $g^{\text{opt}}(X)$ satisfies

$$g^{\text{opt}}(X) = \arg\max_{g \in \mathcal{G}} E\{Y^*(g)\} = \arg\max_{g \in \mathcal{G}} E\{C(X)g(X)\} = I\{C(X) > 0\}.$$

2.2. *Background and motivation.* It is easy to see from the discussion above that estimation of the optimal treatment regime is closely related to estimation of the contrast function $C(X)$ between treatments. In the usual parametric outcome regression method, one posits parametric regression model for $E(Y \mid A, X) = \mu(A, X; \beta)$ and estimate the contrast function by $\mu(1, X; \widehat{\beta}) - \mu(0, X; \widehat{\beta})$, where $\widehat{\beta}$ is an estimator for the unknown parameter β. The optimal treatment regime is then estimated by $I\{\mu(1, x; \widehat{\beta}) - \mu(0, x; \widehat{\beta}) > 0\}$. However, the performance of the resulting estimator for the optimal treatment regime heavily depends on correctness of the specified outcome regression model. Alternatively, one may posit a semiparametric model for $E(Y \mid A, X) = h(X) + A \cdot C(X; \phi)$, where $h(X)$ is an unspecified function and $C(X; \phi)$ is a parametric model for the contrast function, and estimate ϕ using G-estimation (Robins, 2004). Then, one can estimate g^{opt} by $I\{C(x; \widehat{\phi}) > 0\}$. It is expected that this estimator is more robust than the parametric method; however, the performance still largely depends on how close the specified parametric form of the contrast function $C(X; \phi)$ is to the truth.

Our method builds upon the robust methods of Zhang et al. (2012a, 2012b). In the method of Zhang et al. (2012a), one does not directly model the contrast function $C(X)$ or the conditional mean function $\mu(a, X)$. Instead, it directly estimates $E\{Y^*(g)\}$ by viewing this as a missing data problem and proposes to estimate $E\{Y^*(g)\}$ by the doubly robust augmented inverse probability weighted estimator (AIPWE). For a regime that can be indexed by parameter η, that is, $g = g(X; \eta) \equiv g_\eta$, the AIPWE of $E\{Y^*(g)\}$ can be written as

$$\text{AIPWE}(\eta) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{R_{\eta,i} Y_i}{\pi_R(X_i; \eta, \widehat{\gamma})} - \frac{R_{\eta,i} - \pi_R(X_i; \eta, \widehat{\gamma})}{\pi_R(X_i; \eta, \widehat{\gamma})} m(X_i; \eta, \widehat{\beta}) \right\},$$

where $R_{\eta,i} = A_i g(X_i; \eta) + (1 - A_i)\{1 - g(X_i; \eta)\}$ and is an indicator of whether $Y_i^*(g)$ is observed or not; $\pi_R(X; \eta, \gamma) = \pi(X; \gamma)g(X; \eta) + \{1 - \pi(X; \gamma)\}\{1 - g(X; \eta)\}$ with $\pi(X; \gamma)$ being a posited model for the propensity score $P(A = 1 \mid X) \equiv \pi(X)$; $m(X; \eta, \beta) = \mu(1, X; \beta)g(X; \eta) + \mu(0, X; \beta)\{1 - g(X; \eta)\}$ is a model for $E\{Y^*(g_\eta) \mid X\} = \mu(1, X)g(X; \eta) + \mu(0, X)\{1 - g(X; \eta)\}$, as $\mu(A, X; \beta)$ is a model for $E(Y \mid A, X)$, and $\widehat{\beta}$ and $\widehat{\gamma}$ are an estimator for β and γ, respectively. Then, Zhang et al. (2012a) proposed to estimate g^{opt} by directly maximizing the AIPWE of $E\{Y^*(g)\}$ across a class of regimes indexed by η. The method is more robust than methods that directly estimate $E(Y \mid A = a, X)$, as it is well known that the AIPWE possesses the double-robustness property, that is, AIPWE(η) consistently estimates $E\{Y^*(g_\eta)\}$ if either the model for $\pi(X)$ or the model for $E(Y \mid A = a, X)$ are correctly specified. For randomized clinical trials, as $\pi(X)$ can always be correctly modeled, the AIPWE is consistent regardless of whether the model for Y is correct or not and, therefore, the AIPWE(η) is robust.

Zhang et al. (2012b) and Zhang and Zhang (2018b) showed that the AIPWE method of Zhang et al. (2012a) leads to an estimator for the contrast function $C(X)$, which we denote by $\widehat{C}_{\text{AIPWE}}(X)$; maximizing the AIPWE of $E\{Y^*(g)\}$ with respect to g is equivalent to minimizing an objective function involving $C(X)$. Specifically, we have

$$\widehat{C}_{\text{AIPWE}}(X) = \left\{ \frac{A}{\pi(X)} Y - \frac{A - \pi(X)}{\pi(X)} \mu(1, X; \widehat{\beta}) \right\}$$

$$-\left\{\frac{1-A}{1-\pi(X)}Y - \frac{\pi(X)-A}{1-\pi(X)}\mu(0,X;\widehat{\beta})\right\}.$$

We comment that in the above expression if we replace $\mu(a, X; \widehat{\beta})$, $a = 0, 1$, by 0, that is, no outcome regression models are fit, then this is equivalent to the outcome weighted learning (Zhao et al. (2012), as discussed in Zhang et al. (2012b). As it does not exploit information in outcome models, it is less efficient than AIPWE-based methods. Zhang et al. (2012b) showed that the optimal treatment regime satisfies

$$g^{\mathrm{opt}}(X) = \arg\min E\{|C(X)|I[g(X) \neq I\{C(X) > 0\}]\},$$

and, therefore, the optimal treatment regime can be identified by minimizing the empirical analog of the above function. Explicitly, one can estimate the optimal treatment regime by minimizing

$$(2) \qquad 1/n \sum_{i=1}^{n} [\widehat{W}_i I\{g(X_i) \neq \widehat{Z}_i\}],$$

where $\widehat{W}_i = |\widehat{C}_{\mathrm{AIPWE}}(X_i)|$, $\widehat{Z}_i = I\{\widehat{C}_{\mathrm{AIPWE}}(X_i) > 0\}$. Basically, $\widehat{W}_i$ and $\widehat{Z}_i$ indicate the magnitude and sign of the estimated contrast function $\widehat{C}_{\mathrm{AIPWE}}(X_i)$ at X_i, respectively. Thus, (2) can be interpreted as a weighted misclassification error rate of the classifier $g(X_i)$, with $\widehat{W}_i$ being the weight and $\widehat{Z}_i$ the class label. Unlike Zhang et al. (2012a, 2012b) focused only on the part of $E(Y \mid A = a, X)$ that is relevant for treatment decision making, that is, the treatment contrast. This representation allows one to consider a larger class of regimes, as opposed to regimes indexed by parameters as in Zhang et al. (2012a). In practice, one needs to build models for $\mu(a, X; \beta)$, $a = 0, 1$, and we refer to these models as the outcome models. In this step the goal is to build the best predictive models which is separated from the optimization step for optimizing decision rules. Good predictive models improve performances in terms of estimating the optimal decision rule but do not directly dictate the form of the decision rules, contrary to the traditional outcome model-based methods. In principle, all commonly used modeling techniques can be used here to build better models. In particular, in our simulations we have considered linear regression models combined with lasso for variable selection which applies in the traditional setting as well as the high-dimensional covariates setting. In other papers cited above, other model techniques are also explored.

2.3. *Robust classification-based lasso selection.* The work of Zhang et al. (2012b) focuses on transforming estimation of the optimal treatment regime (or, equivalently, subgroup identification) into a classification problem and proposes a general weighted classification framework for subgroup identification. The general classification framework is very flexible and powerful, as demonstrated by Zhang et al. (2012b). It was pointed out by a recent paper (Athey and Wager (2021)) that this method is semiparametric efficient. However, this methodology has not been fully developed yet. In this article we focus on further developing this methodology within the general classification framework when the dimension of covariates is high.

The high dimensionality of covariates leads to challenges. First, in principle, one would like to minimize (2) with respect to $g(X)$. However, the optimization is difficult in practice, especially when the dimension of X_i is high because this is a nonconvex optimization problem due to the zero-one loss function corresponding to the indicator function. A remedy for this would be to replace the indicator function by some smooth function. Second, the class of possible regimes that can be constructed from X become too large, making the task of searching for the optimal one very difficult in practice. Although the true optimal treatment regime may take any form, we assume that the true optimal treatment is of a linear form.

That is, we assume there exists η_* such that $I\{C(X) > 0\} = I(\eta'_* H_X > 0)$, where H_X is a $(p + 1)$-dimensional basis functions of baseline covariates X and always includes an intercept, and restrict consideration of regimes to the class $\{g(X) : g(X) = I(\eta' H_X > 0)\}$. We focus on decision rules of this linear form because, often times, it leads to reasonable and interpretable decision rules. In consideration of practicality, linear decision rules are preferred than more complicated decision rules. In addition, most existing methods on estimating the optimal treatment regimes focus on this form. In fact, it can represent a large and flexible class of decision rules by choosing the basis functions. In practice, one might include polynomial basis functions, splines or other commonly used basis functions. Considerations may include interpretation and how well the chosen basis functions can approximate the true functional form of covariates.

