Easy-to-use tool for evaluating the elevated acute kidney injury risk against reduced cardiovascular disease risk during intensive blood pressure control

Mikko S. Venäläinen[a], Riku Klén[a], Mehrad Mahmoudian[a,b], Olli T. Raitakari[c,d,e], and Laura L. Elo[a]

Objective: The Systolic Blood Pressure Intervention Trial (SPRINT) reported that lowering SBP to below 120 mmHg (intensive treatment) reduced cardiovascular morbidity and mortality among adults with hypertension but increased the incidence of adverse events, particularly acute kidney injury (AKI). The goal of this study was to develop an accurate risk estimation tool for comparing the risk of cardiovascular events and adverse kidney-related outcomes between standard and intensive antihypertensive treatment strategies.

Methods: By applying Lasso regression on the baseline characteristics and health outcomes of 8760 participants with complete baseline information in the SPRINT trial, we developed predictive models for primary cardiovascular disease (CVD) outcome and incidence of AKI. Both models were validated against an independent test set of the SPRINT trial (one third of data not used for model building) and externally against the cardiovascular and renal outcomes available in Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial, consisting of 4733 participants with type 2 diabetes mellitus.

Results: Lasso regression identified a subset of variables that accurately predicted the primary CVD outcome and the incidence of AKI (areas under receiver-operating characteristic curves 0.70 and 0.77, respectively). Based on the validated risk models, an easy-to-use risk assessment tool was developed and made available as an easy-to-use online tool.

Conclusion: By predicting the risks of CVD and AKI at baseline, the developed tool can be used to weigh the benefits of intensive versus standard blood pressure control and to identify those who are likely to benefit most from intensive treatment.

Keywords: acute kidney injury, antihypertensive agents, cardiovascular diseases, clinical decision support, hypertension, machine learning

Abbreviations: ACCORD-BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GUI, graphical user interface; SPRINT, Systolic Blood Pressure Intervention Trial

INTRODUCTION

The Systolic Blood Pressure Intervention Trial (SPRINT) reported recently that aiming for a SBP of less than 120 mmHg (intensive treatment) resulted in significantly lower rates of fatal and nonfatal cardiovascular disease (CVD) outcomes than the commonly recommended target of less than 140 mmHg (standard treatment) among nondiabetic adults at high risk for cardiovascular events [1]. However, significantly higher rates of serious adverse events [hypotension, syncope, electrolyte abnormalities, and acute kidney injury (AKI) or failure] were reported in the intensive than in the standard treatment group. The most significant difference between the two treatment strategies was observed in the incidence rates of AKI or acute renal failure, which are common complications in hospitalized patients and are associated with increased mortality rates, longer hospital stays, and increasing costs [2,3]. For optimal treatment outcomes, it is therefore crucial to identify the individuals at high risk for serious adverse events to maximize the benefit from intensive treatment of hypertension.

Recently, models trained using data from the SPRINT trial have been introduced to predict individualized risk of major cardiovascular events and serious adverse events for standard and intensive antihypertensive treatment strategies [4–6]. For serious adverse events, three models have been introduced, all of which consider only the composite outcome of all treatment-related serious adverse events. As different risk factors are likely related to different types of adverse events, this approach may compromise the prediction accuracy of individual adverse outcomes. Other limitations of previous studies include lack of proper

Journal of Hypertension 2020, 38:511–518

[a]Turku Bioscience Centre, University of Turku and Åbo Akademi University, [b]Department-Department of Future Technologies, [c]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, [d]Centre for Population Health Research, University of Turku and Turku University Hospital and [e]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland

Correspondence to Laura L. Elo, PhD, Turku Bioscience Centre, University of Turku and Åbo Akademi University, Tykistökatu 6 A, FI-20520 Turku, Finland. Tel: +358 50 468 0795; e-mail: laura.elo@utu.fi

Received 26 March 2019 **Revised** 17 September 2019 **Accepted** 20 September 2019

DOI:10.1097/HJH.0000000000002282

evaluation of the discrimination performance of the models in an independent test set and/or lack of practical implementation of the models.

The aim of this study was to develop an easy-to-use comparison tool for CVD and AKI risk based on the SPRINT trial data. In contrast to the previous risk prediction models for general treatment-related serious adverse events, we aimed at an accurate risk prediction model specifically designed for AKI. To ensure ease of use of the risk models in clinical practice, we aimed at a minimum number of variables needed for accurate predictions and made the developed risk comparison tool available online with an intuitive graphical user interface (GUI).

METHODS

Study cohort

SPRINT (November 2010–August 2015, ClinicalTrials.gov: NCT01206062) was a multicenter clinical trial sponsored by the National Institutes of Health to compare two antihypertensive treatment strategies and their effects on cardiovascular and renal outcomes [1]. In SPRINT, a total of 9361 nondiabetic participants with an increased CVD risk were randomly assigned to either standard or intensive antihypertensive treatment. The design, eligibility, and baseline characteristics of the SPRINT participants are publicly available [7] and the data on the primary outcomes are available on request from the National Heart, Lung and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC, https://biolincc.nhlbi.nih.gov/). Here, the patient-level SPRINT data were obtained after approval from The Ethics Committee of the University of Turku. In the current study, we restricted the cohort to participants with a complete set of baseline characteristics ($N = 8760$). For model validation, we randomly divided the data into a training set ($N = 5840$, two thirds of the data) and an independent test set ($N = 2920$, one third of the data).

