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DYNAMIC COMPETING RISK MODEL FOR MULTI-TYPE RECURRENT EVENTS WITH DEPENDENT TERMINATION

ALOKANANDA GHOSH

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A DYNAMIC COMPETING RISK MODEL FOR MULTI-TYPE RECURRENT EVENTS WITH
DEPENDENT TERMINATION

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Cardiovascular disease (CVD), defined by the World Health Organization (WHO) as diseases that involve the heart and/or blood vessels is the number one cause of morbidity and mortality worldwide. In the United States more health care dollars are spent managing and treating CVD and/or its complications than any other disease process. Coronary heart disease (CHD) is the leading cause of deaths (43.8%) attributable to CVD, followed by stroke (16.8%), hypertension (9.4%) and heart failure (HF) (9%). CVD-related deaths and attendant morbidities, which include lifelong disability are in many cases preventable.

This research proposes a dynamic risk model that handles multi-type recurrent events with a dependent terminating event in a competing risk framework, specifically nonfatal MI, stroke and HF, with all-cause mortality (death) as the dependent terminating event. A unique feature of this model is that it directly quantifies the baseline hazard for each recurrent CVD event and death, and the additional hazard that each recurrent event confers to its own recurrence and all other events. Positive and negative associations and relationships between all event types, recurrent and terminating, are established. The baseline hazard is dynamically updated with each event occurrence and affected by the types and number of events up to

that point. The model is validated with a simulation study and applied to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study. A procedure to assess the goodness of fit of the model is detailed.

The model is further extended to incorporate risk factors for MI, stroke, HF and death such that each event type has unique risk factors [intrinsic hazards covariate model 1 (IHCM 1)]. Risk factors for the 4 event types imparted by antecedent nonfatal events is also established [intrinsic and recurrent hazards covariate model (IRHCM)]. Heterogeneity of ALLHAT treatment arm effects (amlodipine vs chlorthalidone; lisinopril vs chlorthalidone) on hazards by subgroup [sex, diabetes, race (black/nonblack), age, kidney disease, atrial fibrillation, hypertension treated at baseline, and stage 1/stage 2 hypertension] is studied (IHCM 2).

Stabilization, fine tuning and validation of the model is performed by supervised learning, utilizing bagged training sets (70% and 60%) and test sets (30% and 40%) of IHCM 1 (250 bagged sets) and IRHCM (200 bagged sets, 70/30 training/test sets). Parameters are tuned and 95% confidence intervals (CI's) constructed by the mean and standard deviation of the estimated parameters of the bagged training sets, respectively. Training set parameters applied to corresponding test sets yield similar and consistent goodness of fit measures for IHCM 1 and IRHCM, which suggests good generalization of the model without overfitting. Given the enormous global burden of CVD, this model is of great clinical import with significant potential to prevent and reduce future CVD events and develop into a risk assessment tool/decision rule, particularly in high-risk patients and delineate optimal treatment strategies tailored to the individual's clinical profile.

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CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Cardiovascular disease

Cardiovascular disease (CVD), defined by the World Health Organization (WHO) as diseases that involve the heart and/or blood vessels is the number one cause of morbidity and mortality worldwide.¹ According to WHO statistics, of the 57 million global deaths in 2008, 17.3 million (30%) were due to CVD, of which 7.3 million were attributed to myocardial infarctions (MI) and 6.2 million were due to strokes.¹ The impact of CVD on human health, quality of life and longevity cannot be overstated. In the United States alone, more health care dollars are spent managing and treating CVD and/or its complications than any other disease process.² In 2015, 2.7 million resident deaths were registered in the United States, and 10 leading causes of death, of which heart disease was number one and stroke was 5th, accounted for 74.2% of those deaths.² Coronary heart disease (CHD) is the leading cause of deaths (43.8%) attributable to CVD, followed by stroke (16.8%), hypertension (9.4%) and heart failure (HF) (9%). Deaths and attendant morbidities that arise from CVD are in many cases preventable.^{1,2}

According to the latest figures from the American Heart Association (AHA)², by 2035 over 135 million adults in the United States (45.1%) are projected to have CVD of some type, and total costs of CVD are expected to reach \$1.1 trillion, with direct medical costs projected to reach \$748.7 billion and indirect costs \$368 billion.

Subtypes, pathophysiology and risk factors

There are two main types of CVD. The first type is due to atherosclerosis¹ and includes coronary artery disease (CAD)/ischemic heart disease, cerebrovascular disease such as stroke, and diseases of the aorta and arteries, which include hypertension and peripheral vascular

disease. The second type of CVD includes congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias.¹⁻³ Atherosclerotic CVD is much more common and furthermore, deaths due to myocardial infarction (MI) and stroke comprise the vast majority of CVD deaths.¹⁻³ The vast majority of strokes are ischemic (87%), and the remainder hemorrhagic, which is secondary to rupture of a blood vessel that is usually secondary to hypertension.²

Atherosclerosis is the underlying disease process that results in MI and the vast majority of strokes. The pathophysiology of atherosclerosis is complex, and a brief summary will be presented here. Atherosclerosis is an inflammatory process that affects medium and large vessels.^{1,3} The endothelium of these vessels, when exposed to elevated levels of low-density lipoprotein (LDL) particles and other substances such as free radicals, becomes permeable to lymphocytes and monocytes. These cells migrate into the intimal layer (second layer, just below the endothelium) of the blood vessel. LDL particles are further attracted to this site due to a series of reactions, and are engulfed by the monocytes, which then transform into macrophages (foam cells). Smooth muscle cells migrate to the site from the tunica media (the deeper layer of the vessel, below the intimal layer). A fibrous cap eventually forms, consisting of smooth muscle and collagen. The foam cells begin to die, which forms a necrotic core that is covered by the fibrous cap. These lesions are known as atheromatous plaques, and they enlarge as cells and lipids continue to accumulate in them. The plaque begins to bulge into the vessel lumen, and as the process continues, the fibrous cap thins out, accompanied by fissuring of the endothelial surface of the plaque. This plaque may rupture, and when it does, lipid fragments and cellular debris are released into the vessel lumen. These fragments and debris are exposed to thrombogenic agents on the endothelial surface, which starts a cascade that results in a thrombus, or blood clot. If the

thrombus is large enough, and it results in blockage of a coronary artery or cerebral artery, it causes an MI or stroke, respectively.^{1,3}

HF occurs when an abnormality of cardiac function results in failure to provide adequate blood flow, or perfusion to meet the body's metabolic needs, specifically of tissues and organs. HF also occurs when there is an excessive rise in cardiac filling pressures.³ In the United States, the leading cause of heart failure (HF) is ischemic heart disease.³ The AHA² reports that according to NHANES data from 2011 to 2014, an estimated 6.5 million Americans aged 20 and above had HF, which is an increase from the 5.7 million reported from 2009 to 2012. AHA projects that the prevalence of HF will increase 46% from 2012 to 2030. In 2012, total cost for HF was an estimated \$30.7 billion of which 68% was attributed to direct medical costs. Recurrent hospitalizations after HF diagnosis is a significant source of health care expenditures; additionally, physician office visits and ED visits for HF also contribute to costs.²

Key ALLHAT CVD findings

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a landmark clinical trial that sought to determine whether incidence of fatal CHD or nonfatal MI was lower for high-risk hypertensive patients treated with a calcium channel blocker (CCB) or an angiotensin converting enzyme (ACE) inhibitor as compared to treatment with chlorthalidone, a thiazide diuretic.⁴⁻⁶ Diuretic are less expensive than CCB's and ACE inhibitors; the treatment and complications of hypertension are a significant source of health care costs.² Appropriate treatment of hypertension is imperative given its significant role in CVD, both as a subtype of CVD and as a precipitator of other CVD processes. ALLHAT results showed that incidence of fatal CHD and nonfatal MI combined did not differ between the treatment

groups, and similarly, all-cause mortality also did not differ between the treatment groups. HF was a secondary outcome in ALLHAT; both amlodipine and lisinopril had a higher 6-year rate of HF than chlorthalidone. Lisinopril had a higher 6-year rate of stroke compared to chlorthalidone as well. Chlorthalidone also performed well in controlling hypertension; it outperformed both amlodipine and lisinopril in controlling systolic blood pressure (SBP) at the 5-year mark.⁴ A later paper by Cushman et al.⁶ examined post-trial ALLHAT results 8-13 years post-randomization and found similar results for the primary endpoint of combined fatal CHD and nonfatal MI; there were no significant differences between the 3 treatment arms. For secondary outcomes, amlodipine had higher HF hazard and lisinopril had higher stroke hazard compared to chlorthalidone.⁶

These important findings from ALLHAT underscore the importance of both the initial incidence of CVD, e.g. MI, stroke or HF, and later incidence of these disease processes in that individual. All three disease processes are recurrent; each individual who does not die from the first manifestation of the disease has the likelihood – usually an increased likelihood according to the natural history of the disease – of having it recur. A thorough study of MI, stroke and HF recurrent events in the full cohort of ALLHAT participants randomized to the 3 treatment arms ($n = 33,357$) has never been conducted. Such a study would yield valuable insight into the optimal treatment and important risk factors for high-risk hypertensive individuals - not only to prevent the first occurrence of disease, but also to prevent further recurrences and ultimately, death.

Multi-type recurrent events

The statistical methodology and analysis of recurrent events in survival and longitudinal data in various clinical settings has been explored in the literature. In recurrent events data, an

event of interest can occur more than once in the same individual under observation. Multi-type recurrent events refer to the situation in which more than one particular event type can occur in the same individual, and that event type can occur more than once. These multiple types of recurrent events may or may not be associated, or correlated with one another.⁷ Additionally, multi-type recurrent events may have an accompanying terminal event, such as death, after which no further events can occur. This terminal event may or may not be related to the recurrent events.⁷

Cook and Lawless⁷ included a chapter on various approaches for multi-type recurrent events, including intensity-based models, random effects models, rate and mean functions, and multistate models. These models can be extended to the multivariate case to include covariates associated with the events themselves, and which may explain relationships between the different event types. Furthermore, these models can also be extended to handle a dependent or independent terminal event. Intensity-based models are flexible; they can be modified to capture possible associations between multiple event types if event types are related, and to potentially handle multiple event types in conjunction with a co-occurring dependent termination process such as death. However, the authors suggest that parsimonious models are preferred in this context so the number of covariates may be limited and characterizing the associations between event types can be challenging. Random effects models are also flexible, but may require some specification of the variance-covariance matrix of the component random effects to describe associations between different event types, and may prove challenging to estimate depending on the likelihood function and optimization method.⁷ Multistate models are

not ideal for multi-type recurrent events as too many states are likely to appear which significantly increases computational burden.⁷

Numerous authors have proposed and utilized recurrent events models in various clinical settings for single-type and multi-type recurrent events with and without (possibly dependent) termination. Clegg, Cai and Sen⁸ proposed a multivariate marginal mixed baseline hazards model and applied the model to analyze two types of recurrent events: coronary heart disease (CHD) and cerebrovascular accident (CVA) in individuals from the Framingham Heart Study. The sampling unit was a cluster, i.e. family unit (for example, a married couple with children). The study utilized different baseline hazards for recurrent events CHD and CVA, and identical baseline hazard for siblings. A strength of the study was the ability to avoid imposing specific dependence structures on the different recurrent event types that are usually required in most frailty models. However, an important drawback of this model and study is that it did not account for death as a dependent termination event⁸; both CHD and CVA are known to increase mortality.¹⁻³

Mazroui et al.⁹ utilized a multivariate frailty model for two types of recurrent events and their association with each other, and with a dependent terminal event in the setting of breast cancer. They proposed two estimation models for their model: likelihood maximization for models with a parametric piecewise constant baseline hazard function and maximization of the penalized likelihood for models with baseline hazard functions approximated by M-splines. The two recurrent event types were locoregional and metastatic relapse after breast cancer diagnosis. A major strength of their model is that the two recurrent event processes may not be independent or conditional on frailties and covariates; thus, the related processes of the two types of recurrent relapse after breast cancer diagnosis are accounted for, along with death as

the dependent, terminating event. Details of their parameter estimation procedures and model diagnostics/validation can be found in the paper.⁹

Zhu et al.¹⁰ proposed a joint modeling approach of semiparametric transformation models that was an extension of previous models for univariate recurrent and terminal events, to handle multivariate, multi-type recurrent events in the setting of a dependent terminal event. The EM algorithm was utilized for maximum likelihood estimation of parameters. They applied their model in the setting of childhood cancer survival, with the two recurrent event types being (1) recurrence of the original cancer and (2) occurrence of new cancers, and death being the dependent terminal event. Cai and Shaubel¹¹ developed a class of semi-parametric marginal means/rates regression models for multi-type recurrent events (hospitalizations and physician office visits) in the setting of childhood asthma outcomes; however, their model does not account for a potentially dependent terminal event, nor provide inferences on the possible correlation structures between event types.