Restricting consideration of regimes to $\{g(X) : g(X) = I(\eta' H_X > 0)\}$, then $I\{\widehat{Z}_i \neq g(X_i)\}$ in (2) becomes $I\{\widehat{Z}_i \neq I(\eta' H_{X_i} > 0)\}$ which is equal to $I\{(2\widehat{Z}_i - 1)\eta' H_{X_i} \leq 0\}$. In our proposed method, we replace the indicator function $I(x \leq 0)$ by a convex function $l(x)$ which is its upper bound. Specifically, we choose $l(x) = \ln(1 + e^{-x})$ for its convenience in implementation, as detailed below. Replacing the indicator function by the chosen convex function, the new objective function becomes

$$(3) \qquad \sum_{i=1}^{n} [\widehat{W}_i \ln\{1 + e^{-(2\widehat{Z}_i - 1)\eta' H_{X_i}}\}].$$

Then, minimizing the new objective function can be conveniently achieved by fitting a logistic regression model. Specifically, based on the classification data set $(H_{X_i}, \widehat{W}_i, \widehat{Z}_i)$, treating $\widehat{Z}_i$ as the response and H_{X_i} as independent variables, we fit the following logistic regression model:

$$\ln\left\{\frac{P(\widehat{Z} = 1 \mid X)}{1 - P(\widehat{Z} = 1 \mid X)}\right\} = \eta' H_X,$$

or, equivalently,

$$P(\widehat{Z} = 1 \mid X) = \frac{e^{\eta' H_X}}{1 + e^{\eta' H_X}} = \frac{1}{1 + e^{-\eta' H_X}}.$$

Denoting $P_i = 1/(1 + e^{-\eta' H_{X_i}})$, the weighted log-likelihood function can be written as

$$\ln L(\eta) = \sum_{i=1}^{n} \widehat{W}_i\{\widehat{Z}_i \ln P_i + (1 - \widehat{Z}_i)\ln(1 - P_i)\}$$

$$= -\sum_{i=1}^{n} \widehat{W}_i\{\widehat{Z}_i \ln(1 + e^{-\eta' H_{X_i}}) + (1 - \widehat{Z}_i)\ln(1 + e^{\eta' H_{X_i}})\}$$

$$= -\sum_{i=1}^{n} \widehat{W}_i \ln\{1 + e^{-(2\widehat{Z}_i - 1)\eta' H_{X_i}}\}.$$

It follows that $\arg\max_\eta \ln L(\eta) = \arg\min_\eta \sum_{i=1}^{n} \widehat{W}_i \ln\{1 + e^{-(2\widehat{Z}_i - 1)\eta' H_{X_i}}\}$. That is, minimization of (3) can be implemented by fitting the above logistic regression model through maximizing a weighted likelihood function, and this can be carried out by many standard software.

Variable selection of important prescriptive variables (i.e., variables important for treatment decision making) is often necessary in order to achieve interpretable and stable estimate of the optimal decision rule. One natural idea would be to incorporate a penalty to the

objective function (3) to penalize the size of variables being selected. We may add an L_1 (lasso-type) penalty, and then the objective function to be minimized becomes

$$(4) \qquad \sum_{i=1}^{n} \widehat{W}_i \ln\{1 + e^{-(2\widehat{Z}_i - 1)\eta' H_{X_i}}\} + \lambda\|\eta\|_1,$$

where $\|\eta\|_1 = \sum_{j=1}^{p} |\eta_j|$. We note that this step can be conveniently implemented by standard software. For example, the function cv.glmnet with "family = binomial" in R package glmnet can easily incorporate weights to minimize this weighted and penalized objective function. We comment that in the proposed method we choose to use the logistic loss function (binomial deviance) to replace the indicator function (zero-one loss) for its computational convenience. Other common loss functions (e.g., hinge loss, squared error loss) can be used in principle. The logistic loss function is appealing because it allows convenient implementation using the off-the-shelf software, and it can easily incorporate weights and shrinkage methods for variable selection.

2.4. *Backward elimination.* In the presence of a high dimensional set of variables, especially when the number of covariates is greater than the sample size ($p > n$), dimension reduction is often a necessary step. Although the L_1 penalty idea discussed above helps in reducing the dimension of variables, based on our experience, with the tuning parameter λ set at the default value based on cross-validation, often it results in too many unimportant variables being selected, leading to unnecessarily too complicated decision rules. However, adding a bigger penalty would then result in too few variables being selected and worse performance of the estimated regimes. An intuitive explanation for this is that, when one tries to do a global search of important variables from among a high dimensional set of potential variables, a single lens size is often either too coarse or too fine. A better strategy might be to do an initial global search with an appropriate size of lens (i.e., λ) and then to zoom in to further refine the search. In light of this and within the weighted classification framework, we further propose a backward elimination algorithm and couple it with the L_1 penalization method.

The backward elimination algorithm is based on the empirical weighted misclassification error rate corresponding to a regime $g(X)$, defined in (2). Suppose minimization of (4), implemented by a weighted logistic regression with lasso selection, results in m selected variables $\{H_X^{j^1}, \ldots, H_X^{j^m}\}$ with corresponding estimated coefficients $\widehat{\eta}_{j^1}, \ldots, \widehat{\eta}_{j^m}$. Note, we use superscript only in Section 2.4 to indicate individual variables in H_X. The proposed backward elimination algorithm proceeds as follows.

Step 1: We construct a composite variable $M_X^{\mathcal{F}^0} = \sum_{j \in \mathcal{F}^0} \widehat{\eta}_j H_X^j$, where $\mathcal{F}^0 = \{j^1, \ldots, j^m\}$, and define the weighted misclassification error rate corresponding to $M_X^{\mathcal{F}^0}$ as

$$\text{err}(M_X^{\mathcal{F}^0}) = \min_{\eta_0} n^{-1} \sum_{i=1}^{n} \widehat{W}_i I\{\widehat{Z}_i \neq I(M_{X_i}^{\mathcal{F}^0} > \eta_0)\},$$

which can be interpreted as the minimal empirical weighted misclassification error rate among all regimes in class $\{g(X_i) : g(X_i) = I(M_{X_i}^{\mathcal{F}^0} > \eta_0), \eta_0 \in \mathcal{R}\}$. Correspondingly, define

$$\widehat{\eta}_0^{\mathcal{F}^0} = \arg\min_{\eta_0} n^{-1} \sum_{i=1}^{n} \widehat{W}_i I\{\widehat{Z}_i \neq I(M_{X_i}^{\mathcal{F}^0} > \eta_0)\}.$$

Step 2: Let $M_X^{\mathcal{F}^0 \setminus j^k} = \sum_{j \in \mathcal{F}^0 \setminus j^k} \widehat{\eta}_j H_X$, where $\mathcal{F}^0 \setminus j^k = \{j^1, \ldots, j^{k-1}, j^{k+1}, \ldots, j^m\}$, and define

$$(5) \qquad \text{err}(M_X^{\mathcal{F}^0 \setminus j^k}) = \sum_{i=1}^{n} \widehat{W}_i I\{\widehat{Z}_i \neq I(M_{X_i}^{\mathcal{F}^0 \setminus j^k} > \widehat{\eta}_0^{\mathcal{F}^0})\}.$$

We can quantify the importance of $H_X^{j^k}$ in $M_X^{\mathcal{F}^0}$ by

$$(6) \qquad \text{prop}^{(j^k, \mathcal{F}^0)} = \frac{\text{err}(M_X^{\mathcal{F}^0 \setminus j^k}) - \text{err}(M_X^{\mathcal{F}^0})}{\max_{j^i \in \mathcal{F}^0}\{\text{err}(M_X^{\mathcal{F}^0 \setminus j^i}) - \text{err}(M_X^{\mathcal{F}^0})\}}.$$

We set $\mathcal{S}^0 = \{j^k : \text{prop}^{(j^k, \mathcal{F}^0)} \leq \alpha, j^k \in \mathcal{F}^0\}$, where α is a cut-off point and delete these variables from $\mathcal{F}^0$, leading to $\mathcal{F}^1 = \mathcal{F}^0 \setminus \mathcal{S}^0$.

Next, starting with $\mathcal{F}^1$, repeat steps 1 and 2, leading to $\mathcal{S}^1$ and $\mathcal{F}^2 = \mathcal{F}^1 \setminus \mathcal{S}^1$, accordingly. Specifically, for $l = 1, 2, 3, \ldots$

$$\text{prop}^{(j^k, \mathcal{F}^l)} = \frac{\text{err}(M_X^{\mathcal{F}^l \setminus j^k}) - \text{err}(M_X^{\mathcal{F}^l})}{\max_{j^i \in \mathcal{F}^l}\{\text{err}(M_X^{\mathcal{F}^l \setminus j^i}) - \text{err}(M_X^{\mathcal{F}^l})\}}.$$

Then, $\mathcal{S}^l = \{j^k : \text{prop}^{(j^k, \mathcal{F}^l)} \leq \alpha, j^k \in \mathcal{F}^l\}$ and $\mathcal{F}^{l+1} = \mathcal{F}^l \setminus \mathcal{S}^l$.