In addition to validation within the SPRINT cohort, we evaluated the performance of our models against the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) clinical trial (January 2001–June 2009, ClinicalTrials.gov: NCT00000620), which had a similar study design to SPRINT but involved only participants with type 2 diabetes mellitus ($N = 4733$) [8,9]. The data from the ACCORD-BP trial are available by request at BioLINCC.

Study variables and outcomes

We examined the association between the baseline characteristics of the SPRINT participants and the occurrence of primary composite CVD outcome [the first occurrence of myocardial infarction (MI), acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes] and the occurrence of AKI or acute renal failure (coded if the diagnosis was listed in the hospital discharge summary and was reported by the safety officer to be one of the top three reasons for admission or continued hospitalization) [1], here referred to simply as AKI outcome. The available baseline variables included both demographic data such as age, sex, and race, as well as clinical and laboratory data such as BMI, baseline blood pressure (BP), and serum creatinine. A complete list of descriptive baseline characteristics used for predictive modeling is presented in Table 1. Features derived using other available quantities, including estimated glomerular filtration rate (eGFR) and Framingham 10-year CVD risk score, were excluded from the model training. Due to strongly skewed distribution of urine albumin to creatinine ratios, the reported values were $\log_{10}$-transformed before use.

In the ACCORD-BP dataset, the primary composite CVD outcome was defined as the first occurrence of MI, stroke, or death from cardiovascular causes. No information about AKI events with the same definition as in SPRINT was available and hence the performance of our risk prediction model was tested against other relevant, predefined outcomes related to kidney function, referred to as nephropathy outcomes: serum creatinine doubling or a decrease of more than 20 ml/min in eGFR, development of macroalbuminuria (a urine albumin to creatinine ratio >300 mg/g), and renal failure, end-stage renal disease or serum creatinine more than 3.3 mg/dl. In addition, we tested the performance of our model against only those renal failures reported to be attributed to BP medications.

Model building

Binary classification models for the primary CVD outcome and AKI were developed using Lasso penalized logistic regression [10] and the baseline characteristics of the training set. In brief, Lasso is a regression analysis method that aims to maximize the generalizability and prediction accuracy of the models by shrinking some of the model coefficients to zero. Here, to reduce potential instability resulting from the random subsampling when optimizing the model using cross-validation [11,12], the model training was repeated several times to obtain models that were consistent between multiple runs. More in-depth details about the development of the Lasso models can be found in Supplementary Information, http://links.lww.com/HJH/B157.

In addition to Lasso regression, we tested the utility of the gradient boosting algorithm [13,14] to create alternative, more flexible models efficiently utilizing all available variables. Gradient boosting is an ensemble learning technique that is capable of capturing nonlinearities and complex interactions in the data and has demonstrated high performance in a variety of classification tasks [15–17].

All statistical analyses and mathematical modeling were carried out using R statistical computing environment version 3.4.1 (R Core Team, 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Lasso and gradient boosting algorithms were implemented in the R packages *glmnet* [18] and *gbm*, respectively.

Model validation

The performance of all models was evaluated in terms of the area under the receiver operating characteristic curve (AUROC) and were tested both against the independent SPRINT test set that was not used for our model building ($N = 2920$, one third of the data), and the completely independent ACCORD-BP trial dataset ($N = 4733$). Statistical significance of the differences in the AUROC values between the models was determined using the DeLong method [19] implemented in the R package *pROC* [20].

TABLE 1. Baseline characteristics of the Systolic Blood Pressure Intervention Trial participants in the training and test cohorts ($N = 8760$)[a]