Chen and Cook¹² utilized cumulative mean functions for multi-type recurrent events with dependent termination (death) by conducting separate marginal analyses, with each analysis focusing on one recurrent event type. They applied their methods to patients with breast cancer metastasis to bone experiencing multiple types of skeletal complications, and the effect of bisphosphonate therapy on such recurrences. A subsequent paper by Chen et al.¹³ developed methods based on marginal models for multi-type interval-censored recurrent events, i.e. when the precise event times are unobserved, but the event is known to have occurred within a certain time interval. They utilized the Gibbs sampling algorithm to aid in model fitting and inference.

For single-type recurrent events approaches in multiple clinical scenarios, we refer to Chang, Chan and Kapadia ¹⁴; Lin, Wei, Yang, et al.¹⁵ Ghosh and Lin ¹⁶; Liu, Wolfe and Huang ¹⁷; Yu and Liu ¹⁸; Belot, Rondeau, Remontet, et al.¹⁹ and Maugen, Rachet, Mathoulin-Pelissier, et al.²⁰

Recurrent events in CVD

There are very few studies that examine the multi-type recurrent events process with death as the dependent terminal event in the important clinical setting of cardiovascular disease. A recent paper by Lin, Luo, Chen, et al.²¹ proposed a model that handles multi-type recurrent events with dependent termination in the setting of cardiovascular disease on a smaller subset of the ALLHAT clinical trial (ALLHAT-LLT). Theirs is a multivariate joint frailty model with nonparametric covariate functions in a Bayesian inference framework. They used the cubic-B-spline basis for their nonparametric covariate functions, and Bayesian inference based on Markov Chain Monte Carlo (MCMC) to estimate the parameters. They compared the performance of three models in simulation studies: the joint model, the reduced model (the recurrent and terminal events were modeled independently) and the parametric model (the nonparametric covariate functions were modeled as linear functions). For their datasets, they generated two types of recurrent events and a terminal event in two different simulation settings. For simulation setting I there was no correlation between multi-type recurrent events and the terminal event. For setting II there was a positive correlation between recurrent events and the terminal event such that the subjects with higher risks of recurrent events were at higher risk of the terminal event. The joint model performed well in both simulation settings; in the first setting of independent termination (consistent with the reduced model), the joint model performed comparably to the reduced model, and in the second setting of dependent termination, the joint

model markedly outperformed the reduced model. The joint and reduced models outperformed the parametric models in both simulation settings. When they applied all three models to the ALLHAT-LLT data, the models' performances were similar to that of the simulations. Their key findings included significant positive correlation between risk of CHD and stroke, and risk of CHD and heart failure conditional on the observed risk factors. This suggests that subjects with one type of CVD event are very likely to experience another type of CVD as compared to those without. They also found that risks of recurrent CHD were positively associated with death/all-cause mortality conditional on the observed risk factors, although stroke and HF did not show significant correlation with death. For further details on their statistical models, simulation studies and ALLHAT-LLT results, we refer to Lin, Luo, Chen, et al.²¹

We wanted to develop a new statistical model for multi-type recurrent events with a dependent terminal event that can characterize the possible relationships between the different event types and the relationship of each event type with the terminal event. Furthermore, we wanted our model to be easily extended to the multivariate case such that covariates can be included. We aim for our model to be straightforward in its derivation and implementation, and flexible and adaptable to a variety of clinical settings. Our proposed statistical model is motivated by the ALLHAT clinical trial, specifically the in-trial cohort randomized to the treatment arms chlorthalidone, amlodipine and lisinopril.^{4,5}

Public health and clinical significance

CVD is one of the most important clinical and public health problems of our time, bar none. Prevention of CVD by identifying important risk factors and optimal treatment strategies once CVD has developed in an individual would go a long way towards reducing the burden of

disease and mortality, both globally and right here in the United States. Health care costs of CVD would be reduced in a significant way. A key component of CVD prevention and effective management is to not only reduce the incidence of first disease, but also recurrent disease processes that are related to the first. MI and stroke are acute, often severe and life-threatening manifestations of CVD that have an underlying, shared component of atherosclerosis, upon which plaque rupture and the subsequent cascade of events that leads to thrombus formation in the artery is the precipitating event.^{1,3} HF is known to have MI and coronary heart disease (CHD) as one of its main causes³ and is a chronic disease process with acute exacerbations that may be severe and life-threatening. We believe that studying these three particular related disease processes that are recurring and comprise such a huge portion of CVD burden in the statistical framework of multi-type recurrent events with dependent termination, in this case death i.e. all-cause mortality, is urgently needed.

Aims and objectives

Aim 1: To derive and develop a statistical model to describe dynamic risk of multi-type recurrent events in a competing risk framework.

Aim 2: Apply the model specifically to examine the competing risks of three types of recurrent CVD events: MI, stroke, and heart failure (HF) in the ALLHAT dataset and the dependent terminating event, death.

Aim 3: Utilize the model to identify and quantify important clinical risk factors and treatment options for each of the three multi-type recurrent events, and death.

Aim 4: Develop a supervised learning approach for parameter tuning with variable selection, model stabilization and model validation.

CHAPTER 2: JOURNAL ARTICLE 1

A dynamic competing risk model for multi-type recurrent events with dependent termination

Abstract

Multi-type recurrent events are a common feature of longitudinal studies. In many cases, there is a terminating event such as death, after which no further events can occur. The terminating event may or may not be associated with the recurrent events. We propose a dynamic risk model that handles multi-type recurrent events with a dependent terminating event in a competing risk framework. A unique feature of our model is that it directly provides the baseline hazard for each type of recurrent event and the terminating event, and the additional hazard that each recurrent event confers to all other events. In this manner, positive and negative associations and relationships between all event types, recurrent and terminating, are established. The baseline hazard is dynamically updated with each event occurrence, and is affected by event history (the number and types of past events) and covariates. We validate our model with a simulation study. The model is applied to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study and the findings described. Furthermore, a procedure developed to assess goodness of fit of the model is detailed. We provide a discussion of the results and their clinical implications.

Keywords: baseline hazard; competing risk; multi-type recurrent events; dependent termination; cardiovascular disease

1. Introduction

Recurrent events, where one or more types of events can occur repeatedly in the same individual are a common feature of longitudinal studies. Examples of single-type recurrent events include cancer relapses, chronic obstructive pulmonary disease (COPD) exacerbations, recurring opportunistic infections and recurrent heart failure (HF) episodes. Multi-type recurrent events refer to the situation in which more than one particular event type can occur in the same individual, and that event type can occur more than once. Such multiple types of recurrent events may or may not be associated or correlated with one another. In both single-type and multi-type recurrent events, death from any cause will be a terminating event after which no further events can occur. The terminating event may be associated with preceding events; for example, it is known that nonfatal myocardial infarction (MI), nonfatal stroke and nonfatal HF individually increase the risk of subsequent death.¹

Recurrent events models are widely reported in the literature. For single-type recurrent events models in various clinical scenarios, we highlight the works of Lin *et al.*,² Chang *et al.*,³ Ghosh and Lin,⁴ Liu *et al.*,⁵ Yu and Liu,⁶ Belot *et al.*⁷ and Maugen *et al.*⁸ For multi-type recurrent events, Cook and Lawless⁹ included a chapter on various approaches, including intensity-based models, random effects models, rate and mean functions, and multistate models. An important aspect of multi-type recurrent events models in particular is their ability to characterize potential associations between recurrent events; an event can increase the risk of a subsequent event of the same type, or of a different type, or both. Furthermore, such a model should also characterize the association between each type of recurrent event and a dependent terminal event if it exists.

In clinical contexts, the dependent terminal event is usually death. We briefly mention several models that meet these demands here.

Zhu *et al.*¹⁰ proposed a joint modeling approach of semiparametric transformation models that was an extension of previous models for univariate recurrent and terminal events, in the setting of childhood cancer survival with the two recurrent event types being recurrence of the original cancer and occurrence of new cancers, and death being the dependent terminal event. Mazroui *et al.*¹¹ utilized a multivariate frailty model for two types of recurrent events and their association with each other, with death as the dependent terminal event in the setting of breast cancer. Lin *et al.*¹² proposed a multivariate joint frailty model with nonparametric covariate functions in a Bayesian inference framework that handles coronary heart disease (CHD), stroke and HF as multi-type recurrent events with death as the dependent terminating event.

The baseline hazards of events, including recurrent events are often of significant interest in longitudinal studies. The semi-parametric Cox proportional hazards model reduces to the product limit estimate in the case of no covariates, which provides an estimate of the baseline hazard function as a straightforward transformation of the survival function.¹³ Breslow¹⁴ provided a similar estimate. However, these approaches do not address baseline hazard functions for recurrent events. Furthermore, parametric baseline hazard functions for recurrent events may be desired in certain situations. To our knowledge, there has not been to date a multi-type recurrent events model that can accomplish the following: 1) directly quantify the specific baseline hazard, or absolute risk, that each nonfatal event confers on itself to recur, every other nonfatal event of interest to occur or recur in future, and death (the terminating event) to occur;

2) update the baseline hazard of every nonfatal event and death with the occurrence of each nonfatal event; 3) express the dynamic risk of each nonfatal event and death as an accumulation of separate, unique baseline hazards that arise from the event history, which yields new information and insights into the clinical problem being studied. In this paper, we show that our model, motivated by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study meets these objectives and several additional ones. Throughout this paper, we will use the terms hazard and risk interchangeably.

The remainder of this paper is organized as follows. In Section 2, we introduce our multi-type recurrent events model with a dependent terminal event. Statistical inference of the model parameters and numerical approaches are described in Section 3. In Section 4, we present a simulation study that validates our estimation methods. Section 5 details the application of our model to the landmark ALLHAT clinical trial. We provide discussion of our results and state our conclusions in Section 6.

2. Model

2.1 Model Formulation

Let T_M , T_S , T_H and T_D be the times at which the next MI, stroke, HF episode (henceforth referred to as HF and all of these events will be assumed to be nonfatal) and death from any cause (henceforth death) occur, respectively; specifically: T_M , T_S , T_H and T_D represent the times elapsed from the time point of interest. We assume that (1) two or more events cannot occur simultaneously, i.e. in an infinitesimally small time interval Δt only one event can occur; (2) the probability of occurrence of any type of event in the future depends on the cumulative number

and types of events up to the current time. From (1), for any event type w (where w represents MI, stroke, HF or death) and W the number of event types,

$$P(t < T_w < t + \Delta t | \text{history up to } t) = \alpha_w \Delta t + o(\Delta t) \text{ for } w = 1, \dots, W$$

$$P(T_w > t + \Delta t | \text{history up to } t) = 1 - \sum_{w=1}^W \alpha_w \Delta t + o(\Delta t)$$

We let $s(t) = P(T_M > t, T_S > t, T_H > t, T_D > t)$

Then,

$$s'(t) = s(t)(-\alpha_M - \alpha_S - \alpha_H - \alpha_D)$$

or equivalently,

$$s(t) = e^{-(\alpha_M + \alpha_S + \alpha_H + \alpha_D)t}$$

where $s(t)$ represents event-free survival of duration t , $t \geq 0$; and $\alpha_M, \alpha_S, \alpha_H$ and α_D represent the hazard of the next MI, stroke, HF and death, respectively.