The algorithm continues the elimination process until $\mathcal{S}^l$ is empty or $\mathcal{F}^l$ contains only one element. When $\mathcal{F}^l$ contains only one variable, one would not be able to evaluate the importance of one variables relative to the composite variable $M_X^{\mathcal{F}^l}$, as described above. In this case we then compare the corresponding $\text{err}(M_X^{\mathcal{F}^l})$ with $\text{err}^{(0)}$, where $\text{err}^{(0)}$ is the weighted misclassification error rate by assigning the treatment with better average treatment effect to all patients regardless of their characteristics. That is,

$$\text{err}^{(0)} = \min_{a \in \{0,1\}} n^{-1} \sum_{i=1}^{n} \widehat{W}_i I(\widehat{Z}_i \neq a).$$

If $\frac{\text{err}^{(0)} - \text{err}(M_X^{\mathcal{F}^l})}{\text{err}^{(0)}} < \alpha$, then we delete $\mathcal{F}^l$, leading to an empty set of selected prescriptive variables. The final estimated regime is

$$\arg \min_{a \in \{0,1\}} n^{-1} \sum_{i=1}^{n} \widehat{W}_i I(\widehat{Z}_i \neq a),$$

indicating that there is no subgroup, and everyone should be treated with the same treatment. Otherwise, the algorithm reaches the point when $\mathcal{S}^l$ is empty, the final selected variables are $\mathcal{F}^l$ and the estimated regime is $I(M_{X_i}^{\mathcal{F}^l} > \widehat{\eta}_0^{\mathcal{F}^l})$.

As with most variable selection methods, the proposed backward elimination process involves a tuning parameter α. One may prespecify α using some ad hoc way. Alternatively, one may use a five- or 10-fold cross-validation with the chosen α, leading to the smallest value of (2) on validation data sets. As argued in Zhang and Zhang (2018a), when decision rules are similar in terms of values (the expected potential outcomes) and error rates, one would prefer a decision rule that is both simpler and more convenient to use from a practical point of view. Therefore, one may even incorporate considerations of the cost of collecting variables and other clinical/subject matter knowledge to set the tuning parameter. In our simulation studies and data application, a five-fold cross-validation was used for choosing the tuning parameter.

3. Simulations. This section reports on results of simulations studies conducted to evaluate performances of the proposed methods relative to existing methods. For each Monte Carlo data set, covariates $X_i = (X_{i1}, \ldots, X_{ip})^T$, $p = 50$ or 1000 were generated from a multivariate normal distribution with mean 0 and variance 1. Correlation coefficients (ρ) between covariates were all set to either 0.2, 0.5 or 0.8. Treatment A_i was generated from Bernoulli distributions with probability $\pi(X_i)$, as specified below, or with probability 0.5. The error term ϵ_i in outcome models, specified below, was normally distributed with mean 0 and variance 1. Specifically, two scenarios were considered, and the corresponding outcome and treatment models were specified below:

– Scenario I

   Outcome model: $Y_i = \exp\{2 + X_{i1} - X_{i2} - |1 + 1.5X_{i1} - 2X_{i2}|(A_i - g_i^{\text{opt}})^2\} + \epsilon_i$, where $g_i^{\text{opt}} = I(X_{i7}^2 + 1.5X_{i8}^2 + 2X_{i9} + 1.5X_{i10} > 0)$.
   Treatment model: $\text{logit}\{\pi(X_i)\} = 0.1 + 0.25X_{i1} + 0.25X_{i5}$.

– Scenario II

   Outcome model: $Y_i = \exp\{2 + X_{i1} - X_{i2} - |1 + 1.5X_{i1} - 2X_{i2}|(A_i - g_i^{\text{opt}})^2\} + \epsilon_i$, where $g_i^{\text{opt}} = I(0.1 + X_{i9} + X_{i10} > 0)$.
   Treatment model: $\pi(X_i) = 0.5$.

In scenarios I and II, p is 50 and 1000, respectively. Note, in both scenarios outcomes are nonlinearly related with covariates. However, in scenario I the optimal treatment decision rule is nonlinear in covaraites, but in scenario II the optimal rule is linear in covariates. For each data generating scenario, we considered sample sizes $n = 300$ and 600. In the Supplementary Material we also report results on scenario III where outcome is related to covariates through a linear regression model. Code for implementing the method is provided in the Supplementary Material (Zhang and Zhang (2022)).

We studied two versions of the proposed methods. In C-AIPWE-lasso (denoted by CAL), we minimize the L_1 penalized empirical weighted misclassification error rate based on AIPWEs within a classification framework, implemented by fitting a weighted logistic regression model. In C-AIPWE-lasso-backward (denoted by CALB), the C-AIPWE-lasso is further coupled with the proposed backward elimination process. Regarding choice of the tuning parameter α in CALB, we set $\alpha = 0.05, 0.10, 0.15$ and 0.20 and used five-fold cross-validation to select the best α with the smallest weighted misclassification error. We compare the proposed methods with the following existing methods. In "RegL," we fit a linear regression with all main effects of covariates (not limited to linear terms) and their interaction with treatment and use lasso to select variables to be included in the final model. SAS denotes the sequential advantage selection method of Fan, Lu and Song (2016). We also compare with the augmented modified-covariate method of Tian et al. (2014) and the forward minimal misclassification error rate (ForMMER) method of Zhang and Zhang (2018a). The proposed methods (CAL and CALB), "RegL" and the "Tian" method involve building outcome models with lasso. For these methods we built models, considering all linear and quadratic terms in scenarios I and III and linear terms only in scenario II, with the default setting in the R package *glmnet* for choosing tuning parameter using cross-validation. To be consistent, the same set of variables, depending on the scenario, were also considered in SAS. For scenario I, where treatment is not randomized, logistic models with lasso selection were fit for modeling treatment in the proposed method with default setting as well.

Methods are evaluated based on the following metrics. The value ratio (VR) is the value of the estimated decision rule over the value of the true optimal decision rule. By definition, value takes into account both whether a treatment decision is correct and also the magnitude of contrast between an incorrect decision and a correct decision. Therefore, this can be viewed as the most important metric in terms of measuring the quality of estimated decision rules.

Error rate (ER) is the error rate of decisions made by the estimated treatment rules, estimated by $\sum_{j=1}^{N}\{\widehat{g}(X_j) \neq g^{\mathrm{opt}}(X_j)\}/N$, j indexes subjects from a large independent sample from the same population. Additionally, we are interested in the performance in terms of prescriptive variable selection. For treatment decision rules leading to similar decisions and values, one would prefer those that are simpler. To evaluate this, we report the size of the estimated decision rules, where the size is defined as the number of variables in the final estimated rule, and the number of true prescriptive (TP) variables selected. In addition to ER, the false positive (FPR) and false negative (FNR) rates in terms of classifying patients to the subgroup with optimal treatment 1 are reported; for example, FPR is the rate of falsely classifying patients that should be in the subgroup with optimal treatment 0 to the subgroup with optimal treatment 1. For every metric the Monte Carlo average based on 500 Monte Carlo data sets are reported, and values and error rates of decision rules are estimated by $N = 100{,}000$ Monte Carlo replicates.

Figures 1 and 2 show boxplots of value ratios and error rates, respectively, for all methods under various scenarios. In addition to VR and ER, in Table 1 we additionally report TP, FPR, FNR and the average number of selected prescriptive variables (i.e., size). Method "RegL" has the worst performance overall in scenarios I and II which is not surprising as the true outcome models are nonlinear. We note when the true relationship is linear, it has the best performance as expected; see results on scenario III in the Supplementary Material. Other than "RegL," SAS has worse performances than other methods. The main reason for this is that SAS selects prescriptive variables sequentially, and at each step it relies on regression models conditional only on selected variables. As a result, the method will not be able to take advantage of variables that only have a main effect but not interaction effect on outcomes, leading to unsatisfying performances. All other methods are able to take advantage of all predictive variables. The proposed methods have better performances than other existing methods, with the C-AIPWE-Lasso-Backward (CALB) having the best and most robust performance. The improvement over "RegL" is due to that outcome regression-based methods are heavily dependent on the correctness of the specified model, whereas the proposed methods do not rely on correct specification of outcome models and are more robust. Therefore, even with the use of lasso, due limitations of the framework, the performance of "RegL" is not robust. We note, even when the true outcome model is linear, in which case "RegL" should be the best, the proposed methods (CAL and CALB) have comparable performance as "RegL;" see additional simulations in the Supplementary Material. Under scenarios I and II, the proposed methods also significantly improve over the "Tian" method. The main reason for this difference is that the "Tian" method depends on the assumption that the contrast function satisfies $C(X) = \eta' H_X$ for some η, whereas the proposed method does not require this strong assumption, and we only assume $I\{C(X) > 0\} = I(\eta' H_X > 0)$ for some η which is a much weaker assumption. Therefore, when the assumption $C(X) = \eta' H_X$ does not hold, the "Tian" method has unsatisfying performances. When the assumption of the "Tian" method does hold, the performance of the "Tian" method improves and is comparable to the proposed methods, as shown in the Supplementary Material.