Characteristic	Training set		Test set	
	Standard treatment, $N = 2882$	Intensive treatment, $N = 2958$	Standard treatment, $N = 1480$	Intensive treatment, $N = 1440$
Age (years)	67.9 ± 9.5	67.9 ± 9.3	67.9 ± 9.5	68.0 ± 9.5
Female sex – no. (%)	1006 (34.9)	1037 (35.1)	551 (34.8)	538 (37.4)
History of CVD – no. (%)				
Clinical	500 (17.3)	521 (17.6)	247 (16.7)	219 (15.2)
Subclinical	163 (5.7)	167 (5.6)	69 (4.7)	71 (4.9)
Race or ethnic group – no. (%)				
Non-Hispanic black	881 (30.6)	869 (29.4)	470 (31.8)	434 (30.1)
Hispanic	294 (10.2)	321 (10.9)	161 (10.9)	158 (11.0)
Non-Hispanic white	1657 (57.5)	1715 (58.0)	829 (56.0)	809 (56.2)
Other	50 (1.7)	53 (1.8)	20 (1.4)	39 (2.7)
Baseline blood pressure (mmHg)				
SBP	139.8 ± 15.3	139.6 ± 15.8	139.7 ± 15.9	139.8 ± 15.7
DBP	78.2 ± 12.2	78.3 ± 11.9	77.8 ± 11.8	78.0 ± 11.8
Serum creatinine (mg/dl)	1.08 ± 0.34	1.08 ± 0.35	1.08 ± 0.33	1.07 ± 0.34
Ratio of urinary albumin (mg) to creatinine (g)	39.6 ± 149.5	44.1 ± 173.2	44.7 ± 162.4	42.8 ± 188.3
Fasting total cholesterol (mg/dl)	189.4 ± 40.0	189.8 ± 40.9	189.9 ± 41.6	191.5 ± 43.0
Fasting HDL cholesterol (mg/dl)	52.7 ± 14.7	52.5 ± 14.2	52.6 ± 14.5	53.5 ± 14.8
Fasting total triglycerides (mg/dl)	125.5 ± 76.9	124.7 ± 74.2	128.9 ± 88.2	127.1 ± 108.7
Fasting plasma glucose (mg/dl)	98.9 ± 13.2	98.7 ± 13.8	98.8 ± 13.8	99.2 ± 13.8
Statin use – no. (%)	1295 (44.9)	1272 (43.0)	669 (45.2)	608 (42.2)
Aspirin use – no (%)	1460 (50.7)	1519 (51.4)	741 (50.1)	746 (51.8)
Current smoker – no (%)	363 (12.6)	427 (14.4)	207 (14.0)	185 (12.8)
Framingham 10-year CVD risk score (%)	23.3 ± 11.8	23.3 ± 11.7	23.2 ± 11.5	23.1 ± 11.9
BMI (kg/m^2)	29.9 ± 5.8	30.0 ± 5.9	29.8 ± 5.7	29.8 ± 5.7
Antihypertensive agents – no./participant	1.8 ± 1.1	1.9 ± 1.0	1.8 ± 1.0	1.8 ± 1.0

CVD, cardiovascular disease.
[a]Values containing plus–minus sign are means ± SD. There were no significant differences ($P < 0.05$) between training and test cohorts for any variable.

In addition, we identified high-risk and low-risk subgroups according to the predicted, individualized risk scores. The risk thresholds were optimized on the basis of the training cohort using Youden's J statistic, which optimizes the classifier's discrimination ability when equal weight is given to sensitivity and specificity [21,22]. Among several approaches for diagnostic threshold selection, Youden's index is a popular choice as it ties nicely into the ROC framework [23] and has been suggested to be robust to between-study variation [24]. Finally, the time from the beginning of the treatment to the first occurrence of CVD or AKI event was compared between the risk groups. Here, Cox proportional hazards regression, implemented in the R package *survival* [25], was used to estimate the hazard ratios.

Comparison with previously introduced models

The performance of our CVD and AKI models were compared against three recently published prediction models for the primary composite CVD outcome and composite outcome of all treatment-related serious adverse events developed by Patel *et al.* [4], Ferreira *et al.* [5], and Basu *et al.* [6] using data from the SPRINT trial. The previous models were all based on different regression analysis and feature selection methods. However, all previous models include five common variables for both outcomes, namely, age, antihypertensive treatment strategy, current smoking status, serum creatinine, and number of antihypertensive agents, but also a varying number of additional variables such as results from the lipid profile test (i.e. total cholesterol, HDL cholesterol, and triglyceride levels). A more detailed summary of the previously introduced models and their implementation in the current study can be found in Supplementary Information, http://links.lww.com/HJH/B157.

RESULTS

Model development

The Lasso regression modeling identified from the available baseline variables (Table 1) a subset of seven variables that predicted both the primary composite CVD outcome [AUROC 0.72, 95% confidence interval (CI) 0.69–0.75] and AKI (AUROC 0.77, 95% CI 0.73–0.80). These variables included antihypertensive treatment strategy, age, previous history of clinical CVD, current smoking status, number of antihypertensive agents, serum creatinine, and urine albumin to creatinine ratio. The coefficients of CVD and AKI models are summarized in Table 2. All other variables except for the antihypertensive treatment strategy increased the risk of the predicted outcome in both models. Intensive treatment decreased the probability of CVD events, whereas increased the probability of AKI. According to Youden's J statistic, the optimal cutoffs for identifying high-risk individuals for CVD and AKI were event probabilities of 6.1 and 3.1%, respectively.

Validation in the independent Systolic Blood Pressure Intervention Trial test set

After building the models, we first confirmed their performance in the independent test set from the SPRINT cohort (one third of the SPRINT cohort not used for model building). Importantly, the performance of the models in the test

TABLE 2. Coefficients of the Lasso regression models for cardiovascular disease and acute kidney injury

Baseline variable	Coefficient in CVD model	Coefficient in AKI model
Intercept	−6.51	−8.20
Age (per 1 year)	0.03	0.03
History of clinical CVD	0.83	0.51
Current smoking status	0.56	0.53
Serum creatinine (per +1 mg/dl)	0.33	1.06
Urine albumin to creatinine ratio (per 1 log increase)	0.60	0.73
Number of antihypertensive agents	0.11	0.12
Assignment to intensive treatment	−0.31	0.46

The coefficients indicate the impact of 1 unit change in a predictor variable on the response variable when the other predictors are held constant. AKI, acute kidney injury; CVD, cardiovascular disease.

set was similar as in the training set for both CVD and AKI (Table 3). In addition, comparison of the Lasso models to the more complex gradient boosting models showed non-significant differences for both CVD (AUROC 0.70, 95% CI 0.66–0.74, $P = 0.80$) and AKI (AUROC 0.77, 95% CI 0.73–0.83, $P = 0.82$), supporting the use of the simpler Lasso models. Finally, for both Lasso models, the predicted risks matched well with the observed rates (Supplementary Fig. 1, http://links.lww.com/HJH/B157).