We formulate our model on the basis of the above results. The hazards $\alpha_M, \alpha_S, \alpha_H$ and α_D for each individual are assumed to be dependent on that individual's event history. A reasonable rationale for that dependence structure is to assume that there is an intrinsic hazard for each event (MI, stroke, HF and death). Each nonfatal event then imposes an additional hazard to itself (its own recurrence) and an additional, almost certainly different, hazard to each of the other two nonfatal events and death. Death, being the terminal event, has its own intrinsic hazard plus additional hazards accrued from any nonfatal events (MI, stroke, HF) that have occurred in an individual's event history.

Our model therefore updates the hazards $\alpha_M, \alpha_S, \alpha_H$, and α_D dynamically as nonfatal events occur in each individual, with death as the terminal dependent event:

$$\begin{aligned}
\alpha_{M_{i,j}} &= \mathbf{X}'_{M_i}(t)\boldsymbol{\mu}_M + \mathbf{X}'_{MM_i}(t)\boldsymbol{\beta}_{MM}m_{ij} + \mathbf{X}'_{MS_i}(t)\boldsymbol{\beta}_{MS}n_{ij} + \mathbf{X}'_{MH_i}(t)\boldsymbol{\beta}_{MH}p_{ij} \\
\alpha_{S_{i,j}} &= \mathbf{X}'_{S_i}(t)\boldsymbol{\mu}_S + \mathbf{X}'_{SM_i}(t)\boldsymbol{\beta}_{SM}m_{ij} + \mathbf{X}'_{SS_i}(t)\boldsymbol{\beta}_{SS}n_{ij} + \mathbf{X}'_{SH_i}(t)\boldsymbol{\beta}_{SH}p_{ij} \\
\alpha_{H_{i,j}} &= \mathbf{X}'_{H_i}(t)\boldsymbol{\mu}_H + \mathbf{X}'_{HM_i}(t)\boldsymbol{\beta}_{HM}m_{ij} + \mathbf{X}'_{HS_i}(t)\boldsymbol{\beta}_{HS}n_{ij} + \mathbf{X}'_{HH_i}(t)\boldsymbol{\beta}_{HH}p_{ij} \\
\alpha_{D_{i,j}} &= \mathbf{X}'_{D_i}(t)\boldsymbol{\mu}_D + \mathbf{X}'_{DM_i}(t)\boldsymbol{\beta}_{DM}m_{ij} + \mathbf{X}'_{DS_i}(t)\boldsymbol{\beta}_{DS}n_{ij} + \mathbf{X}'_{DH_i}(t)\boldsymbol{\beta}_{DH}p_{ij}
\end{aligned} \tag{1}$$

where m_{ij} , n_{ij} , and p_{ij} represent the total number of MI's, strokes and HF's, respectively that have occurred prior to event time t_{ij} ; t_{ij} denotes the time of the j^{th} event in the i^{th} individual. Our model postulates two main types of hazards: intrinsic and event-type. The intrinsic hazards for MI, stroke, HF and death are expressed by regression covariate coefficient vectors $\boldsymbol{\mu}_M, \boldsymbol{\mu}_S, \boldsymbol{\mu}_H$ and $\boldsymbol{\mu}_D$ associated with covariate vectors $\mathbf{X}_{M_i}(t), \mathbf{X}_{S_i}(t), \mathbf{X}_{H_i}(t)$ and $\mathbf{X}_{D_i}(t)$, respectively. These intrinsic hazards are the underlying hazards every individual has for MI, stroke, HF and death. The recurrent parameters denoted by regression covariate coefficient vectors $\boldsymbol{\beta}_{MM}, \dots, \boldsymbol{\beta}_{DH}$ and associated with covariate vectors $\mathbf{X}_{MM_i}(t), \dots, \mathbf{X}_{DH_i}(t)$ represent the event-type hazards, i.e. the additional hazard for a particular event, nonfatal or fatal, conferred by a particular preceding nonfatal event. Thus, $\mathbf{X}'_{\bullet M_i}(t)\boldsymbol{\beta}_{\bullet M}$ is the additional hazard for any event type (MI, stroke, HF or death) conferred by preceding MI specifically in the i th individual with covariates $\mathbf{X}_{\bullet M_i}(t)$; $\mathbf{X}'_{\bullet S_i}(t)\boldsymbol{\beta}_{\bullet S}$ is the additional hazard for any event type (MI, stroke, HF or death) conferred by preceding stroke specifically in the i th individual with covariates $\mathbf{X}_{\bullet S_i}(t)$, and so on. The covariate vectors are unique to each hazard type and may be time dependent.

2.2 Likelihood function

The likelihood function for n subjects is thereby constructed as:

$$\prod_{i=1}^n \prod_{j=1}^{k_i} e^{-[\alpha_{M_{i,j}} + \alpha_{S_{i,j}} + \alpha_{H_{i,j}} + \alpha_{D_{i,j}}][t_{i,j} - t_{i,j-1}]} [\alpha_{M_{i,j}}]^{I_{M_{i,j}}} [\alpha_{S_{i,j}}]^{I_{S_{i,j}}} [\alpha_{H_{i,j}}]^{I_{H_{i,j}}} [\alpha_{D_{i,j}}]^{I_{D_{i,j}}} \quad (2)$$

where $i = 1, \dots, n$; such that n represents the number of individuals; $j = 1, \dots, k_i$, where k_i denotes the total number of events for the i^{th} individual; $t_{i,j}$ denotes the j^{th} event time for the i^{th} individual such that $t_{i,j} - t_{i,j-1}$ is the inter-event, or gap time between two successive events for the i^{th} individual; $I_{M_{i,j}}$ is an indicator variable that denotes whether or not MI occurs at $t_{i,j}$; $I_{S_{i,j}}$ is an indicator variable that denotes whether or not stroke occurs at $t_{i,j}$; $I_{H_{i,j}}$ is an indicator variable that denotes whether or not HF occurs at $t_{i,j}$; $I_{D_{i,j}}$ is an indicator variable that denotes whether or not death occurs at $t_{i,j}$.

3. Estimation

A modified Newton-Raphson algorithm is used to obtain the maximum likelihood estimates of the parameters. For computational ease and efficiency, we derived the analytical gradients and hessian matrix from the log likelihood function. We controlled the step size of every iteration to ensure that our parameter values stayed within range; each step size was multiplied by c starting with a small value for c and gradually increasing c closer to 1 as the step size shrank with increasing iterations. With this approach, we gained the benefits of faster convergence with Newton-Raphson while avoiding its common pitfalls of cycling, non-convergence or convergence to the wrong roots. From the hessian matrix at the converged values, we subsequently obtained the standard errors of our parameter estimates and the corresponding 95% Wald confidence intervals (CI) of the estimates.

4. Simulation Study

We conducted a simulation study by simulating datasets comprised of three treatment arms, mimicking the chlorthalidone, amlodipine, and lisinopril treatment arms from ALLHAT (described in detail in Section 5) and estimating the parameters. We utilized the regression parameter values estimated from the ALLHAT data (which we report in Section 5) as the true parameter values for our simulation study.

To simulate each dataset, we first simulated the initial gap time between time 0 (equivalent to randomization time, with each observation assumed to have no prior events) and the first event as the *iid* exponential distribution with rate parameter λ_o equal to the sum of the intrinsic hazards for each event, i.e.

$$\lambda_o = \mathbf{X}'_{M_i}(t)\boldsymbol{\mu}_M + \mathbf{X}'_{S_i}(t)\boldsymbol{\mu}_S + \mathbf{X}'_{H_i}(t)\boldsymbol{\mu}_H + \mathbf{X}'_{D_i}(t)\boldsymbol{\mu}_D$$

and mean $\frac{1}{\lambda_o}$, where $\mathbf{X}'_{M_i}(t) = \mathbf{X}'_{S_i}(t) = \mathbf{X}'_{H_i}(t) = \mathbf{X}'_{D_i}(t) = [1, I_{Amlodipine_i}, I_{Lisinopril_i}]$; $I_{Amlodipine_i}$ and $I_{Lisinopril_i}$ are indicator variables that denote whether or not the i th individual is in the amlodipine or lisinopril treatment arms, respectively. The reference group in this scenario is the chlorthalidone arm. At the end of this initial gap time, we simulated the first event as a single random sample from a multinomial distribution, with each event type probability equivalent to its relative proportion, namely

$$p_M = \frac{\mathbf{X}'_{M_i}(t)\boldsymbol{\mu}_M}{\lambda_o},$$

$$p_S = \frac{\mathbf{X}'_{S_i}(t)\boldsymbol{\mu}_S}{\lambda_o},$$

$$p_H = \frac{\mathbf{X}'_{H_i}(t)\boldsymbol{\mu}_H}{\lambda_o},$$

$$p_D = \frac{X'_{D_i}(t)\mu_D}{\lambda_0}$$

If a nonfatal event (MI, stroke or HF) occurred, the next gap time (event-free survival) followed the exponential distribution with updated rate parameter λ_1 in accordance with the increased risk that arose from the new event in the manner described by (1) in Section 2. The subsequent event was simulated in the same manner as the first, with its event probability equivalent to its updated relative proportion. The relevant time units for the simulation study are in years.

For each observation, this process continued until death or noninformative right censoring intervened. We chose a study endpoint $Y = 8$ such that each observation in the simulated dataset that remained alive was automatically right censored at that time. Furthermore, we simulated another form of noninformative censoring for each observation as an independent exponential distribution with a separate rate parameter $\lambda_c = 0.05$; this represented study drop-out. Therefore, total follow up time of each observation was $\min(T_C, T_D, Y)$ where T_C represents the noninformative censoring time (study drop-out) that arises from $iid \exp(\lambda_c)$, T_D represents the time of death if it occurred in the individual, and Y represents the end of the study. We simulated 501 datasets with the first discarded as burn-in to yield 500 datasets, each with 30,000 observations (10,000 observations each for chlorthalidone, amlodipine and lisinopril). We estimated the parameters for each dataset as described in Section 3.

Our simulation study results are in Table 1. For each parameter, we computed the bias as the average of its estimated parameters minus the true value; the standard error (SE) as the average of its estimated parameters' standard errors; the standard deviation (SD) of the

estimated parameters; and the coverage probability (CP) as the proportion of the simulation runs whose 95% CI covers the true parameter value. Our results show that the bias is small, the SE of each parameter is close or equal to the SD and the CP for every parameter is near or at the nominal value of 95%.