The two proposed methods (CAL and CALB) as well as ForMMER are all based on the robust classification framework. Decision rules from FoMMER have larger error rates and smaller values than the proposed methods. In addition, ForMMER sometimes exhibits larger variability, as shown in scenario I when sample size is small ($n = 300$) and correlation is high ($\rho = 0.8$). These are likely due to two main reasons. First, ForMMER is based on a forward selection that at each step it looks one step forward and is known to be a myopic process, whereas the proposed method features an overall lasso selection coupled with backward elimination for fine-tuning. Second, the objective function of ForMMER involves an indicator function which is not smooth and leads to difficulty in optimization when the sample size
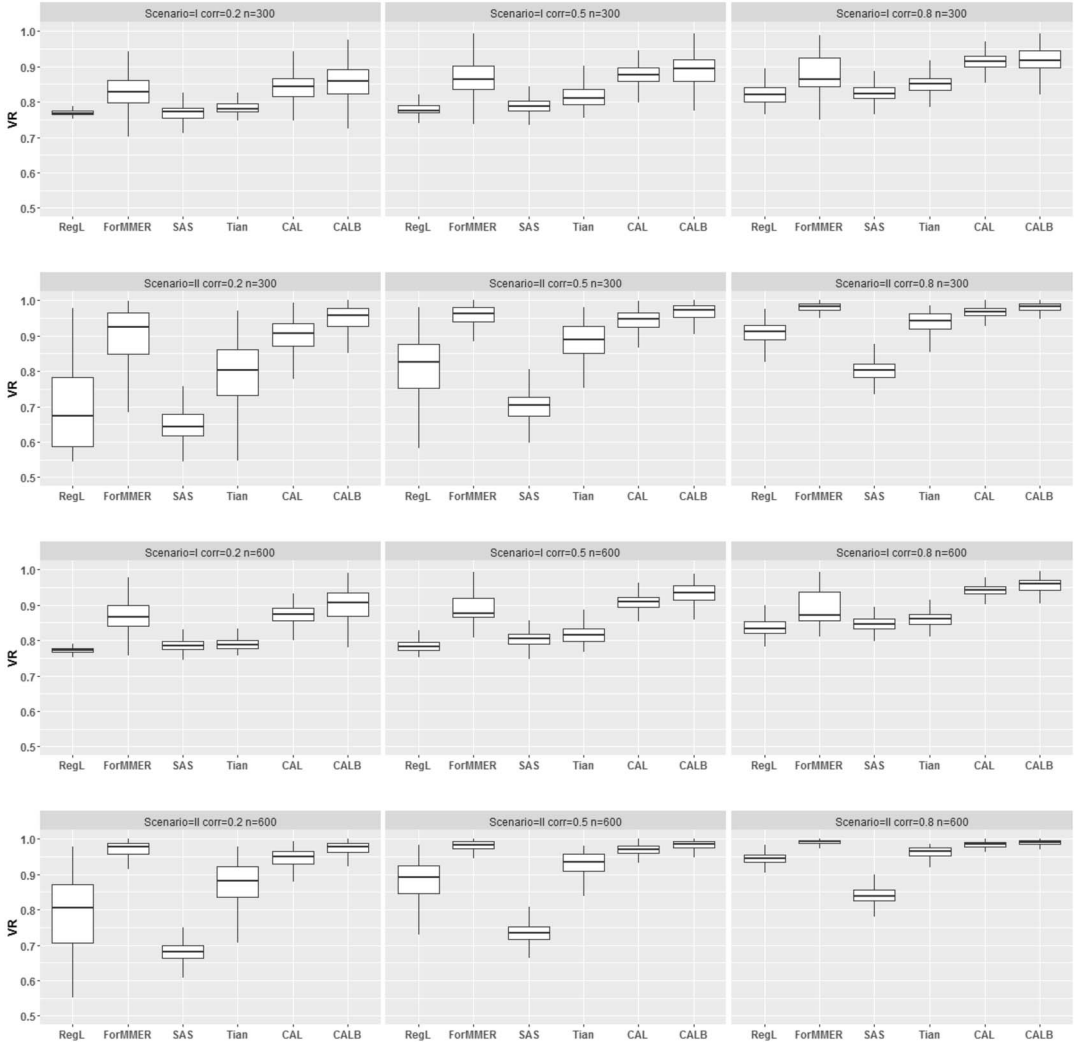
FIG. 1.   *Simulation results for scenarios I and II: Value ratio (VR) of estimated decision rules relative to the true optimal decision rule, value is the expectation of potential outcomes. From top to bottom, rows correspond to scenario I, $n = 300$, scenario II, $n = 300$, scenario I, $n = 600$ and scenario II, $n = 600$. From left to right, columns correspond to $\rho = 0.2, 0.5$ and 0.8.*

is small. The proposed methods are able to address these two issues, leading to much better overall performances in making the right treatment decision. Regarding the two proposed methods, comparatively, CALB is better than CAL in terms of VR, ER and other metrics, demonstrating the added benefit of the backward elimination process. Notably, CALB leads to considerably simpler estimated decision rules, while improving accuracy of making the right treatment decisions. Overall CALB has the best and most robust performances in terms of VR and ER. In addition, the good performance is achieved with much simpler treatment decision rules than other methods (Tables 1 and 2). For example, under scenario II ($\rho = 0.5$) and when $n = 600$, better performance of CALB is achieved with an average size of 2, whereas the average size of SAS, the "Tian" method and CAL are 27.6, 14.3, 7.1, respectively.

4. Application.   As introduced in Section 1, both heparin and bivalirudine are commonly used anticoagulants for patients with acute myocardial infarction undergoing PCI. With multiple large scale clinical trials demonstrating its superiority in bleeding risk, bivalirudine
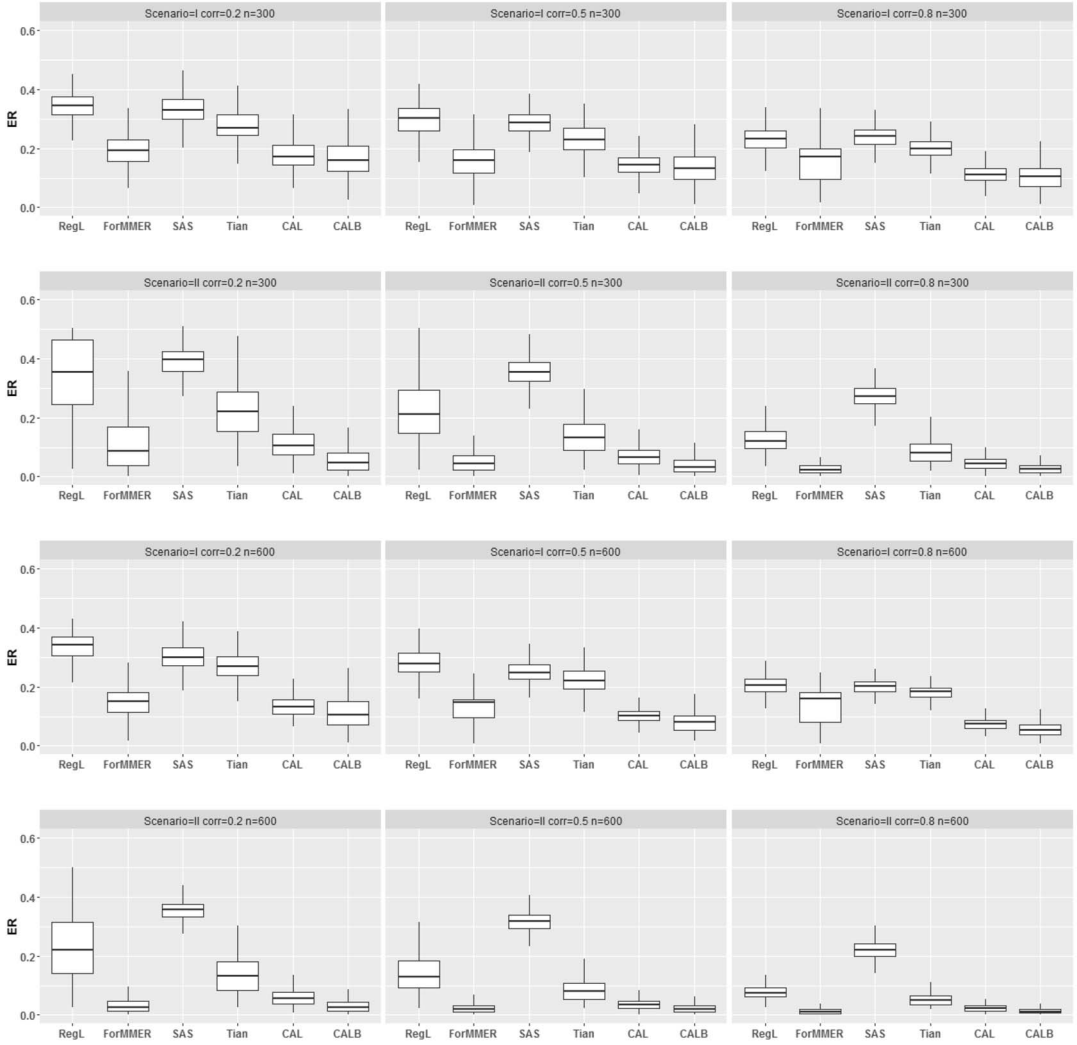
FIG. 2. *Simulation results for scenarios I and II: Error rate (ER) of estimated decision rules relative to the true optimal decision rule. From top to bottom, rows correspond to scenario I, $n = 300$, scenario II, $n = 300$, scenario I, $n = 600$ and scenario II, $n = 600$. From left to right, columns correspond to $\rho = 0.2, 0.5$ and 0.8.*