Despite of having fewer variables, our CVD model performed similarly as the recently introduced CVD models by Patel *et al.* [4], Ferreira *et al.* [5], and Basu *et al.* [6] (Table 3, Supplementary Fig. 2A, http://links.lww.com/HJH/B157). On the contrary, for predicting the occurrence of AKI, our model performed better than the prediction models for serious adverse outcome (Table 3, Supplementary Fig. 2B, http://links.lww.com/HJH/B157).

Stratification of the participants into high-risk and low-risk subgroups confirmed that participants with high predicted risk for CVD at baseline ($N = 1022$) had significantly higher rates of CVD (hazard ratio = 3.04, 95% CI 2.24–4.12, $P < 0.001$) than those predicted to have low risk (Supplementary Fig. 2C, http://links.lww.com/HJH/B157). In addition, participants with high predicted risk for AKI ($N = 852$) had significantly higher rates of AKI (hazard ratio = 7.25, 95% CI 4.70–11.18, $P < 0.001$) than those predicted to have low risk (Supplementary Fig. 2D, http://links.lww.com/HJH/B157). For comparison, in the entire SPRINT cohort, the hazard ratio for CVD events associated with standard treatment was only 1.32 (95% CI 1.12–1.57, $P < 0.001$) and the hazard ratio for AKI associated with intensive treatment was 1.66 (95% CI 1.32–2.08, $P < 0.001$), highlighting the utility of our risk stratification model in assessing the most suitable antihypertensive treatment strategy for an individual [1].

Validation in the independent Action to Control Cardiovascular Risk in Diabetes Blood Pressure cohort

Our CVD model performed well also in the independent ACCORD-BP cohort (AUROC 0.69), being similar to that of the recently introduced CVD models by Patel *et al.* [4] and Ferreira *et al.* [5] with larger numbers of variables (Table 4, Supplementary Fig. 3A, http://links.lww.com/HJH/B157). As compared with the model by Basu *et al.* [6], our model performed significantly better ($P < 0.001$).

To assess the performance of our AKI model in the ACCORD-BP cohort, we used it to predict all the three available outcomes related to kidney function (refer to the METHODS section). Notably, our model developed for predicting AKI performed well in predicting the incidence of macroalbuminuria (AUROC 0.79), significantly outperforming all of the previously introduced risk models for serious adverse events (Table 4, Supplementary Fig. 3B,

TABLE 3. Discrimination performance in terms of areas under the receiver operating characteristic curve in the independent Systolic Blood Pressure Intervention Trial test set

	CVD		AKI	
Model	AUROC (95% CI)	*P* value	AUROC (95% CI)	*P* value
Our model	0.70 (0.66–0.74)	–	0.77 (0.73–0.82)	–
Patel *et al.*	0.70 (0.66–0.75)	0.39	0.72 (0.67–0.77)	<0.001
Ferreira *et al.*	0.70 (0.66–0.74)	0.10	0.74 (0.69–0.79)	<0.001
Basu *et al.*	0.69 (0.65–0.73)	0.66	0.75 (0.70–0.80)	0.08

The *P* values are reported for comparisons between our model versus the previously introduced risk calculators by Patel *et al.* [4], Ferreira *et al.* [5], and Basu *et al.* [6]. AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CVD, cardiovascular disease.

TABLE 4. Discrimination performance in terms of areas under the receiver operating characteristic curve in the independent Action to Control Cardiovascular Risk in Diabetes Blood Pressure cohort

	CVD		Macroalbuminuria	
Model	AUROC (95% CI)	*P* value	AUROC (95% CI)	*P* value
Our model	0.69 (0.67–0.72)	–	0.79 (0.76–0.81)	–
Patel *et al.*	0.69 (0.66–0.71)	0.42	0.62 (0.58–0.65)	<0.001
Ferreira *et al.*	0.69 (0.66–0.71)	0.90	0.74 (0.71–0.77)	<0.001
Basu *et al.*	0.64 (0.61–0.66)	<0.001	0.60 (0.56–0.64)	<0.001

The *P* values are reported for comparisons between our model versus the previously introduced risk calculators by Patel *et al.* [4], Ferreira *et al.* [5], and Basu *et al.* [6]. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CVD, cardiovascular disease.