5. Application to ALLHAT

5.1 Study population

The details of ALLHAT's study population have been described elsewhere.¹⁵⁻²⁰ Briefly, ALLHAT was a double-blind, randomized controlled trial that was conducted from February 1994 through March 2002. Participants were aged 55 or older with hypertension and at least one other cardiovascular disease (CVD) risk factor (including previous [> 6 months] MI or stroke, left ventricular hypertrophy [LVH], history of Type 2 diabetes, current cigarette smoking, HDL < 35 mg/dl, or documentation of other atherosclerotic CVD) from 623 centers in North America, specifically the United States, Canada, Puerto Rico and the US Virgin Islands. A total of 33,357 individuals were randomized to one of three treatment arms: chlorthalidone ($N = 15,255$), amlodipine ($N = 9,048$) and lisinopril ($N = 9,054$) for planned follow-up of approximately 4 to 8 years. Mean follow-up time was 4.9 years. The primary endpoint was combined: fatal CHD or nonfatal MI. Major pre-specified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (the primary outcome, coronary revascularization, and hospitalized angina), and combined CVD (combined CHD, stroke, other treated angina, HF [fatal, hospitalized, or treated non-hospitalized] and peripheral arterial disease). ALLHAT was designed to determine whether the occurrence of fatal CHD or nonfatal MI (the primary endpoint) is lower for high-risk patients with hypertension treated with a calcium channel blocker (amlodipine) or an ACE

inhibitor (lisinopril), each compared to diuretic treatment (chlorthalidone).¹⁵⁻¹⁸ A fourth treatment arm, the α -blocker doxazosin was terminated early when it became apparent that doxazosin had a very low (< 0.05) probability of having a statistically significant lower incidence of the primary endpoint compared to chlorthalidone at the end of the study based on the data up to that point. A second reason was that a large excess of HF became evident in the doxazosin arm as compared to chlorthalidone.^{19,20}

We applied our method to the in-trial ALLHAT dataset ($N = 33,357$) for the nonfatal, potentially recurrent events MI, stroke and HF, and death as the terminating event. Each observation in the dataset contained the event times in years from the date of randomization to the event. If multiple events occurred during the same visit or hospitalization, or within the same day, for which no further resolution with respect to exact event times was possible, we elected to assign 0.001 years (8.77 hours) of elapsed time between the two events. With respect to event order, we assumed that MI preceded HF and stroke, and stroke preceded HF; HF is a common sequela of MI both acutely and in the long-term. We estimated the parameters and their attendant standard errors for three different models: (1) base (intercept only) model; (2) intrinsic hazards covariate model; and (3) intrinsic and recurrent hazards covariate model. We did so using the statistical inference described in Section 3. We will hereafter refer to the base model, intrinsic hazards covariate model, and intrinsic and recurrent hazards covariate model as BM, IHCM and IRHCM, respectively.

5.2 ALLHAT Results

Table 2 displays results for the BM. The intrinsic parameters are all positive and statistically significant, representing the intrinsic hazards of MI, stroke, HF and death for each observation.

The intrinsic hazard for death is highest (0.0273 [0.0264 - 0.0281]), more than twice the intrinsic hazard of MI (0.0106 [0.0101 - 0.0111]), which in turn is higher than HF (0.0066 [0.0062 - 0.0070]) and stroke (0.0063 [0.0059 - 0.0067]). The recurrent parameters are all positive and statistically significant, implying that each nonfatal event increases the hazard of every event type. For MI, the recurrent parameter β_{MM} is higher (0.0559 [0.0492 - 0.0627]) than β_{MS} (0.0127 [0.0070 - 0.0183]) and β_{MH} (0.0154 [0.0102 - 0.0206]). Thus, the risk that a preceding MI imparts to future MI is higher than the risk that a preceding stroke or HF imparts to future MI. Similarly, the recurrent parameter β_{SS} is much higher (0.0249 [0.0186 - 0.0312]) than β_{SM} (0.0038 [0.0014 - 0.0063]) and β_{SH} (0.0049 [0.0018 - 0.0080]). Thus, antecedent stroke imparts a higher risk to future stroke than it does to future MI or HF. The same trend continues for HF; the recurrent parameter β_{HH} is higher (0.1270 [0.1155 - 0.1384]) than β_{HM} (0.0584 [0.0514 - 0.0654]) and much higher than β_{HS} (0.0150 [0.0094 - 0.0205]). Overall, each of these nonfatal events imparts the greatest risk to its own recurrence, and smaller, but still significant, risks to future occurrence of other event types. For death, preceding HF imparts the greatest risk (0.0730 [0.0634 - 0.0826]), followed by stroke (0.0533 [0.0430 - 0.0635]) and then MI (0.0146 [0.0092 - 0.0199]).

Our results for the IHCM are in Table 3. For this model, we introduced the treatment arms chlorthalidone, amlodipine and lisinopril for the intrinsic hazards and report the results for chlorthalidone and lisinopril as the reference group, respectively. In both situations, the intercept parameter corresponds to the intrinsic hazard for that event in the reference group (either chlorthalidone or lisinopril). Two indicator variables correspond to the remaining two treatment arms; the covariate parameters of the two indicator variables corresponding to the treatment arms represent the excess hazard in that treatment arm over that of the reference group. This

excess hazard may be positive or negative. The sum of the excess hazard and the intrinsic hazard of the reference group yields the intrinsic hazard for that treatment arm. In this manner, we compare the results for amlodipine vs chlorthalidone (A vs C), lisinopril vs chlorthalidone (L vs C) and amlodipine vs lisinopril (A vs L). We provide the intrinsic baseline hazards for all three treatment arms in the leftmost column. Moreover, we chose to report the excess hazard for the non-reference group treatment arms this way in order to clearly show whether or not the difference in the two treatment arms' hazards from that of the reference group was statistically significant. Of note, we have omitted the excess hazard for chlorthalidone over lisinopril (C vs L), because the excess hazard for lisinopril over chlorthalidone (L vs C) is already provided.

With chlorthalidone as the reference group (A vs C and L vs C), we found that the amlodipine treatment arm has a significant, positive excess intrinsic hazard for HF (0.0029 [0.0019, 0.0039]) over the chlorthalidone treatment arm. With lisinopril as the reference group (A vs L), the amlodipine arm has a significant, negative excess intrinsic hazard for stroke (-0.0014 [-0.0024, -0.0003]), and a significant, positive excess intrinsic hazard for HF (0.0021 [0.0009, 0.0033]) over lisinopril. As expected, the recurrent parameters, corresponding to the additional hazards contributed by preceding nonfatal events, remain essentially unchanged from the BM.

Our results for the IRHCM are shown in Table 4. For this model, we introduced the treatment arms chlorthalidone, amlodipine and lisinopril for both the intrinsic hazards and recurrent hazards, and we again report the results for chlorthalidone and lisinopril as the reference group, respectively in a manner analogous to that described for the IHCM.

With chlorthalidone as the reference group (A vs C and L vs C), the amlodipine arm had a significant, positive excess intrinsic hazard for HF (0.0029 [0.0019, 0.0040]) over chlorthalidone.

The lisinopril arm had a significant, positive excess hazard for stroke conferred by an antecedent MI (0.0097 [0.0023, 0.0170]) over chlorthalidone. The lisinopril arm also had a significant, negative excess hazard for HF conferred by a preceding HF (-0.0337 [-0.0614, -0.0059]) over chlorthalidone. With lisinopril as the reference group (A vs L), the amlodipine arm had a significant, negative excess intrinsic hazard for stroke (-0.0013 [-0.0024, -0.0002]) over lisinopril. The amlodipine arm had a significant, negative excess hazard for stroke conferred by an antecedent MI (-0.0086 [-0.0164, -0.0008]) over lisinopril. The amlodipine arm also had a significant, positive excess intrinsic hazard for HF (0.0021 [0.0009, 0.0033]) over lisinopril.

Overall, the IRHCM shows that the amlodipine arm had a significantly higher intrinsic hazard for HF than both the chlorthalidone and lisinopril arms. The lisinopril arm had a significantly higher intrinsic hazard for stroke than the amlodipine arm. These two results mirror that of the IHCM. Moreover, the lisinopril arm had a significantly higher hazard for stroke conferred by an antecedent MI than both the chlorthalidone and the amlodipine arms. Finally, the lisinopril arm had a significantly lower hazard for HF conferred by a preceding HF than the chlorthalidone arm.

5.3 Model Selection and Goodness of Fit

We chose to utilize the Akaike information criterion (AIC) to assess the quality of our models relative to one another. We present the AIC for all three models in Table 5. The IHCM had the lowest AIC, followed by the IRHCM; the BM had the highest AIC. These results suggest that the IHCM provides a better fit to the data than the BM or the IRHCM. The BM performs the least, suggesting that treatment arm plays at least some role in event occurrence.

We also wanted to assess our models' dynamic predictive capabilities, specifically their ability to predict future event occurrence as events accrue over time. For each model, we chose to predict event-free survival at 1-year, 2-year, 3-year and 4-year increments for all observations at baseline ($N = 33,357$), observations that had 1 or more events ($N = 3,631$), observations that had 2 or more events ($N = 1,015$), observations that had 3 or more events ($N = 392$) and observations that had 4 or more events ($N = 155$). Our dataset contained the true survival for that observation (i.e. a binary result of whether or not that individual had any event, nonfatal or fatal, within that time frame). We subsequently obtained the estimated area under the curve (AUC) and its standard error of the resulting receiver operating characteristic (ROC) curve for each time frame and number of events. If an observation was censored within the time frame of interest such that true survival for that time frame could not be established, we sampled from a Bernoulli (p) distribution, with p equal to the model's predicted probability of survival for that observation. We assigned the resulting value (1 = event-free survival, 0 = event occurred) to that observation and repeated the sampling process for a total of 100 samples. We then averaged the AUC estimates and their standard errors to arrive at a final estimated AUC and standard error. The results for the BM, the IHCM and the IRHCM are presented in Tables 7, 8 and 9, respectively. The corresponding number and percentage of censored observations is provided in Table 6.

As the BM contains no covariates, all of the observations at baseline (0 events) have the same probability of event-free survival for any given time frame, which yields a fixed AUC of 0.50 for the 1-year, 2-year, 3-year and 4-year time points. For individuals with 1+ events, there is a statistically significant increase in AUC (0.58 [0.56, 0.60]) at year 1 which persists to the 4-year mark. A similar result is seen in individuals with 2+ events; the AUC at 1 year dips slightly ([0.56

(0.52, 0.59)) from the 1+ individuals, but it catches up by the 3-year mark (0.58 [0.54, 0.62]) and persists at the 4-year mark. For individuals with 3+ events, the 1-year AUC is higher (0.59 [0.53, 0.64]) than that of individuals with fewer events, and the AUC increases over time elapsed up to year 3 (0.65 [0.58, 0.73]) after which it dips slightly (0.63 [0.52, 0.73]) at year 4. Observations with 4+ events have a marked increase in AUC at the 1-year mark (0.65 [0.56, 0.73]) than that of individuals with fewer events, and their AUC rises steadily over time, peaking at the 4-year mark (0.71 [0.57, 0.85]). Overall, these results suggest that the number and type of events in an individual's clinical history is predictive of future event occurrence.

The IHCM results are similar, and slightly improved from that of the BM. A key feature is the predictive role of the treatment arms at baseline (0 events); at the 1-year mark, there is a small but statistically significant rise in AUC (0.52 [0.51, 0.54]) which stems from the amlodipine arm having an increased hazard of HF over both the chlorthalidone and lisinopril arms. This effect of amlodipine appears to dissipate over time, as the AUC dips down to 0.50 by the 3-year mark (0.50 [0.49, 0.51]) and is no longer significant. The remaining results mirror that of the BM, with the highest AUC in individuals with 4+ events (0.66 [0.57, 0.74]) that increases to 0.71 (0.59, 0.83) by the 3-year time point.

The IRHCM is similar to the IHCM, with a slightly increased AUC of individuals with 2+ events starting at 1 year, and individuals with 3+ events at the 2-year mark, when compared to the IHCM. This most likely reflects the treatment arms effects on recurrent events. For the individuals with 4+ events, the AUC for the IRHCM is slightly lower than that of both the IHCM and the BM at each time point. Overall, the results for all three models suggest that hazards

accrued from events as they occur play a major role in dynamic risk, and the treatment arm plays a relatively minor role in prediction of future event occurrence and recurrence.

6. Discussion

In this work, we presented a multi-type recurrent events model with dependent termination in a competing risk framework that provides a dynamic risk trajectory over time. Our model is well suited for longitudinal studies, which often feature recurrent events. The model provides the baseline hazard, or absolute risk, for each competing event type at any desired time point and incorporates the previous types and numbers of events in that individual in doing so. This allows a straightforward quantification of the relationship, if any, between different event types; the recurrent event parameters represent the additional hazard that a preceding nonfatal event confers to the event of interest. If this hazard is zero, it suggests a lack of association, or correlation, between those event types.