gradually became the mainstay of anticoagulation, relative to heparin, the traditionally standard treatment. Use of bivalirudine increased since 2009 but, with more and conflicting results from clinical trials and observational studies, fell after 2013 (Andreou, Maniotis and Koutouzis (2017)). 'Til now, whether bivalirudine offers more advantage remains controversial, and U.S. PCI guidelines leave the choice of procedural anticoagulant to the discretion of the operating physician. Although no consensus has been reached regarding the comparative effectiveness, many studies have found that a main factor impacting results from various studies is the different use of glycoprotein IIb/IIIa inhibitors (GPI), an antiplatelet agent often used concomitantly for patients with certain risk factors (Cavender and Sabatine (2014)).

We aim to identify the subgroup of patients who would benefit from bivalirudine ($A = 1$) relative to heparin ($A = 0$) from the perspective of optimal treatment regime. Our analysis included 1191 patients who underwent PCI at the University of Michigan Medical Center from 2007 to 2009 and were treated with bivalirudine (603) or with heparin (588), using data from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (Perdoncin et al. (2013)). The outcome of interest is postoperative hemoglobin (g/dl)), a continuous measure

TABLE 1
Simulation results for Scenario I. Size: Number of selected prescriptive variables; TP: Number of true prescriptive variables selected; FPR and FNR: False positive rate and false negative rate, respectively, in terms of classifying patients to the subgroup with optimal treatment 1; ER: Error rate of treatment decisions; VR (value ratio): Ratio of the value of the estimated regime relative to that of the true optimal regime, where value is the expectation of potential outcomes. Parameter ρ indicates correlation coefficient. The most important metric, VR, is in bold. Numbers in parentheses are Monte Carlo standard deviations

Method	ρ	Size	TP	FPR	FNR	ER	**VR**
					$n = 300$		
RegL	0.2	15.9	1.9	62.2	24.5	34.1 (4.8)	**76.9 (1.4)**
ForMMER		2.5	1.4	42.9	14.6	21.9 (7.5)	**81.3 (5.5)**
SAS		10.4	2.0	43.7	30.2	33.5 (5.3)	**76.4 (3.4)**
Tian		16.3	2.5	52.7	19.2	27.7 (5.3)	**78.5 (2.5)**
CAL		29.3	3.6	42.1	9.9	18.1 (5.3)	**83.9 (3.9)**
CALB		3.9	2.4	31.5	12.1	17.2 (6.9)	**85.5 (5.1)**
RegL	0.5	19.6	2.7	54.4	20.1	29.6 (5.4)	**78.4 (2.4)**
ForMMER		2.8	1.9	30.8	11.9	17.1 (5.4)	**85.6 (4.4)**
SAS		10.0	2.2	41.3	24.0	28.8 (4.2)	**78.8 (2.7)**
Tian		20.2	3.3	39.2	16.8	23.0 (5.0)	**81.7 (3.3)**
CAL		25.1	3.8	32.6	7.9	14.7 (4.0)	**87.6 (3.1)**
CALB		3.6	2.8	20.6	10.7	13.5 (5.7)	**88.9 (4.3)**
RegL	0.8	23.9	3.3	42.8	14.5	23.2 (4.1)	**82.2 (2.8)**
ForMMER		2.7	1.8	23.8	13.2	16.4 (5.6)	**87.0 (4.4)**
SAS		9.6	2.2	36.6	18.4	24.0 (3.4)	**82.4 (2.4)**
Tian		26.3	3.5	32.0	14.6	19.9 (3.6)	**85.0 (2.6)**
CAL		22.7	3.9	22.5	6.5	11.4 (3.0)	**91.2 (2.3)**
CALB		3.4	3.0	15.6	8.5	10.7 (5.0)	**91.6 (3.9)**
					$n = 600$		
RegL	0.2	20.2	2.7	56.5	25.7	33.6 (4.7)	**77.4 (1.1)**
ForMMER		2.4	1.9	35.6	10.7	17.0 (5.8)	**85.1 (4.3)**
SAS		12.3	2.8	39.5	27.4	30.5 (4.9)	**78.4 (2.4)**
Tian		21.5	3.3	45.1	21.0	27.1 (5.0)	**79.2 (2.1)**
CAL		32.9	4.0	30.4	8.0	13.7 (3.8)	**87.2 (2.8)**
CALB		3.7	3.1	18.9	9.1	11.6 (5.9)	**90.2 (4.3)**
RegL	0.5	25.1	3.5	49.9	19.7	28.0 (4.8)	**78.7 (2.0)**
ForMMER		2.7	2.2	23.3	10.6	14.1 (4.3)	**88.1 (3.6)**
SAS		10.9	3.0	37.9	20.5	25.4 (3.7)	**80.5 (2.0)**
Tian		26.2	3.8	37.1	16.4	22.1 (4.3)	**81.8 (2.8)**
CAL		26.5	4.0	23.7	5.4	10.4 (2.7)	**90.7 (2.2)**
CALB		3.7	3.5	12.3	6.9	8.4 (3.9)	**93.0 (3.2)**
RegL	0.8	30.4	3.9	38.4	12.7	20.5 (3.0)	**83.7 (2.3)**
ForMMER		2.6	2.2	17.9	11.9	13.7 (5.6)	**89.2 (4.5)**
SAS		10.2	3.1	33.1	14.5	20.1 (2.4)	**84.7 (1.8)**
Tian		34.9	3.9	31.1	12.6	18.2 (2.4)	**86.0 (2.0)**
CAL		20.8	4.0	15.6	4.0	7.5 (2.1)	**94.2 (1.6)**
CALB		3.8	3.7	8.3	5.1	6.1 (3.4)	**95.3 (2.6)**

with higher value indicating less bleeding. About 50 baseline covariates are used in analyses including patient demographics, preoperative hemoglobin, comorbidities/prior procedures, measures of cardiac status and medications (Perdoncin et al. (2013)). We implemented four methods in our analysis: the proposed C-AIPWE-lasso-backward method (CALB), ForMMER, SAS and the "Tian" method. Both CALB and ForMMER involved building a propensity score model for the probability of receiving bivalirudin conditional on patient charac-

TABLE 2

Simulation results for Scenario II. Size: Number of selected prescriptive variables; TP: Number of true prescriptive variables selected; FPR and FNR: False positive rate and false negative rate, respectively, in terms of classifying patients to the subgroup with optimal treatment 1; ER: Error rate of treatment decisions; VR (value ratio): Ratio of the value of the estimated regime relative to that of the true optimal regime, where value is the expectation of potential outcomes. Parameter ρ indicates correlation coefficient. The most important metric, VR, is in bold. Numbers in parentheses are Monte Carlo standard deviations