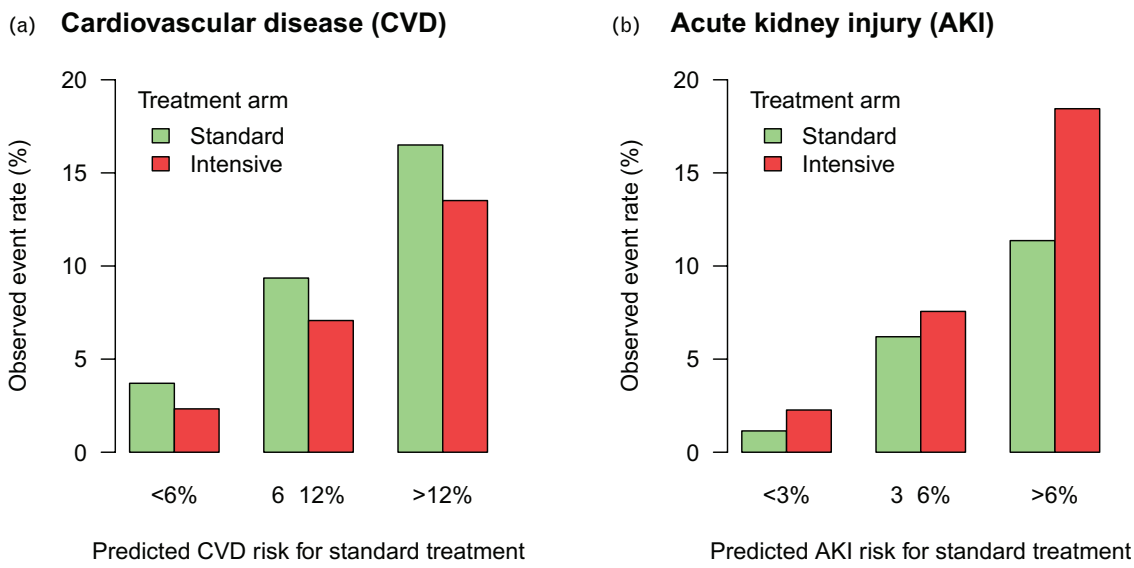

FIGURE 1 Comparison between the predicted risks and the observed event rates of (a) cardiovascular disease and (b) acute kidney injury in the Systolic Blood Pressure Intervention Trial cohort. The participants were divided into three risk groups based on their predicted risks for the standard treatment.

http://links.lww.com/HJH/B157). For the other two nephropathy outcomes (i.e., serum creatinine doubling or a decrease of more than 20 ml/min in eGFR, and renal failure, end-stage renal disease, or serum creatinine of >3.3 mg/dl), the discrimination performance was poor (AUROC less than 0.6) for all models, including our AKI model.

In addition, we tested our AKI model in predicting only the renal failures attributed to BP medications. For this outcome, our model reached good performance (AUROC 0.77, 95% CI 0.55–0.98) and performed better than the models by Patel *et al.* [4] (AUROC 0.68, 95% CI 0.37–1.00, $P = 0.20$), Ferreira *et al.* [5] (AUROC 0.72, 95% CI 0.43–1.00, $P = 0.27$), and Basu *et al.* [6] (AUROC 0.61, 95% CI 0.27–0.94, $P = 0.15$). However, due to low number of these events, the improvement did not reach significance.

The stratification of the participants into high-risk and low-risk subgroups revealed that belonging to the group at high risk of CVD ($N = 1723$) was associated with significantly higher rates of CVD events than the low-risk group (hazard ratio = 3.10, 95% CI 2.56–3.77, $P < 0.001$) (Supplementary Fig. 3C, http://links.lww.com/HJH/B157). Also, belonging to the group at high risk of AKI ($N = 875$) was associated with significantly higher incidence rates of macroalbuminuria than belonging to the low-risk group (hazard ratio = 6.29, 95% CI 4.91–8.06, $P < 0.001$) (Supplementary Fig. 3D, http://links.lww.com/HJH/B157).

Assessing the risks of intensive versus standard treatment

Antihypertensive treatment strategy was identified as an important variable in both the CVD and AKI risk models and can therefore be used as a modifiable risk factor to estimate the effect treatment strategy on both CVD and AKI risk estimates. To illustrate the interpretation of the risk estimates, we compared the predicted risks with the observed risks in the SPRINT cohort. Importantly, the observed and predicted CVD and AKI risks were well in line among the participants assigned to the standard treatment group. Participants assigned to the intensive treatment group showed reduced CVD risk (Fig. 1a), but increased AKI risk (Fig. 1b). Notably, in the subgroup with the highest predicted AKI risk, the observed AKI event rate was nearly doubled in the intensive treatment group compared with the standard treatment group (18 versus 11%).

Online tool for clinical use

To provide an easy-to-use analysis tool for clinicians to enable future assessment of risks and benefits of intensive versus standard BP control, we developed an intuitive GUI using the R package *shiny*. The only information required to estimate the risk of both CVD and AKI of an individual are six pretreatment baseline variables: age, previous history of clinical CVD, current smoking status, number of antihypertensive agents, serum creatinine, and urine albumin to creatinine ratio. The calculator estimates the risks of CVD events and AKI for both intensive and standard treatment (Fig. 2). In addition to the estimated risks, the calculator indicates if the individual is at high-risk for either of the events. To easily compare the effect of the treatment strategy on the risk estimates, the tool also provides the user with a simple risk score plot, illustrating simultaneously the changes in the CVD and AKI risks depending on the treatment. The developed GUI is freely available at the Shinyapps.io (RStudio Inc., Boston, Massachusetts, USA). service-platform (https://elolab.shinyapps.io/ahtriskcalculator/).