Our simulation study, patterned after the IRHCM, introduced covariates to the intrinsic hazards and the recurrent hazards. The simulation showed that our model can handle covariates for both the intrinsic and recurrent parameters, which results in a fairly large number of parameters, with relative ease. This has the potential to yield unique and important insights. Our work was motivated by the ALLHAT study, and our model was developed in the setting of multi-type recurrent events in CVD that are associated with one another based on the known pathophysiology of CVD. Our model, when applied to the in-trial ALLHAT study, yielded results consistent with the main ALLHAT findings, particularly the increased intrinsic hazard for nonfatal HF in the amlodipine arm over that of both the chlorthalidone and lisinopril arms, and the increased hazard for nonfatal stroke in the lisinopril arm over that of amlodipine.^{16,17}

Additionally, the IRHCM yielded new insights from the ALLHAT study in terms of treatment arm effects on recurrent events. In particular, the lisinopril arm had a lower hazard of HF conferred by a preceding HF compared to the chlorthalidone arm. This suggests that individuals with known HF may receive a benefit from lisinopril over chlorthalidone in preventing future HF events. ACE inhibitors are a first line agent for HF management, partly because they have been shown to reduce hospitalizations for recurrent HF²¹ and our results provide further support for the role of ACE inhibitors in reducing recurrent HF risk.

A unique aspect of our method is that it provides a dynamic risk trajectory for an individual based on their event history, and that risk is updated with each event as it occurs. This can yield potent predictive capabilities for future events and can direct optimal strategies for event-free survival tailored to that individual's clinical profile. We have already demonstrated that our models have good predictive ability for event-free survival for individuals with 4+ events from the 3-year mark onward, and reasonable prediction of event-free survival for individuals with 3+ events from the 3-year mark onward. In that regard, the BM is surprisingly competitive with both the IHCM and the IRHCM in terms of its ability to predictive future event occurrence over time. There was little difference in predictive ability between the models, which suggests that the hazards accrued over time by events as they occur play the dominant role in predicting event-free survival. This underscores a central tenet of our methodology, which is that accumulated events impart hazards that are cumulative, updated with each event occurrence over time. Moreover, we applied our model to the full in-trial ALLHAT dataset with no missing observations, another key strength of our study.

We acknowledge two limitations. First, the three models we applied to the ALLHAT data take between 5-10 minutes to converge, which is a reasonable time frame. For our simulation study, we deliberately chose to simulate each dataset ($N = 30,000$) to approximate the size of ALLHAT, so the 500 simulation runs took several days to complete. This can be addressed by simulating smaller datasets and/or fewer simulation runs, or the use of a supercomputer. A second limitation of our study is the somewhat large proportion of right censored observations for the individuals with 1+, 2+, 3+ and 4+ events starting at the 3-year mark. The handling of censored observations is a ubiquitous problem in survival analysis with manifold approaches. We elected to address it via random sampling from our model's predicted survival probability. Alternative approaches to censored observations in this setting would be an interesting and worthwhile future research endeavor.

Lastly, we anticipate a marked enhancement of our model's dynamic risk prediction capabilities with the incorporation of additional suitable covariates into both the intrinsic hazards and recurrent hazards. This will involve tailored model building and selection involving a potentially large number of parameters. We also wish to explore possible treatment arm differences for specific subgroups including age, gender and race which involve interaction terms as covariates in our models. We will address these important queries in our next paper, which will provide further insights into the recurrent nature of CVD.

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Table 1. Simulation study.

	Parameter	Truth	Estimate	Bias	SE	SD	CP
MI	μ_M	C	0.0109	0.0110	0.0001	0.0004	0.954
		A	-0.0005	-0.0005	<0.0001	0.0006	0.952
		L	-0.0007	-0.0008	-0.0001	0.0006	0.952
	β_{MM}	C	0.0588	0.0590	0.0002	0.0053	0.954
		A	-0.0056	-0.0059	-0.0003	0.0074	0.950
		L	-0.0055	-0.0060	-0.0005	0.0075	0.958
	β_{MS}	C	0.0135	0.0138	0.0003	0.0046	0.932
		A	0.0019	0.0021	0.0002	0.0068	0.944
		L	-0.0043	-0.0047	-0.0004	0.0060	0.954
	β_{MH}	C	0.0123	0.0122	-0.0001	0.0039	0.946
		A	0.0075	0.0078	0.0003	0.0055	0.960
		L	0.0027	0.0029	0.0002	0.0057	0.960
Stroke	μ_S	C	0.0063	0.0063	<0.0001	0.0003	0.944
		A	-0.0006	-0.0006	<0.0001	0.0005	0.950
		L	0.0007	0.0007	<0.0001	0.0005	0.926
	β_{SM}	C	0.0013	0.0013	<0.0001	0.0016	0.930
		A	0.0011	0.0010	-0.0001	0.0025	0.956
		L	0.0097	0.0098	0.0001	0.0032	0.950
	β_{SS}	C	0.0248	0.0248	<0.0001	0.0050	0.958
		A	0.0022	0.0023	0.0001	0.0074	0.940
		L	-0.0020	-0.0018	0.0002	0.0069	0.946
	β_{SH}	C	0.0031	0.0033	0.0002	0.0022	0.918
		A	0.0061	0.0058	-0.0003	0.0034	0.930
		L	-0.0008	-0.0012	-0.0004	0.0032	0.912
HF	μ_H	C	0.0056	0.0055	-0.0001	0.0003	0.936
		A	0.0029	0.0029	<0.0001	0.0005	0.960
		L	0.0008	0.0008	<0.0001	0.0005	0.958
	β_{HM}	C	0.0522	0.0518	-0.0004	0.0050	0.938
		A	0.0161	0.0165	0.0004	0.0078	0.938

		L	0.0079	0.0082	0.0003	0.0076	0.0073	0.966
	β_{HS}	C	0.0175	0.0176	0.0001	0.0046	0.0048	0.932
		A	-0.0082	-0.0081	0.0001	0.0062	0.0063	0.960
	β_{HH}	L	-0.0019	-0.0019	<0.0001	0.0062	0.0064	0.940
		C	0.1431	0.1435	0.0004	0.0100	0.0097	0.958
		A	-0.0213	-0.0217	-0.0004	0.0127	0.0123	0.952
		L	-0.0337	-0.0346	-0.0009	0.0132	0.0130	0.952
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Death	μ_D	C	0.0279	0.0279	<0.0001	0.0007	0.0007	0.958
		A	-0.0015	-0.0016	-0.0001	0.0010	0.0010	0.966
		L	-0.0008	-0.0008	<0.0001	0.0010	0.0010	0.948
	β_{DM}	C	0.0163	0.0167	0.0004	0.0042	0.0043	0.942
		A	-0.0029	-0.0033	-0.0004	0.0059	0.0062	0.944
		L	-0.0039	-0.0042	-0.0003	0.0060	0.0061	0.956
	β_{DS}	C	0.0540	0.0541	0.0001	0.0084	0.0084	0.962
		A	-0.0017	-0.0012	0.0005	0.0119	0.0121	0.956
		L	-0.0011	-0.0008	0.0003	0.0114	0.0115	0.952
	β_{DH}	C	0.0752	0.0754	0.0002	0.0080	0.0080	0.932
		A	-0.0096	-0.0095	0.0001	0.0102	0.0103	0.944
		L	0.0039	0.0040	0.0001	0.0112	0.0109	0.954

SE, standard error; SD, standard deviation; CP, coverage probability; C, chlorthalidone; A, amlodipine; L, lisinopril.

Table 2. Base (intercept only) model.

	Parameter	Estimate (95% CI)
MI	μ_M	0.0106 (0.0101, 0.0111)
	β_{MM}	0.0559 (0.0492, 0.0627)
	β_{MS}	0.0127 (0.0070, 0.0183)
	β_{MH}	0.0154 (0.0102, 0.0206)
Stroke	μ_S	0.0063 (0.0059, 0.0067)
	β_{SM}	0.0038 (0.0014, 0.0063)
	β_{SS}	0.0249 (0.0186, 0.0312)
	β_{SH}	0.0049 (0.0018, 0.0080)
HF	μ_H	0.0066 (0.0062, 0.0070)
	β_{HM}	0.0584 (0.0514, 0.0654)
	β_{HS}	0.0150 (0.0094, 0.0205)
	β_{HH}	0.1270 (0.1155, 0.1384)
Death	μ_D	0.0273 (0.0264, 0.0281)
	β_{DM}	0.0146 (0.0092, 0.0199)
	β_{DS}	0.0533 (0.0430, 0.0635)
	β_{DH}	0.0730 (0.0634, 0.0826)

Table 3. Intrinsic hazards covariate model.

Baseline hazard			Excess hazard	
			Reference Group: Chlorthalidone (A vs C and L vs C)	Reference Group: Lisinopril (A vs L)
Parameter	Estimate (95% CI)		Estimate (95% CI)	Estimate (95% CI)
MI	μ_M			
	C	0.0109 (0.0102, 0.0117)		--
	A	0.0105 (0.0096, 0.0115)	-0.0004 (-0.0017, 0.0008)	0.0003 (-0.0010, 0.0017)
	L	0.0102 (0.0092, 0.0111)	-0.0008 (-0.0020, 0.0005)	
	β_{MM}	0.0559 (0.0492, 0.0626)		
	β_{MS}	0.0127 (0.0070, 0.0183)		
	β_{MH}	0.0155 (0.0103, 0.0206)		
Stroke	μ_S			
	C	0.0062 (0.0056, 0.0068)		--
	A	0.0057 (0.0050, 0.0065)	-0.0005 (-0.0014, 0.0004)	-0.0014 (-0.0024, -0.0003)*
	L	0.0071 (0.0063, 0.0079)	0.0009 (-0.0001, 0.0019)	
	β_{SM}	0.0037 (0.0012, 0.0062)		
	β_{SS}	0.0249 (0.0186, 0.0312)		
	β_{SH}	0.0050 (0.0019, 0.0081)		
HF	μ_H			
	C	0.0056 (0.0050, 0.0061)		--
	A	0.0085 (0.0076, 0.0093)	0.0029 (0.0019, 0.0039)*	0.0021 (0.0009, 0.0033)*
	L	0.0064 (0.0056, 0.0071)	0.0008 (-0.0001, 0.0017)	
	β_{HM}	0.0583 (0.0513, 0.0653)		

	β_{HS}	0.0152 (0.0096, 0.0207)		
	β_{HH}	0.1269 (0.1154, 0.1383)		
Death	μ_D			
	C	0.0279 (0.0267, 0.0291)		--
	A	0.0263 (0.0248, 0.0278)	-0.0016 (-0.0036, 0.0003)	-0.0008 (-0.0030, 0.0014)
	L	0.0271 (0.0255, 0.0287)	-0.0008 (-0.0028, 0.0011)	
	β_{DM}	0.0145 (0.0091, 0.0199)		
	β_{DS}	0.0533 (0.0430, 0.0635)		
	β_{DH}	0.0731 (0.0635, 0.0826)		

*statistically significant excess hazard over that of the reference group

C, the baseline hazard for chlorthalidone (left column); A, the baseline hazard for amlodipine (left column), the excess hazard over chlorthalidone for amlodipine (middle column) and excess hazard over lisinopril for amlodipine (right column); L, the baseline hazard for lisinopril (left column) and the excess hazard over chlorthalidone for lisinopril (middle column).

Table 4. Intrinsic and recurrent hazards covariate model.