Method	ρ	Size	TP	FPR	FNR	ER	VR
					$n = 300$		
RegL	0.2	14.7	1.2	38.3	31.3	34.5 (11.9)	69.0 (10.6)
ForMMER		2.5	1.7	14.4	13.0	13.6 (14.0)	87.8 (12.5)
SAS		20.8	1.4	40.0	38.9	39.3 (4.8)	64.7 (4.3)
Tian		15.9	1.7	25.2	21.8	23.4 (10.7)	78.9 (9.7)
CAL		17.2	2.0	12.3	11.0	11.5 (6.3)	89.6 (5.6)
CALB		2.1	1.9	7.4	6.3	6.9 (7.0)	93.9 (6.2)
RegL	0.5	19.3	1.7	22.5	22.8	22.7 (10.8)	80.9 (9.2)
ForMMER		2.4	2.0	6.3	5.2	5.7 (6.1)	95.2 (5.1)
SAS		18.6	1.4	35.9	35.3	35.5 (4.3)	70.2 (3.6)
Tian		14.8	1.9	12.2	15.4	13.8 (6.8)	88.4 (5.7)
CAL		10.3	2.0	6.7	7.1	6.9 (3.6)	94.2 (3.0)
CALB		2.0	2.0	4.8	3.5	4.2 (3.6)	96.5 (3.0)
RegL	0.8	29.2	1.9	11.1	14.6	12.9 (4.7)	90.6 (3.5)
ForMMER		2.3	2.0	3.1	2.3	2.7 (2.0)	98.0 (1.4)
SAS		13.0	1.3	25.8	28.7	27.1 (4.0)	80.3 (2.9)
Tian		13.1	2.0	6.9	10.4	8.7 (4.5)	93.7 (3.3)
CAL		7.2	2.0	3.4	5.6	4.6 (2.3)	96.7 (1.6)
CALB		2.0	1.9	3.4	2.9	3.1 (2.6)	97.8 (1.9)
					$n = 600$		
RegL	0.2	18.4	1.8	23.4	23.9	23.6 (11.9)	78.4 (10.9)
ForMMER		2.1	2.0	4.2	3.2	3.7 (5.7)	96.6 (5.1)
SAS		29.5	1.9	36.2	35.5	35.8 (3.8)	67.8 (3.4)
Tian		15.4	1.9	13.1	15.5	14.3 (8.0)	87.0 (7.4)
CAL		11.0	2.0	5.9	6.1	6.0 (3.1)	94.6 (2.8)
CALB		2.0	2.0	3.4	2.9	3.1 (2.5)	97.2 (2.3)
RegL	0.5	28.5	2.0	12.6	15.9	14.3 (7.0)	87.8 (6.2)
ForMMER		2.1	2.0	2.5	2.3	2.4 (1.8)	98.0 (1.5)
SAS		27.6	1.9	31.8	31.6	31.7 (3.5)	73.4 (2.9)
Tian		14.3	2.0	6.5	10.4	8.6 (4.2)	92.8 (3.6)
CAL		7.1	2.0	3.4	4.0	3.7 (1.9)	96.9 (1.6)
CALB		2.0	2.0	2.3	1.9	2.2 (1.5)	98.2 (1.3)
RegL	0.8	32.9	2.0	5.8	9.6	7.8 (2.4)	94.3 (1.7)
ForMMER		2.2	2.0	1.4	1.3	1.3 (0.9)	99.0 (0.7)
SAS		17.1	1.8	19.8	24.1	22.1 (3.2)	83.9 (2.3)
Tian		12.7	2.0	3.3	7.3	5.4 (2.5)	96.1 (1.8)
CAL		5.9	2.0	1.5	3.1	2.3 (1.2)	98.3 (0.9)
CALB		2.0	2.0	1.5	1.3	1.4 (1.0)	99.0 (0.7)

teristics and risk factors. Logistic regression model was used for modeling bivalirudine, and variables included in the final model were selected using lasso with the default setting. For CALB the R package glmnet with default setting was used to minimize (4), and α in backward elimination was chosen by cross-validation, as described in Section 3. The estimated optimal regimes by ForMMER, SAS, the "Tian" method and C-AIPWE-lasso-backward(CALB) are,

respectively,

$$\widehat{g}_{\text{ForMMER}}^{\text{opt}} = I(2.08 + 0.105\text{HGB} - 0.018\text{HT} > 0),$$

$$\begin{aligned}
\widehat{g}_{\text{SAS}}^{\text{opt}} = I(&-1.28 + 0.459\text{CHF} + 0.579\text{CVA} - 0.013\text{ICD} + 0.331\text{VALVE} \\
&- 0.627\text{TRANSP} + 0.100\text{HGB} - 2.427\text{VASO} + 0.33\text{FEMALE} \\
&- 0.312\text{MI} - 0.575\text{GPI} + 0.473\text{PRIORITY1} - 0.037\text{PRIORITY2} \\
&+ 0.305\text{SMOKER1} + 1.193\text{BMI0} - 0.304\text{BMI1} > 0),
\end{aligned}$$

$$\begin{aligned}
\widehat{g}_{\text{Tian}}^{\text{opt}} = I(&0.150\text{CVA} + 0.009\text{HGB} - 0.834\text{VASO} + 0.081\text{SMOKER1} \\
&+ 0.35\text{BMI0} + 0.017\text{BMI2} + 0.281\text{PRIORITY1} > 0),
\end{aligned}$$

$$\begin{aligned}
\widehat{g}_{\text{CALB}}^{\text{opt}} = I(&0.965 + 0.044\text{HGB} - 0.006\text{HT} - 0.280\text{BB} + 0.462\text{CVA} \\
&- 0.342\text{BMI1} - 0.339\text{GPI} - 0.097\text{SMOKER2} - 0.06\text{PRIORITY2} > 0),
\end{aligned}$$

where HGB is preoperative hemoglobin level; CHF, CVA, MI, ICD, VALVE, TRANSP are comorbidities/prior procedures and indicate congestive heart failure, stroke, myocardial infarction, implantable cardioverter defibrillator, Valve repair/replacement, cardiac transplant, respectively; VASO (vasopressor), BB (beta blocker) and GPI (glycoprotein IIb/IIIa inhibitor) are medications prior to or during the procedure; $\text{BMI0} = I(\text{BMI} < 18.5)$, $\text{BMI1} = I(18.5 \leq \text{BMI} < 25)$ and $\text{BMI2} = I(25 \leq \text{BMI} < 30)$, indicating underweight, normal and overweight (but not obese), respectively; HT is height (cm), SMOKER 1 and 2 indicate former and current smoker, respectively; and PRIORITY 1 and 2 indicate emergent and urgent patients, respectively. For example, the decision rule from CALB says that the treatment decision for each patient depends on eight variables. Patients with $\widehat{g}_{\text{CALB}}^{\text{opt}} = 1$ belong to the subgroup of patients that should be treated with bivalirudine; otherwise, they belong to the subgroup that should be treated with heparin.

Applying the estimated decision rules to our data, the estimated decision rule from the "Tian" method would prescribe bivalirudine to every patient in our data except for two patients. It does not identify a meaningful subgroup of patients that would benefit from heparin. Although for a real data application we do not know the true optimal decision rule, this result seems not consistent with the most recent clinical knowledge. According to Table 3, The estimated decision rule from ForMMER identified a small group of patients (149, 12.5%) that should be treated with heparin and two factors affect the treatment decision. Both SAS and CALB identified a relatively larger subgroup of patients that would benefit from heparin, that is, 47.4% and 35.0% patients should preferably be treated with heparin, using the decision rules from SAS and CALB, respectively. In particular, we note the treatment decision rules from both SAS and CALB involve GPI. In both rules, heparin tends to be the preferred treatment if GPI is necessary. This is in line with the prior finding in clinical literature that bivalirudine offers less or no benefit for patients with GPI in terms of bleeding risk.

We strongly think that an independent study is needed to evaluate the performance of estimated decision rules. Even with an independent study, it would still be a challenging task because in real data the treatment rules are not randomized and the potential outcomes under different rules are subject to nonrandom missingness. Valid inferences on mean outcomes under optimal treatment regimes have recently been studied by Luedtke and van der Laan (2016) and Shi, Lu and Song (2020). Since our decision rules are estimated from the data, one should be careful and not over interpret summary results on data used for estimation regarding different decision rules. With these caveats in mind, we report the following summary data to shed some light on performances of various decision rules. Table 3 reports averages of outcomes for subgroups of patients identified from different methods by the actual treatment

TABLE 3
Data analysis results: The average (standard deviation, n) of postoperative hemoglobin for identified subgroups from various methods by the actual received treatment. The second number in parenthesis is the number of patients. For example, $\widehat{g}_{CALB}^{opt} = 1$ denotes the subgroup of patients identified by CALB that should receive treatment 1

| | | Actual Received Treatment | |
| | | Bivalirudine ($A = 1$) | Heparin ($A = 0$) |
Estimated optimal treatment	n	Average postoperative hemoglobin (SD, n)	
$\widehat{g}_{ForMMER}^{opt} = 1$	1042	12.85 (1.81, 511)	12.54 (1.80, 531)
$\widehat{g}_{ForMMER}^{opt} = 0$	149	10.34 (1.78, 77)	10.65 (2.03, 72)
$\widehat{g}_{SAS}^{opt} = 1$	627	12.91 (1.82, 419)	12.30 (1.98, 208)
$\widehat{g}_{SAS}^{opt} = 0$	564	11.54 (2.07, 169)	12.32 (1.91, 395)
$\widehat{g}_{Tian}^{opt} = 1$	1189	12.53 (1.99, 587)	12.32 (1.93, 602)
$\widehat{g}_{Tian}^{opt} = 0$	2	8.6 (−, 1)	10.5 (−, 1)
$\widehat{g}_{CALB}^{opt} = 1$	774	12.82 (1.83, 494)	12.51 (1.90, 280)
$\widehat{g}_{CALB}^{opt} = 0$	417	10.94 (2.08, 94)	12.14 (1.94, 323)

received. Overall, we see that, among patients within an estimated subgroup that should be treated with $a, a = 0, 1$, patients that actually received a have better outcomes than patients that did not receive a which gives face validity of the estimated regimes. Table 4 reports the estimated value for each estimated decision rule, that is, the expected potential postoperative hemoglobin had everyone in the population receive treatment according to the decision rule. We observe that the estimated values of the decision rules from SAS and CALB are close with overlapping confidence intervals and much larger than other decision rules. Again, we comment that the confidence intervals are Wald-type confidence intervals based on sandwich variance estimates and do not account for all the uncertainty, for example, the uncertainty due to that decision rules are estimated from the same data. Table 5 shows treatment decisions made by different methods. Although the form of the decision rules from SAS and CALB seems very different, the treatment decisions are actually more similar, with 74% of patients having had consistent treatment decisions from the two methods. Notably, consistent with results in our simulations, the decision rule from SAS is much more complicated than that from CALB, with the decision rule from SAS involving twice as many variables.