DISCUSSION

The current study introduces predictive models for estimating the risk of CVD and AKI events. The models were developed using machine learning algorithms in the SPRINT cohort of nondiabetic adults with hypertension. Both models were validated externally using an independent test set of the SPRINT participants that were not used for model training as well as using a separate ACCORD-BP

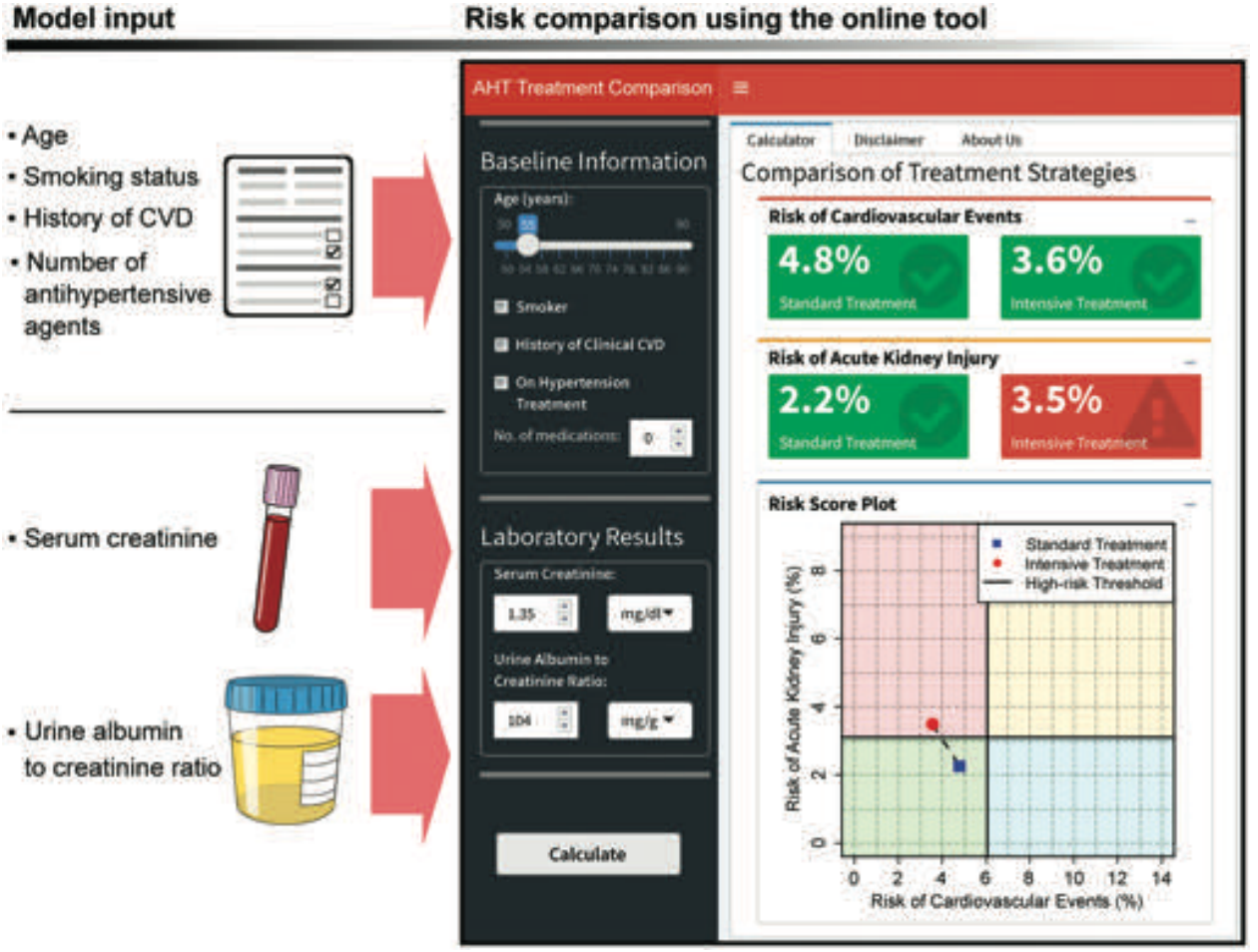

FIGURE 2 An easy-to-use online risk calculator for comparing the risks of cardiovascular disease events and acute kidney injuries between standard and intensive antihypertensive treatment strategies. Based on baseline information on six variables identified as most important for the prediction, the tool returns the absolute risk for both outcomes and treatment strategies. If the estimated risk exceeds the optimal cutoff determined for each outcome, the tool will inform the user about elevated risk with graphical cues. The differences in risk for the two treatment strategies can easily be explored from the acute kidney injury versus cardiovascular disease risk plot.

cohort of adults with type 2 diabetes. Importantly, we identified a subset of only seven variables that most accurately predicted both the CVD and AKI outcomes. In addition to antihypertensive treatment strategy, the identified variables included six easily accessible or measurable baseline variables required for predictions. Finally, a practical online tool was developed based on the validated models to enable easy risk–benefit assessment of intensive versus standard antihypertensive treatment of any new individual.