Baseline hazard			Excess hazard	
			Reference Group: Chlorthalidone (A vs C and L vs C)	Reference Group: Lisinopril (A vs L)
Parameter	Estimate (95% CI)		Estimate (95% CI)	Estimate (95% CI)
MI	μ_M			
	C	0.0109 (0.0102, 0.0117)		--
	A	0.0105 (0.0095, 0.0115)	-0.0005 (-0.0017, 0.0008)	0.0003 (-0.0011, 0.0016)
	L	0.0102 (0.0093, 0.0112)	-0.0007 (-0.0020, 0.0005)	
	β_{MM}			
	C	0.0588 (0.0489, 0.0688)		--
	A	0.0532 (0.0403, 0.0661)	-0.0056 (-0.0219, 0.0107)	-0.0001 (-0.0183, 0.0182)
	L	0.0533 (0.0403, 0.0663)	-0.0055 (-0.0219, 0.0108)	
	β_{MS}			
	C	0.0135 (0.0050, 0.0220)		--
	A	0.0154 (0.0033, 0.0275)	0.0019 (-0.0129, 0.0167)	0.0062 (-0.0091, 0.0215)
	L	0.0092 (-0.0002, 0.0186)	-0.0043 (-0.0170, 0.0083)	
	β_{MH}			
	C	0.0123 (0.0047, 0.0199)		--
	A	0.0198 (0.0099, 0.0297)	0.0075 (-0.0049, 0.0200)	0.0049 (-0.0089, 0.0186)
	L	0.0149 (0.0053, 0.0246)	0.0027 (-0.0096, 0.0149)	
Stroke	μ_S			
	C	0.0063 (0.0057, 0.0069)		--
	A	0.0057 (0.0050, 0.0064)	-0.0006 (-0.0015, 0.0003)	-0.0013 (-0.0024, -0.0002)*
	L	0.0070 (0.0062, 0.0078)	0.0007 (-0.0003, 0.0017)	
	β_{SM}			
	C	0.0013 (-0.0016, 0.0042)		--
	A	0.0024 (-0.0015, 0.0063)	0.0011 (-0.0038, 0.0059)	-0.0086 (-0.0164, -0.0008)*

	L	0.0110 (0.0042, 0.0177)	0.0097 (0.0023, 0.0170)*	
	β_{SS}			
	C	0.0248 (0.0154, 0.0342)		--
	A	0.0270 (0.0140, 0.0401)	0.0022 (-0.0139, 0.0183)	0.0042 (-0.0130, 0.0213)
	L	0.0228 (0.0117, 0.0339)	-0.0020 (-0.0165, 0.0126)	
	β_{SH}			
	C	0.0031 (-0.0015, 0.0077)		--
	A	0.0093 (0.0028, 0.0157)	0.0061 (-0.0018, 0.0141)	0.0069 (-0.0011, 0.0150)
	L	0.0023 (-0.0025, 0.0072)	-0.0008 (-0.0075, 0.0059)	
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HF	μ_H			
	C	0.0056 (0.0050, 0.0061)		--
	A	0.0085 (0.0076, 0.0093)	0.0029 (0.0019, 0.0040)*	0.0021 (0.0009, 0.0033)*
	L	0.0064 (0.0056, 0.0071)	0.0008 (-0.0001, 0.0018)	
	β_{HM}			
	C	0.0522 (0.0427, 0.0617)		--
	A	0.0683 (0.0533, 0.0833)	0.0161 (-0.0016, 0.0338)	0.0082 (-0.0121, 0.0285)
	L	0.0601 (0.0463, 0.0739)	0.0079 (-0.0089, 0.0246)	
	β_{HS}			
	C	0.0175 (0.0089, 0.0261)		--
	A	0.0094 (-0.0010, 0.0198)	-0.0082 (-0.0217, 0.0053)	-0.0062 (-0.0206, 0.0081)
	L	0.0156 (0.0057, 0.0255)	-0.0019 (-0.0150, 0.0112)	
	β_{HH}			
	C	0.1431 (0.1239, 0.1623)		--
	A	0.1218 (0.1019, 0.1418)	-0.0213 (-0.0490, 0.0064)	0.0124 (-0.0158, 0.0406)
	L	0.1094 (0.0894, 0.1294)	-0.0337 (-0.0614, -0.0059)*	
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Death	μ_D			
	C	0.0279 (0.0266, 0.0291)		--
	A	0.0264 (0.0248, 0.0279)	-0.0015 (-0.0035, 0.0005)	-0.0007 (-0.0029, 0.0015)
	L	0.0271 (0.0255, 0.0287)	-0.0008 (-0.0028, 0.0012)	

β_{DM}			
C	0.0163 (0.0082, 0.0244)		--
A	0.0134 (0.0036, 0.0231)	-0.0029 (-0.0156, 0.0098)	0.0010 (-0.0133, 0.0153)
L	0.0124 (0.0019, 0.0228)	-0.0039 (-0.0172, 0.0093)	
β_{DS}			
C	0.0540 (0.0386, 0.0695)		--
A	0.0524 (0.0318, 0.0729)	-0.0017 (-0.0274, 0.0240)	-0.0006 (-0.0282, 0.0269)
L	0.0530 (0.0346, 0.0714)	-0.0011 (-0.0251, 0.0229)	
β_{DH}			
C	0.0752 (0.0596, 0.0907)		--
A	0.0655 (0.0496, 0.0815)	-0.0096 (-0.0319, 0.0127)	-0.0135 (-0.0380, 0.0110)
L	0.0790 (0.0605, 0.0976)	0.0039 (-0.0203, 0.0281)	

*statistically significant excess hazard over that of the reference group

C, the baseline hazard for the corresponding category (intrinsic, recurrent) for chlorthalidone (left column); A, the baseline hazard for the corresponding category (intrinsic, recurrent) for amlodipine (left column), the excess hazard over chlorthalidone for the corresponding category (intrinsic, recurrent) for amlodipine (middle column) and the excess hazard over lisinopril for the corresponding category (intrinsic, recurrent) for amlodipine (right column); L, the baseline hazard for the corresponding category (intrinsic, recurrent) for lisinopril (left column) and the excess hazard over chlorthalidone for lisinopril (middle column).

Table 5. Model AIC.

	BM	IHCM	IRHCM
Number of parameters	16	24	48
AIC	98349.81	98321.82	98342.98

Table 6. Number and percentage of censored observations.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=33,357	N=3,631	N=1,015	N=392	N=155
	n (%)	n (%)	n (%)	n (%)	n (%)
1	111 (0.33)	385 (10.60)	126 (12.41)	52 (13.27)	24 (15.48)
2	141 (0.42)	845 (23.27)	229 (22.56)	87 (22.19)	32 (20.65)
3	206 (0.62)	1241 (34.18)	331 (32.61)	120 (30.61)	37 (23.87)
4	2426 (7.27)	1592 (43.84)	390 (38.42)	143 (36.48)	45 (29.03)

Table 7. Area under the curve for the BM.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=33,357	N=3,631	N=1,015	N=392	N=155
1	0.50 —	0.58 (0.56, 0.60)	0.56 (0.52, 0.59)	0.59 (0.53, 0.64)	0.65 (0.56, 0.73)
2	0.50 —	0.59 (0.57, 0.60)	0.57 (0.54, 0.61)	0.62 (0.56, 0.68)	0.67 (0.56, 0.77)
3	0.50 —	0.58 (0.56, 0.60)	0.58 (0.54, 0.62)	0.65 (0.58, 0.73)	0.70 (0.57, 0.82)
4	0.50 —	0.58 (0.56, 0.60)	0.58 (0.54, 0.63)	0.63 (0.52, 0.73)	0.71 (0.57, 0.85)

Table 8. Area under the curve for the IHCM.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=33,357	N=3,631	N=1,015	N=392	N=155
1	0.52 (0.51, 0.54)	0.59 (0.56, 0.61)	0.55 (0.52, 0.59)	0.59 (0.53, 0.64)	0.66 (0.57, 0.74)
2	0.51 (0.50, 0.52)	0.59 (0.57, 0.61)	0.57 (0.53, 0.60)	0.61 (0.55, 0.68)	0.67 (0.57, 0.78)
3	0.50 (0.49, 0.51)	0.58 (0.56, 0.60)	0.58 (0.54, 0.62)	0.65 (0.57, 0.72)	0.71 (0.59, 0.83)
4	0.50 (0.49, 0.51)	0.58 (0.56, 0.60)	0.58 (0.53, 0.63)	0.62 (0.51, 0.72)	0.70 (0.55, 0.85)

Table 9. Area under the curve for the IRHCM.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=33,357	N=3,631	N=1,015	N=392	N=155
1	0.52 (0.51, 0.54)	0.59 (0.57, 0.61)	0.57 (0.53, 0.60)	0.59 (0.54, 0.65)	0.63 (0.54, 0.72)
2	0.51 (0.50, 0.52)	0.59 (0.57, 0.61)	0.58 (0.54, 0.61)	0.62 (0.55, 0.68)	0.66 (0.55, 0.77)
3	0.50 (0.49, 0.51)	0.58 (0.57, 0.60)	0.59 (0.55, 0.63)	0.65 (0.58, 0.73)	0.69 (0.55, 0.83)
4	0.50 (0.49, 0.51)	0.59 (0.57, 0.61)	0.60 (0.55, 0.64)	0.62 (0.52, 0.72)	0.70 (0.55, 0.85)

CHAPTER 3: JOURNAL ARTICLE 2

Competing risks of recurrent cardiovascular events with all-cause mortality

ABSTRACT

Despite a number of established risk scores for cardiovascular disease (CVD), none to date provide a risk assessment of multiple, competing CVD outcomes that incorporates number and type of CVD events along with clinical profile. We extend our previously reported multi-type recurrent events model to develop several models (IHCM 1, IHCM 2 and IRHCM) that were applied to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study. IHCM 1 and IRHCM quantified the dynamic risks of nonfatal myocardial infarction (MI), stroke and heart failure (HF), and all-cause mortality (death) given risk factors for each event-type, with risks updated after every event occurrence. IHCM2 examined interactions between selected CVD risk factors and treatment arms. Baseline age, diabetes, history of MI or stroke, kidney disease and smoking are risk factors common to all 4 event-types. Diabetes and kidney disease each impart more risk to death than nonfatal events. Atrial fibrillation confers more risk to HF than it does to death or stroke. IHCM 2 showed significant interactions between diabetes and amlodipine for HF; black race and lisinopril for stroke; atrial fibrillation and amlodipine and lisinopril for death. IRHCM outperformed IHCM 1 in predicting event-free survival, and both models performed best at baseline (0 events) and in individuals with 4+ events. IHCM 1 and IRHCM are useful in identifying and quantifying risk factors for CVD and predicting risk trajectory and event-free survival, with significant potential to develop into a dynamic CVD risk score that guides individualized therapeutic management.

BACKGROUND

Major risk factors for cardiovascular disease (CVD) are well established.¹⁻³ The Framingham risk score is widely used in clinical practice and epidemiological research^{2,4}; it was originally developed to calculate 10-year risks of coronary heart disease (CHD) utilizing several of these established risk factors: age, dyslipidemia, blood pressure, diabetes, and smoking.^{2,4} Subsequently, cerebrovascular events, peripheral artery disease (PAD) and heart failure (HF) were added to formulate a more general CVD risk assessment tool, expanding the Framingham risk score to include 10-year risks of CVD^{2,5}.