Overall, this analyses suggest that, although for most of the patients bivalirudine seems to be the optimal treatment in terms of bleeding risk, there is a large subgroup of patients

TABLE 4
Data analysis results: The estimated value, that is, expectation of potential outcomes, of the estimated optimal treatment decision rules. The first two rows correspond to the two decision rules that assign all patients to heparin or bivalirudine, respectively. The values are estimated using the augmented inverse probability weighted method. Numbers in parenthesis are 95% Wald-type confidence intervals based on sandwich variance estimates

Treatment decision rule	Estimated value
All to Heparin	12.06 (11.80, 12.31)
All to Bivalirudine	12.04 (11.70, 12.38)
ForMMER	11.99 (11.41, 12.56)
SAS	17.28 (16.47, 18.09)
Tian	12.04 (11.69, 12.38)
CALB	16.74 (15.99, 17.49)

TABLE 5
Data analysis results: Cross tabulation of the number of patients in identified subgroups from different methods

	$\widehat{g}_{\mathrm{CALB}}^{\mathrm{opt}} = 1$	$\widehat{g}_{\mathrm{CALB}}^{\mathrm{opt}} = 0$	Row sum
$\widehat{g}_{\mathrm{ForMMER}}^{\mathrm{opt}} = 1$	710	332	1042
$\widehat{g}_{\mathrm{ForMMER}}^{\mathrm{opt}} = 0$	64	85	149
$\widehat{g}_{\mathrm{SAS}}^{\mathrm{opt}} = 1$	544	83	627
$\widehat{g}_{\mathrm{SAS}}^{\mathrm{opt}} = 0$	230	334	564
$\widehat{g}_{\mathrm{Tian}}^{\mathrm{opt}} = 1$	774	415	1189
$\widehat{g}_{\mathrm{Tian}}^{\mathrm{opt}} = 0$	0	2	2
	$\widehat{g}_{\mathrm{SAS}}^{\mathrm{opt}} = 1$	$\widehat{g}_{\mathrm{SAS}}^{\mathrm{opt}} = 0$	
$\widehat{g}_{\mathrm{ForMMER}}^{\mathrm{opt}} = 1$	588	454	1042
$\widehat{g}_{\mathrm{ForMMER}}^{\mathrm{opt}} = 0$	39	110	149
$\widehat{g}_{\mathrm{Tian}}^{\mathrm{opt}} = 1$	627	562	1189
$\widehat{g}_{\mathrm{Tian}}^{\mathrm{opt}} = 0$	0	2	2
$\widehat{g}_{\mathrm{CALB}}^{\mathrm{opt}} = 1$	544	230	774
$\widehat{g}_{\mathrm{CALB}}^{\mathrm{opt}} = 0$	83	334	417

that would benefit from heparin, the traditional and much cheaper treatment. These results likely explain the rise and fall of the bivaridine in practice over time and conflicting results regarding effect of bivalirudine in the literature. To the best of our knowledge, this is the first study that studies the comparative effectiveness of bivalirudine vs. heparin from the perspective of optimal decision rules.

5. Discussion. This article considers the problem of subgroup identification in the presence of a high dimensional set of covariates, where the number of covariates may be greater than the sample size. It proposes a method for simultaneously selecting important prescriptive variables (i.e., variables important for treatment decision making) and estimating subgroups. The proposed method is developed within the doubly robust AIPWE-based classification framework of Zhang et al. (2012b) and Zhang and Zhang (2018b) for estimating the optimal treatment regimes. We further extend and improve the framework by replacing the nonsmooth 0–1 loss function with a smooth logistic loss. This allows convenient and more stable optimization by taking advantage of standard software for (weighted) logistic regression and, importantly, this modification accommodates the use of lasso for prescriptive variable selection. Finally, we propose to couple the lasso selection with a backward elimination process to fine-tune the selection of prescriptive variables. In this article we have focused on decision rules of the linear form. By flexibly choosing the basis functions H_X, this class can accommodate decision rules that are nonlinear in covariates, and it indeed represents a large class of decision rules, that is, rules that are additive in basis functions. When the true optimal decision rule among all possible ones is outside of this class, the target of this methods is still meaningful, namely, the optimal decision rule within a subclass. In practice, this often can approximate the true optimal decision rule well in terms of treatment decisions and values.

The lasso-type penalty has been used in other settings for variable selection (Qian and Murphy (2011), Tian et al. (2014)). We think that the key difference is not in the penalty that is used for variable selection but in within which framework it is used. The most natural framework for lasso would be the outcome-regression framework, where one models the outcome as a function of covariates, treatment and treatment-covaraite interactions. However, this method will inevitably suffer from the well-known problem of outcome-regression-

based methods (e.g., Q-learning), that is, the performance is heavily dependent on the correctness of the specified regression models. This phenomenon is demonstrated by our simulation studies which show that "RegL" has considerably worse performance than other methods when the outcome regression model is incorrect. The method of Tian et al. (2014) also makes use of lasso. As shown by our simulation studies and discussed in Section 3, this method performs well when $C(X) = \eta' H_X$ for some η and when this assumption does not hold it has unsatisfying performance. In contrast, the proposed methods, implemented using a weighted logistic regression with lasso, assumes a much weaker condition, that is, $I\{C(X) > 0\} = I(\eta' H_X > 0)$ for some η. The proposed methods are based on a "classification data set" within a robust classification framework. It aims to minimize (2), with modifications, among all regimes in $\{g(X) : g(X) = I(\eta' H_X > 0)\}$. It has been shown that the minimizer of (2) is the same as the maximizer of the doubly robust AIPWE $E\{Y^*(g)\}$ for $\{g(X) : g(X) = I(\eta' H_X > 0)\}$. Therefore, one can show that the minimizer of (2) is fisher consistent, as along as the doubly robust AIPWE is consistent, that is, when either the propensity score model or the outcome model is correctly specified. As a result, the lasso selection within this robust classification framework is more robust, as shown by our simulation studies.

In addition to robustness, another important property of the proposed methods is that it is able to target selecting prescriptive variables while taking advantage of predictive variables for improving performance, in contrast to SAS. This is possible because, within our framework, the prescriptive variable selection is based on a "classification data set" $(H_{X_i}, \widehat{W}_i, \widehat{Z}_i)$ with $\widehat{W}_i = |\widehat{C}_{\text{AIPWE}}(X_i)|$, $\widehat{Z}_i = I\{\widehat{C}_{\text{AIPWE}}(X_i) > 0\}$, where $\widehat{Z}_i$ is playing the role of the outcome and $\widehat{W}_i$ is a weight, and, in particular, the estimand of $\widehat{C}_{\text{AIPWE}}(X_i)$, that is, $C(X_i)$, contains all and only information relevant for prescriptive variable selection. However, during the outcome regression step in estimating $E\{Y^*(g)\}$ and, equivalently, in constructing $\widehat{C}_{\text{AIPWE}}(X_i)$, all predictive and prescriptive variables are used to try to best estimate $C(X_i)$.

Both the proposed methods and ForMMER are based on the classification framework. Our simulation studies show that the proposed methods significantly outperform ForMMER, leading to decision rules with much higher value and lower rate of incorrect treatment decisions. In addition, they are more stable and show less variability, especially when sample size is small. The improvement is due to methodological improvement of the proposed methods in several aspects, as discussed at the end of Section 3. First, the proposed methods use a smooth logistic loss function other than the zero-one loss used in ForMMER. The use of a smooth loss function greatly stabilizes computation, leading to improved performances. In addition, it allows convenient implementation of the method by taking advantage of standard off-the-shelf software for logistic regression with lasso. The proposed methods and ForMMER also differ in prescriptive variable selection algorithm. The forward selection process used in ForMMER tends to be myopic, in the sense that it looks only one step forward each time, therefore, likely missing the most important combination of variables in the high-dimensional setting. In addition, the way to handle high dimensionality using a screening step in ForMMER is a bit ad hoc. The proposed methods are able to better address this issue by first doing a global search using lasso, a popular and well-studied method for handling variable selection in high-dimensional settings. After the global search among a possibly high-dimensional set of variables, the proposed CALB then zooms in and fine-tunes the selection using backward elimination.