Hypertension is highly prevalent in adults, affecting over one billion people worldwide [26]. Therefore, finding best antihypertensive treatment strategies is important. Although the recent findings in SPRINT provided evidence of the benefits of a lower SBP target than previously recommended, they also reported significantly higher incidence of adverse events with the intensive treatment [1]. In the current study, we identified a subgroup of individuals where the intensive treatment was associated with increased AKI risk; our model estimated that 38% of the SPRINT participants assigned to intensive treatment were at high risk for AKI. Notably, ~6% of the participants were predicted to have low CVD risk, but high AKI risk, for whom the standard treatment may be a safer option. These at-risk individuals can be identified using our novel predictive tool.

Despite differences in the definition of the primary CVD outcome and participant characteristics between SPRINT and ACCORD-BP cohorts (nondiabetic versus diabetic), our predictive CVD model built using the SPRINT cohort was able to predict major CVD events also in the ACCORD-BP cohort. This suggests that the developed model is applicable for adults both with and without diabetes. This was a somewhat surprising result since the ACCORD-BP study did not find intensive treatment to significantly reduce the rates of primary CVD outcome ($P = 0.20$) [8]. However, it has been suggested that the discrepancies between SPRINT and ACCORD-BP could be explained by the lower statistical power of the ACCORD-BP trial (4733 participants versus 9361 participants in SPRINT) and thus further trials clarifying the benefit of more intensive treatment of hypertension in adults with diabetes are needed [27,28]. Moreover, in a subgroup analysis presented in the appendix of the ACCORD-BP study, a potential interaction ($P = 0.08$) was reported between the intensity of glycemic control and intensive treatment of hypertension on total CVD events,

suggesting a benefit from intensive treatment for individuals with standard glycemic control [8].

The performance of our model for predicting AKI was significantly better than the performance of the previously introduced models for predicting the occurrence of composite serious adverse outcome. This suggests that when predicting individual events, the discrimination performance of a model optimized for predicting composite outcomes may be significantly reduced. Although our AKI model was not specifically developed for nephropathy outcomes reported in ACCORD-BP, it was able to predict the risk of macroalbuminuria and renal failures attributed to BP medications within the cohort. This suggests that our AKI model is able to predict complications related to kidney function also outside the SPRINT cohort. Significantly, it has been reported that albuminuria has a strong independent association with the incidence of AKI [29]. However, due to poor results in predicting the other nephropathy outcomes in ACCORD-BP, which may be explained by the differences in outcome definitions as compared with SPRINT, further comparisons should be carried out to further validate the result.

As compared with the recently published CVD prediction models derived using data from the SPRINT trial [4–6], our new CVD model demonstrated similar performance but with fewer, easily accessible predictors and increasing model usability. This improvement was achieved by the use of Lasso regression and extensive cross-validation during model training to identify the key variables required for generalizable and accurate model predictions. In particular, our results demonstrated that using information from the lipid profile test added only little or no predictive value to the prediction models and could therefore be ignored. Surprisingly, our model performed significantly better than the model by Basu *et al.* [6] in the ACCORD-BP cohort even though similar level of performance was reported in the original study. The underperformance of this model may be due to overfitting to the SPRINT cohort or due to inconsistencies in the used ACCORD-BP data as there was a noticeable difference in the number of current smokers reported in the study by Basu *et al.* [6] (∼1% of the participants) and the original ACCORD-BP study (∼13% of the participants) [8].

The original definition of AKI in SPRINT [1], which was also used in the current study, has potential limitations as compared with other specific conventions of the definitions of AKI (e.g. the Acute Kidney Injury Network (AKIN) or Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [30]). In a more recent study based on the SPRINT trial, all reported AKI events were adjudicated by two nephrologists or physician experts [31]. Even though some of the AKI events were discarded, it did not alter the conclusions of the original study. Therefore, it is expected that our present model is valid also for predicting the adjudicated AKI events. A more accurate definition of AKI or more detailed information about the individual antihypertensive classes hold potential to further improve the model if such data become available in the future. For instance, it is known that patients on diuretics or newly started blockade of the renin–angiotensin system may be more prone to AKI compared with patients on other antihypertensive medications [32].

The prediction models proposed in the current study assume that the relative effect of treatment is the same for everyone. This assumption is supported by the fact that the SPRINT study did not report any significant interactions between the treatment strategy and studied subgroups (e.g., history of CVD) with respect to the primary outcome or death from any cause [1]. In addition, Ferreira *et al.* [5] assessed interactions between the treatment strategy and several candidate predictors for the composite safety outcome that included also AKI, but none were significant. Similarly, our models were compared against models generated using the gradient boosting algorithm, which is able to capture even deep interactions in the data. However, no improved performance over the simpler models was observed.

Even though all the developed models reached good to very good discrimination performance comparable with previous risk calculators in this field (AUROCs between 0.70 and 0.80), it should be noted that some individuals may still be misclassified as having high or low risk of AKI or CVD. Therefore, it is recommended that the risk predictions should only be used to support decision-making alongside the traditional clinical guidelines when the suitability of the intensive antihypertensive treatment in terms of adverse health outcomes is of concern. In these cases, the developed online tool allows for easy checking of the risk levels associated with both treatment strategies.