In spite of the ubiquitous use of risk scores to predict CVD outcomes and preferentially target individuals at particular risk of CVD events in the short and long term, there has not been to our knowledge a risk score or risk assessment of CVD outcomes that incorporate specific number and types of CVD events in an individual's past medical history in conjunction with their clinical and demographic profile. In our previous work,⁶ we introduced a dynamic competing risk model for multi-type recurrent events that is uniquely tailored to quantify baseline hazard, or absolute risk, of future CVD events given the individual's particular event history e.g. a personal history of nonfatal myocardial infarction (MI), stroke and 2 episodes of HF. Recurrent CVD events are a common feature of longitudinal studies, and it is known that each CVD event imparts risk for future CVD events.¹ Therefore, the gap time, or time between CVD events or between a CVD event and death tends to decrease, particularly in the absence of intervention. Our model hypothesizes that each nonfatal CVD event imparts a particular risk to the future occurrence of each type of nonfatal CVD event (including its own recurrence) and a different, also particular, risk of death. The nonfatal CVD events serve as competing risks, with death being a competing

risk as well as a dependent terminal event after which no further events can occur. Moreover, our model assumes that the risk imparted by a particular CVD event on another CVD outcome is explained by a unique set of covariates, possibly time-dependent.

This approach yields valuable clinical insights to the nature of CVD and CVD mortality and the particular risk factors that are most relevant in preventing or ameliorating first occurrence of a CVD event, future occurrence or recurrence of CVD events, and death. Our model would show that certain risk factors such as diabetes, renal insufficiency and atrial fibrillation may pose greater risks to certain CVD events over others. Furthermore, head to head comparisons between drug regimens and other medical therapeutic interventions in their ability to thwart the incidence and recurrence of CVD and CVD-related death can be made. The global disease burden of CVD is enormous and cannot be overstated.⁷ CVD is the leading cause of death worldwide and its chronic, recurrent nature and often devastating consequences including lifelong disability and death make such a detailed CVD risk assessment as provided by our model an urgent clinical and public health imperative.^{1,7}

Our recurrent events statistical model described in our previous paper ⁶ was motivated by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study. In this paper, we return to the ALLHAT dataset to extend our methodology to include relevant clinical covariates for the intrinsic hazard every individual has for CVD events and death. We will further extend our method to select appropriate covariates for recurrent hazards, i.e. the hazard imparted by a CVD event for future CVD events. These two aforementioned models are extensions of the intrinsic hazards covariate model (IHCM) and intrinsic and recurrent hazards covariate model (IRHCM) described in our previous work.⁶ Interactions between selected

clinically important variables and treatment arms will be explored as another variant of the IHCM to examine heterogeneity of treatment effects between subgroups for intrinsic hazards of CVD outcomes.

METHODS

Study Population

ALLHAT's study population has been described elsewhere.^{8,9} Briefly, ALLHAT was a double-blind, randomized controlled trial that was conducted from February 1994 through March 2002. Participants were aged 55 or older with hypertension and at least one additional CVD risk factor [including previous (> 6 months) MI or stroke, left ventricular hypertrophy (LVH), history of Type 2 diabetes (hereafter, diabetes), current cigarette smoking, high-density lipoprotein (HDL) < 35 mg/dl, or documentation of other atherosclerotic CVD (OASCVD)] from 623 centers in North America, specifically the United States, Canada, Puerto Rico and the US Virgin Islands. A total of 33,357 individuals were randomized to one of three treatment arms: chlorthalidone ($N = 15,255$), amlodipine ($N = 9,048$) and lisinopril ($N = 9,054$) for planned follow-up of approximately 4 to 8 years. Mean follow-up time was 4.9 years. The primary endpoint was fatal CHD or nonfatal MI. Major pre-specified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (the primary outcome, coronary revascularization, and hospitalized angina), and combined CVD [combined CHD, stroke, other treated angina, HF (fatal, hospitalized, or treated non-hospitalized) and PAD]. ALLHAT was designed to determine whether the occurrence of fatal CHD or nonfatal MI (the primary endpoint) is lower for high-risk patients with hypertension treated with a calcium channel blocker

(amlodipine) or an ACE inhibitor (lisinopril), each compared to diuretic treatment (chlorthalidone).^{8,9}

Statistical model

Since our model has been described at length in our previous work,⁶ we will quickly recapitulate its salient aspects here before we proceed to describe the IHCM and IRHCM models that comprise the bulk of our statistical analyses. We let α_M , α_S , α_H and α_D denote the hazards (risks) for nonfatal MI, nonfatal stroke, nonfatal HF, and death from any cause (hereafter referred to as death), respectively. From this juncture, MI, stroke and HF will be assumed nonfatal unless otherwise noted. Each of the hazards α_M , α_S , α_H and α_D are assumed to be dependent on that individual's event history. We further assume that there is an intrinsic hazard for each event (MI, stroke, HF and death). Each nonfatal event then imposes an additional hazard to itself (its own recurrence) and an additional, different hazard to each of the other two nonfatal events and death. Death, being the terminal event, has its own intrinsic hazard plus additional hazards accrued from any nonfatal events (MI, stroke, HF) that have occurred up to the point of interest. Throughout this paper, we will use the terms hazard, risk and absolute risk interchangeably.

Our model therefore updates the hazards α_M , α_S , α_H , and α_D dynamically as nonfatal events occur in each individual, with death as the terminal dependent event:

$$\begin{aligned}
 \alpha_{M_{i,j}} &= \mathbf{X}'_{M_i}(t)\boldsymbol{\mu}_M + \mathbf{X}'_{MM_i}(t)\boldsymbol{\beta}_{MM}m_{ij} + \mathbf{X}'_{MS_i}(t)\boldsymbol{\beta}_{MS}n_{ij} + \mathbf{X}'_{MH_i}(t)\boldsymbol{\beta}_{MH}p_{ij} \\
 \alpha_{S_{i,j}} &= \mathbf{X}'_{S_i}(t)\boldsymbol{\mu}_S + \mathbf{X}'_{SM_i}(t)\boldsymbol{\beta}_{SM}m_{ij} + \mathbf{X}'_{SS_i}(t)\boldsymbol{\beta}_{SS}n_{ij} + \mathbf{X}'_{SH_i}(t)\boldsymbol{\beta}_{SH}p_{ij} \\
 \alpha_{H_{i,j}} &= \mathbf{X}'_{H_i}(t)\boldsymbol{\mu}_H + \mathbf{X}'_{HM_i}(t)\boldsymbol{\beta}_{HM}m_{ij} + \mathbf{X}'_{HS_i}(t)\boldsymbol{\beta}_{HS}n_{ij} + \mathbf{X}'_{HH_i}(t)\boldsymbol{\beta}_{HH}p_{ij} \\
 \alpha_{D_{i,j}} &= \mathbf{X}'_{D_i}(t)\boldsymbol{\mu}_D + \mathbf{X}'_{DM_i}(t)\boldsymbol{\beta}_{DM}m_{ij} + \mathbf{X}'_{DS_i}(t)\boldsymbol{\beta}_{DS}n_{ij} + \mathbf{X}'_{DH_i}(t)\boldsymbol{\beta}_{DH}p_{ij}
 \end{aligned} \tag{1}$$

where m_{ij} , n_{ij} , and p_{ij} represent the total number of MI's, strokes and HF's, respectively that have occurred prior to event time t_{ij} ; t_{ij} denotes the time of the j^{th} event in the i^{th} individual. Our model delineates two main types of hazards: intrinsic and event-type. The intrinsic hazards for MI, stroke, HF and death are expressed by regression covariate coefficient vectors μ_M, μ_S, μ_H and μ_D associated with covariate vectors $X_{M_i}(t), X_{S_i}(t), X_{H_i}(t)$ and $X_{D_i}(t)$, respectively. These intrinsic hazards are the underlying hazards every individual has for those events. The recurrent parameters denoted by regression covariate coefficient vectors $\beta_{MM}, \dots, \beta_{DH}$ and associated with covariate vectors $X_{MM_i}(t), \dots, X_{DH_i}(t)$ represent the event-type hazards, i.e. the additional hazard for a particular event, nonfatal or fatal, conferred by a particular preceding nonfatal event. Thus, $X'_{\bullet M_i}(t)\beta_{\bullet M}$ is the additional hazard for any event type (MI, stroke, HF or death) conferred by preceding MI specifically in the i th individual with covariates $X_{\bullet M_i}(t)$; $X'_{\bullet S_i}(t)\beta_{\bullet S}$ is the additional hazard for any event type (MI, stroke, HF or death) conferred by preceding stroke specifically in the i th individual with covariates $X_{\bullet S_i}(t)$, and so on. The covariate vectors are unique to each hazard type and may be time dependent.

Thus, each hazard can be characterized by a unique, possibly time dependent, set of covariates which results in each individual having a tailored hazard for every CVD event and death, at baseline. These hazards update dynamically as the person moves through time and possibly accrues further CVD events. The IHCM and IRHCM are two models that arise naturally from the above rationale. For the IHCM, the intrinsic hazards contain covariates whereas the recurrent hazards do not contain covariates, i.e. they are left as intercepts. For the IRHCM, both the intrinsic and recurrent hazards may contain covariates. For IHCM and IRHCM and the purposes of this paper, all of the estimated parameters represent 1-year hazards; thus, they are

equivalent to the annual incidence of MI, stroke, HF and death. All of our statistical analyses were carried out in R 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria); parameter estimations were carried out by a modified Newton-Raphson algorithm described in our previous work ⁶ and independently verified by R's optim function (provided in the base package) using the BFGS algorithm.

Statistical analyses

The ICHM is the more parsimonious model and we report two separate sub-analyses of epidemiological and clinical significance. We denote the first as IHCM 1, for which we performed a modified stepwise variable selection to determine the most important covariates that comprise the intrinsic hazards for MI, stroke, HF and death.

We began with the full IHCM 1, comprised of the covariates deemed most important for CVD. We included key baseline characteristics of the ALLHAT participants that are known to be associated with CVD: age, race, sex, whether or not hypertension was treated at baseline, stage 1 or stage 2 hypertension as determined from baseline systolic and diastolic blood pressure, smoking, previous MI or stroke, history of coronary revascularization (CABG), OASCVD, major ST depression or T wave inversion, diabetes, left ventricular hypertrophy (LVH) by echocardiogram, CHD, body mass index (BMI) and current aspirin use. For this paper, we used the previous definition of stage 1 hypertension [systolic blood pressure (SBP) 140-160 mm Hg *or* diastolic blood pressure (DBP) 90-100 mm Hg] and stage 2 hypertension [SBP > 160 mm Hg *or* DBP > 100 mm Hg] ¹⁰ to better reflect the ALLHAT in-trial period. Additionally, we added covariates that are known CVD risk factors ¹: baseline or incident atrial fibrillation (hereafter, atrial fibrillation) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² as a marker of kidney disease.

Lastly, we included the treatment arms amlodipine and lisinopril, with chlorthalidone serving as the reference group for a total of 19 covariates for each intrinsic hazard (MI, stroke, HF and death). Notably, we deliberately excluded HDL < 35 mg/dL, one of the ALLHAT baseline characteristics reported in the literature ^{8,9} as a covariate for two main reasons. First and foremost, a subset of the ALLHAT participants were enrolled during the trial into the Lipid-Lowering Trial (ALLHAT-LLT) and were randomly assigned to receive pravastatin vs usual care and followed for a mean of 4.8 years.¹¹ This naturally introduces potential confounding as to the true effect of dyslipidemia as measured by baseline HDL < 35 mg/dL on CVD events over the course of the trial. Secondly, we ran a univariate IHCM with HDL < 35 mg/dL as the only covariate for all of the intrinsic hazards with equivocal results: HDL < 35 mg/dL was not found to impart a statistically significant hazard for MI or HF, and actually found to impart a statistically significant decrease in hazard for stroke and death. These results are consistent with a potentially confounding effect from the ALLHAT-LLT participants in the course of the ALLHAT study. Moreover, we ran a univariate IHCM for each of the 19 covariates included in the full IHCM to determine its univariate statistical significance as part of our model building and stepwise selection process (univariate IHCM results not shown). Table 1 lists the details for the 19 covariates included in the full IHCM 1.