SUPPLEMENTARY MATERIAL

Supplement A: Additional results (DOI: 10.1214/21-AOAS1468SUPPA; .pdf). We provide additional simulation results and a GitHub link to code.

Supplement B: Code (DOI: 10.1214/21-AOAS1468SUPPB; .zip). We provide code for implementing the proposed and comparison methods.

REFERENCES

ANDREOU, C., MANIOTIS, C. and KOUTOUZIS, M. (2017). The rise and fall of anticoagulation with bivalirudin during percutaneous coronary interventions: A review article. *Cardiol Ther* **6** 1–12. https://doi.org/10.1007/s40119-017-0082-x

ATHEY, S. and IMBENS, G. W. (2015). Machine learning methods for estimating heterogeneous causal effects. *Stat* **1050** 1–26.

ATHEY, S. and WAGER, S. (2021). Policy learning with observational data. *Econometrica* **89** 133–161. MR4220385 https://doi.org/10.3982/ecta15732

BARGAGLI STOFFI, F., TORTÚ, C. and FORASTIERE, L. (2020). Heterogeneous treatment and spillover effects under clustered network interference. Available at arXiv:2008.00707.

BARRETT, J. K., HENDERSON, R. and ROSTHØJ, S. (2014). Doubly robust estimation of optimal dynamic treatment regimes. *Stat. Biosci.* **6** 244–260.

BIERNOT, P. and MOODIE, E. E. M. (2010). A comparison of variable selection approaches for dynamic treatment regimes. *Int. J. Biostat.* **6** Art. 6, 20. MR2594878 https://doi.org/10.2202/1557-4679.1178

BRINKLEY, J., TSIATIS, A. and ANSTROM, K. J. (2010). A generalized estimator of the attributable benefit of an optimal treatment regime. *Biometrics* **66** 512–522. MR2758831 https://doi.org/10.1111/j.1541-0420.2009.01282.x

CAVENDER, M. A. and SABATINE, M. S. (2014). Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: A meta-analysis of randomised controlled trials. *Lancet* **384** 599–606.

CHAKRABORTY, B. and MOODIE, E. E. M. (2013). *Statistical Methods for Dynamic Treatment Regimes*. *Statistics for Biology and Health*. Springer, New York. MR3112454 https://doi.org/10.1007/978-1-4614-7428-9

CHEN, S., TIAN, L., CAI, T. and YU, M. (2017). A general statistical framework for subgroup identification and comparative treatment scoring. *Biometrics* **73** 1199–1209. MR3744534 https://doi.org/10.1111/biom.12676

ELGENDY, I. Y. and CAPODANNO, D. (2017). Heparin versus bivalirudin for percutaneous coronary intervention: Has the debate come to an end? *Journal of Thoracic Disease* **9** 4305–4307.

FAN, A., LU, W. and SONG, R. (2016). Sequential advantage selection for optimal treatment regime. *Ann. Appl. Stat.* **10** 32–53. MR3480486 https://doi.org/10.1214/15-AOAS849

FOSTER, J. C., TAYLOR, J. M. G. and RUBERG, S. J. (2011). Subgroup identification from randomized clinical trial data. *Stat. Med.* **30** 2867–2880. MR2844689 https://doi.org/10.1002/sim.4322

GUNTER, L., CHERNICK, M. and SUN, J. (2011). A simple method for variable selection in regression with respect to treatment selection. *Pak. J. Stat. Oper. Res.* 7(2–Sp).

GUNTER, L., ZHU, J. and MURPHY, S. A. (2011). Variable selection for qualitative interactions. *Stat. Methodol.* **8** 42–55. MR2741508 https://doi.org/10.1016/j.stamet.2009.05.003

KOSOROK, M. R. and MOODIE, E. E. M., eds. (2016). *Adaptive Treatment Strategies in Practice*: *Planning Trials and Analyzing Data for Personalized Medicine*. *ASA-SIAM Series on Statistics and Applied Probability*. SIAM, Philadelphia, PA. MR3450070

LU, W., ZHANG, H. H. and ZENG, D. (2013). Variable selection for optimal treatment decision. *Stat. Methods Med. Res.* **22** 493–504. MR3190671 https://doi.org/10.1177/0962280211428383

LUEDTKE, A. R. and VAN DER LAAN, M. J. (2016). Statistical inference for the mean outcome under a possibly non-unique optimal treatment strategy. *Ann. Statist.* **44** 713–742. MR3476615 https://doi.org/10.1214/15-AOS1384

MOODIE, E. E. M., RICHARDSON, T. S. and STEPHENS, D. A. (2007). Demystifying optimal dynamic treatment regimes. *Biometrics* **63** 447–455. MR2370803 https://doi.org/10.1111/j.1541-0420.2006.00686.x

MURPHY, S. A. (2003). Optimal dynamic treatment regimes. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **65** 331–366. MR1983752 https://doi.org/10.1111/1467-9868.00389

PERDONCIN, E., ZHANG, M., RIBA, A., LALONDE, T. A., GRINES, C. L. and GURM, H. S. (2013). Impact of worsening renal dysfunction on the comparative efficacy of bivalirudin and platelet glycoprotein IIb/IIIa inhibitors: Insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Circulation*: *Cardiovascular Interventions* **6** 688–693.

QIAN, M. and MURPHY, S. A. (2011). Performance guarantees for individualized treatment rules. *Ann. Statist.* **39** 1180–1210. MR2816351 https://doi.org/10.1214/10-AOS864

ROBINS, J., ORELLANA, L. and ROTNITZKY, A. (2008). Estimation and extrapolation of optimal treatment and testing strategies. *Stat. Med.* **27** 4678–4721. MR2528576 https://doi.org/10.1002/sim.3301

SHI, C., LU, W. and SONG, R. (2020). Breaking the curse of nonregularity with subagging—inference of the mean outcome under optimal treatment regimes. *J. Mach. Learn. Res.* **21** Paper No. 176, 67. MR4209462

SHI, C., SONG, R. and LU, W. (2019). On testing conditional qualitative treatment effects. *Ann. Statist.* **47** 2348–2377. MR3953454 https://doi.org/10.1214/18-AOS1750

SONG, R., KOSOROK, M., ZENG, D., ZHAO, Y., LABER, E. and YUAN, M. (2015). On sparse representation for optimal individualized treatment selection with penalized outcome weighted learning. *Stat* **4** 59–68. MR3405390 https://doi.org/10.1002/sta4.78

TIAN, L., ALIZADEH, A. A., GENTLES, A. J. and TIBSHIRANI, R. (2014). A simple method for estimating interactions between a treatment and a large number of covariates. *J. Amer. Statist. Assoc.* **109** 1517–1532. MR3293607 https://doi.org/10.1080/01621459.2014.951443

TSIATIS, A. A., DAVIDIAN, M., HOLLOWAY, S. T. and LABER, E. B. (2019). *Dynamic Treatment Regime: Statistical Methods for Precision Medicine*. Chapman & Hall.

WAGER, S. and ATHEY, S. (2018). Estimation and inference of heterogeneous treatment effects using random forests. *J. Amer. Statist. Assoc.* **113** 1228–1242. MR3862353 https://doi.org/10.1080/01621459.2017.1319839

WANG, L., ZHOU, Y., SONG, R. and SHERWOOD, B. (2018). Quantile-optimal treatment regimes. *J. Amer. Statist. Assoc.* **113** 1243–1254. MR3862354 https://doi.org/10.1080/01621459.2017.1330204

ZHANG, B. and ZHANG, M. (2018a). Variable selection for estimating the optimal treatment regimes in the presence of a large number of covariates. *Ann. Appl. Stat.* **12** 2335–2358. MR3875703 https://doi.org/10.1214/18-AOAS1154

ZHANG, B. and ZHANG, M. (2018b). C-learning: A new classification framework to estimate optimal dynamic treatment regimes. *Biometrics* **74** 891–899. MR3860710 https://doi.org/10.1111/biom.12836

ZHANG, B. and ZHANG, M. (2022). Supplement to "Subgroup identification and variable selection for treatment decision making." https://doi.org/10.1214/21-AOAS1468SUPPA, https://doi.org/10.1214/21-AOAS1468SUPPB

ZHANG, B., TSIATIS, A. A., LABER, E. B. and DAVIDIAN, M. (2012a). A robust method for estimating optimal treatment regimes. *Biometrics* **68** 1010–1018. MR3040007 https://doi.org/10.1111/j.1541-0420.2012.01763.x

ZHANG, B., TSIATIS, A. A., DAVIDIAN, M., ZHANG, M. and LABER, E. (2012b). Estimating optimal treatment regimes from a classification perspective. *Stat* **1** 103–114. MR4027418 https://doi.org/10.1002/sta.411

ZHAO, Y., ZENG, D., RUSH, A. J. and KOSOROK, M. R. (2012). Estimating individualized treatment rules using outcome weighted learning. *J. Amer. Statist. Assoc.* **107** 1106–1118. MR3010898 https://doi.org/10.1080/01621459.2012.695674