The current study introduces a practical risk–benefit assessment tool for intensive versus standard BP control and validates it in the SPRINT and ACCORD-BP cohorts. The tool can be applied in clinical practice to help select individuals for intensive BP treatment to gain maximum health benefits and to reduce the risk of adverse events due to AKI.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the National Institutes of Health (NIH) for providing the SPRINT trial dataset and the *New England Journal of Medicine* (*NEJM*) for opening the SPRINT trial challenge. The authors would also like to thank Aidan McGlinchey and Sofia Khan for checking the English language.

L.L.E. reports grants from the European Research Council (ERC) (grant number 677943); the European Union's Horizon 2020 research and innovation programme (grant number 675395); the Academy of Finland (grant numbers 296801, 304995, 310561); Juvenile Diabetes Research Foundation (JDRF) (grant number 2-2013-32); Tekes – the Finnish Funding Agency for Innovation (grant number 1877/31/2016); and Sigrid Juselius Foundation, during the conduct of the study.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, *et al.*, SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.

2. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; 53: 961–973.
3. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. *Am J Kidney Dis* 2007; 50:712–720.
4. Patel KK, Arnold SV, Chan PS, Tang Y, Pokharel Y, Jones PG, *et al*. Personalizing the intensity of blood pressure control. *Circ Cardiovasc Qual Outcomes* 2017; 10:e003624.
5. Ferreira JP, Gregson J, Duarte K, Gueyffier F, Rossignol P, Zannad F, *et al*. Individualizing treatment choices in the systolic blood pressure intervention trial. *J Hypertens* 2018; 36:428–435.
6. Basu S, Sussman JB, Rigdon J, Steimle L, Denton BT, Hayward RA. Benefit and harm of intensive blood pressure treatment: derivation and validation of risk models using data from the SPRINT and ACCORD trials. *PLoS Med* 2017; 14:e1002410.
7. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, *et al*. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials J Soc Clin Trials* 2014; 11:532–546.
8. Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575–1585.
9. Buse JB, The ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol* 2007; 99:S21–S33.
10. Tibshirani R. Regression selection and shrinkage via the Lasso. *J R Stat Soc B* 1996; 58:267–288.
11. Roberts S, Nowak G. Stabilizing the Lasso against cross-validation variability. *Comput Stat Data Anal* 2014; 70:198–211.
12. Bøvelstad HM, Nygård S, Størvold HL, Aldrin M, Borgan Ø, Frigessi A, *et al*. Predicting survival from microarray data – a comparative study. *Bioinformatics* 2007; 23:2080–2087.
13. Friedman JH. Greedy function approximation: a gradient boosting machine. *Ann Stat* 2001; 29:1189–1232.
14. Freund Y, Schapire RE. A decision theoretic generalization of on-line learning and an application to boosting. *Comput Syst Sci* 1997; 57:119–139.
15. Ogutu JO, Piepho H-P, Schulz-Streeck T. A comparison of random forests, boosting and support vector machines for genomic selection. *BMC Proc* 2011; 5:S11.
16. Hirasawa H, Murata H, Mayama C, Araie M, Asaoka R. Evaluation of various machine learning methods to predict vision-related quality of life from visual field data and visual acuity in patients with glaucoma. *Br J Ophthalmol* 2014; 98:1230–1235.
17. Seyednasrollah F, Mäkelä J, Pitkänen N, Juonala M, Hutri-Kähönen N, Lehtimäki T, *et al*. Prediction of adulthood obesity using genetic and childhood clinical risk factors in the cardiovascular risk in young finns study. *Circ Cardiovasc Genet* 2017; 10:e001554.
18. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010; 33:1–22.
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44:837–845.
20. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, *et al*. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; 12:77.
21. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; 3:32–35.
22. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding youden index to discriminate individuals using pooled blood samples. *Epidemiology* 2005; 16:73–81.
23. Perkins NJ, Schisterman EF. The inconsistency of 'optimal' cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol* 2006; 163:670–675.
24. Böhning D, Böhning W, Holling H. Revisiting Youden's index as a useful measure of the misclassification error in meta-analysis of diagnostic studies. *Stat Methods Med Res* 2008; 17:543–554.
25. Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox model*. New York, NY: Springer New York; 2000.
26. World Health Organization. *A global brief on hypertension: silent killer, global public health crisis. World Health Day 2013*. Geneva, Switzerland: World Health Organization; 2013.
27. Sarafidis PA, Lazaridis AA, Ruiz-Hurtado G, Ruilope LM. Blood pressure reduction in diabetes: lessons from ACCORD, SPRINT and EMPA-REG OUTCOME. *Nat Rev Endocrinol* 2017; 13:365–374.
28. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes. *JAMA* 2015; 313:603.
29. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol* 2010; 21: 1757–1764.
30. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J* 2013; 6:8–14.
31. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, *et al*. Effects of intensive blood pressure treatment on acute kidney injury events in the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis* 2018; 71:352–361.
32. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with nonsteroidal anti-inflammatory drugs and risk of acute kidney injury: nested case–control study. *BMJ* 2013; 346:e8525.