Starting with the full IHCM 1, we performed multiple rounds of backward selection. In each round, we only retained the statistically significant covariates, i.e. the covariates which imparted a statistically significant hazard to the total intrinsic hazards for MI, stroke, HF and death, with one important constraint: we retained the treatment arms (amlodipine and lisinopril, with chlorthalidone serving as the reference group) for every intrinsic hazard regardless of clinical

significance throughout in order to adjust for treatment arm. In the first round of background selection only the statistically significant covariates for each intrinsic hazard were retained, and a reduced IHCM 1 model was fitted with these statistically significant covariates from the first round. In this reduced IHCM 1 model (second round), any covariates that were no longer statistically significant were discarded, and so on. The final reduced IHCM 1 contained only those covariates that remained statistically significant in each round of backward selection, with the noted exception of the treatment arms. We also removed a covariate even if it remained statistically significant for a particular intrinsic hazard or set of intrinsic hazards, if it was not statistically significant in the initial set of univariate analyses that we carried out for every covariate in the full IHCM 1 model. And finally, ALLHAT's population, given that every participant had a diagnosis of hypertension and 1 or more additional CVD risk factors at baseline, posed a unique challenge for variable selection; all statistically significant risk factors (covariates) could not be included for stroke, HF and death as it would result in the reference group being too sparse (the reference group being comprised of individuals without any of those risk factors). Therefore, we had to remove additional covariates that remained statistically significant for stroke, HF and death for optimal model stability to avoid the problems that arise with sparse data. Table 2 reports the covariates removed during multiple rounds of backward selection to yield the final IHCM 1 model (henceforth, IHCM 1).

In order to study the possible interactions between treatment arms and selected risk factors, we utilized IHCM 2, which contains as its covariates: the risk factor (binary or categorical), amlodipine, lisinopril and the interaction terms [(risk factor) x (treatment arm)]. The selected risk factors were sex, diabetes, race (black/nonblack), age (categorical, see Table 1), kidney disease,

atrial fibrillation, hypertension treated at baseline and stage 1/stage 2 hypertension at baseline (categorical, see Table 1). Of note, interactions for age, sex, race (black/nonblack) and diabetes were previously studied in ALLHAT⁸; we wanted to reexamine those interactions in a competing risk framework for nonfatal CVD events and death with IHCM 2, and also examine additional risk factors that play a crucial role in CVD: kidney disease, atrial fibrillation and hypertension. The same set of covariates is included for each of the four intrinsic hazards (MI, stroke, HF and death) for every interaction model with the recurrent hazards left as intercepts.

For the IRHCM, we began with IHCM 1 and added the full set of covariates (see Table 1) for each recurrent hazard and performed multiple rounds of backward selection to determine which covariates retained statistical significance for that recurrent hazard. Thus, we began with the full covariates for β_{MM} (corresponding to covariate vector X_{MM_i}) and determined its final set of covariates via rounds of backward of selection. We then proceeded to perform variable selection for β_{MS} in the same manner, retaining the final set of variables for the preceding β_{MM} , and so on, until variable selection for the last regression covariate coefficient vector, β_{DH} was completed. Throughout this variable selection process, we assessed the goodness of fit for the model up to that point using the approach that we described previously.⁶ Very briefly, we predicted event-free survival at 1-year, 2-year, 3-year and 4-year increments for all individuals at baseline, individuals that had 1 or more events, individuals that had 2 or more events, individuals that had 3 or more events and individuals that had 4 or more events. Our dataset contained the binary result of whether or not that individual had any event, nonfatal or fatal, within that time frame; censored observations were handled in a manner identical to that detailed in our previous work.⁶ We obtained the estimated area under the curve (AUC) and its standard error of the

resulting receiver operating characteristic (ROC) curve for each time frame and number of events, and this AUC was a measure of goodness of fit for the model.

For the IRHCM, the goodness of fit played a role in variable selection. If we found that the statistically significant covariates that remained after backward selection for a particular recurrent hazard resulted in lower AUC's for one or more event histories (e.g. individuals with 3+ events, individuals with 4+ events, and so on) then we did not retain those covariates and opted for an intercept term for that recurrent hazard. We report the backward selection process for IRHCM in Table 3.

RESULTS

For IHCM 1 and IRHCM, a total of 3,062 observations (9.18%) were removed from the full ALLHAT in-trial dataset ($N = 33,357$) due to missing values in the covariates, resulting in 30,295 observations for those analyses. For IHCM 2, 1,331 observations were removed for atrial fibrillation due to missing covariates resulting in 32,026 observations; 1,460 observations were removed for kidney disease due to missing covariates resulting in 31,897 observations; 1 observation was removed for hypertension treated at baseline due to a missing covariate resulting in 33,356 observations. The parameter estimates and their 95% confidence intervals (CI's) for IHCM 1 are reported in Table 4. The intercept term for each intrinsic hazard regression covariate coefficient vector (μ_M, μ_S, μ_H and μ_D for MI, stroke, HF and death, respectively) represents the reference group for all of the covariates in that intrinsic hazard. For MI, the intercept term for μ_M corresponds to the reference group for all MI covariates, i.e. individuals 55-64 years of age, nondiabetic, no MI or stroke prior to the study, female, no prior CABG, no history of OASCVD, normal kidney function ($\text{eGFR} \geq 60 \text{ ml/min/1.73m}^2$), no aspirin use,

nonsmokers and in the chlorthalidone treatment arm. The MI intrinsic hazard parameter intercept [0.0011 (0.0001, 0.0022)] represents the annual incidence of MI in these individuals. The remaining parameters that comprise μ_M represent the additional, or excess, hazard contributed by that covariate (which may be positive or negative) such that the covariate may increase or decrease the absolute risk (in this case, annual incidence of MI). Neither amlodipine nor lisinopril conferred statistically significant excess risk to MI as compared to chlorthalidone. As an illustrative example, diabetes would impart an excess hazard of 0.0030, such that a diabetic individual who was in the reference category for all other covariates would have an annual incidence of MI: [0.0011 + 0.0030 = 0.0041]. For MI, age (the 65-79 year and 80+ year age groups), diabetes, prior MI or stroke, male sex, previous CABG, history of OASCVD, kidney disease (eGFR < 60 mL/min/1.73m²), aspirin use and smoking (past and current) are all statistically significant risk factors that directly contribute to the annual incidence of MI. As a further example, a 66-year-old male diabetic with kidney disease and history of OASCVD, who is a past smoker and randomized to the chlorthalidone treatment arm would have an annual incidence of MI: [0.0011 + 0.0035 + 0.0030 + 0.0038 + 0.0020 + 0.0019 + 0.0013 = 0.0166] and 95% CI (0.0144, 0.0188). This corresponding Wald 95% CI is constructed using the standard error obtained from the informative matrix which is itself obtained in the standard manner from the hessian matrix of the log likelihood function detailed in our previous work ⁶ at the converged maximum likelihood estimates.

The recurrent hazards (β_{MM} , β_{MS} and β_{MH}) are intercept terms and they are all positive and statistically significant. Thus, MI, stroke and HF each imparts an additional (or excess) hazard for a future MI. Similar to what we found in our previous work, ⁶ MI imparts the greatest hazard

to its own recurrence [β_{MM} ; 0.0543 (0.0473, 0.0613)], HF imparts the next highest hazard to future MI [β_{MH} ; 0.0123 (0.0070, 0.0175)]; followed by stroke [β_{MS} ; 0.0092 (0.0035, 0.0149)]. The intrinsic hazard of MI (as well as stroke, HF and death) can be calculated for any individual in the dataset using a linear combination of their covariates and the parameter estimates provided in Table 4; furthermore, the total hazard of any event (MI, stroke, HF or death) can be calculated as the sum of that event's intrinsic hazard, and any recurrent hazards accrued from prior nonfatal events (MI, stroke and HF) that have occurred up to that point. To extend our example from the previous paragraph, that very same 66-year-old male if he develops 1 MI, 0 strokes and 1 HF in the course of the study up to the time point of interest, his updated annual incidence of MI would be: $[0.0166 + 0.0543 + 0 + 0.0123 = 0.0832]$ with 95% CI (0.0748, 0.0916).

The full results for MI, stroke, HF and death for IHCM 1 are provided in Table 4. We will highlight the key results. Age, diabetes, previous MI or stroke, kidney disease and smoking are the common risk factors for all of the intrinsic hazards (MI, stroke, HF and death). We first note that age has a linear relationship with intrinsic stroke risk: from age 55 onward, the absolute risk of stroke [0.0023 (0.0020, 0.0026)] increases linearly with every decade. We found in our statistical analyses that the ordinal age variable (see Table 1 for details) provided the best fit (as measured by the Akaike information criterion [AIC]) for univariate and multivariate IHCM models. Furthermore, diabetes imparts a greater intrinsic risk to HF [0.0038 (0.0030, 0.0047)] than it does to MI [0.0030 (0.0019, 0.0040)] and stroke [0.0030 (0.0022, 0.0038)], respectively. Similarly, kidney disease imparts a greater intrinsic risk to HF [0.0037 (0.0024, 0.0050)] than it does to MI [0.0020 (0.0005, 0.0035)] and stroke [0.0013 (0.0002, 0.0024)]. By contrast, prior MI or stroke as a baseline covariate imparts similar risk to MI [0.0046 (0.0030, 0.0061)], stroke [0.0041 (0.0030,

00.0052)] and HF [0.0042 (0.0030, 0.0053)]. Atrial fibrillation imparts more risk to HF [0.0230 (0.0174, 0.0287)] than it does to death [0.0097 (0.0038, 0.0156)] and stroke [0.0089 (0.0049, 0.0130)], but does not pose a statistically significant risk to MI. Stage 2 hypertension at baseline imparts similar risk to stroke [0.0014 (0.0005, 0.0023)] and HF [0.0016 (0.0007, 0.0025)] but not to MI or death. Diabetes imparts a higher risk to death [0.0085 (0.0070, 0.0101)] than it does to the nonfatal events. Kidney disease [0.0145 (0.0119, 0.0172)] and current smoking [0.0141 (0.0120, 0.0163)] also confer a higher risk to death than they do to the nonfatal events. Similarly, history of MI or stroke at baseline imparts approximately twice the risk to death [0.0088 (0.0067, 0.0109)] than it does to nonfatal events. For the treatment arms, there is a statistically significant increase in risk of HF in amlodipine compared to chlorthalidone; lisinopril does not differ from chlorthalidone for intrinsic risk of any of the four outcomes.

As is seen for MI, the recurrent hazards for stroke (β_{SM} , β_{SS} and β_{SH}), HF (β_{HM} , β_{HS} and β_{HH}) and death (β_{DM} , β_{DS} and β_{DH}) are all positive and statistically significant. Therefore, MI, stroke and HF each imparts an additional hazard for its own recurrence, and that of one another event's occurrence or recurrence. Stroke imparts the greatest risk to its own recurrence [β_{SS} ; 0.0226 (0.0160, 0.0291)] as does HF [β_{HH} ; 0.1230 (0.1110, 0.1350)]. HF confers the highest risk to death [β_{DH} ; 0.0678 (0.0579, 0.0777)] followed by stroke [β_{DS} ; 0.0419 (0.0315, 0.0523)] and then MI [β_{DM} ; 0.0086 (0.0036, 0.0137)].

We report the goodness of fit of IHCM 1 in Table 5. A key feature is the predictive role of the covariates starting from baseline (0 events); at the 1-year mark, the AUC is statistically significant and reasonably predictive [0.67 [0.65, 0.68]], which holds steady at 2 years [0.67 (0.66, 0.68)] and rises slightly at the 3-year mark [0.68 (0.67, 0.69)], remaining there at 4 years [0.68

(0.68, 0.69)]. However, the AUC drops for individuals with 1+ events at 1 year [0.61 (0.59, 0.63)], rising to [0.63 (0.61, 0.65)] at the 2-year mark, and remaining there for 3 years [0.63 (0.61, 0.65)] and 4 years [0.63 (0.61, 0.65)], respectively. The AUC drops further for 2+ events at 1 year [0.57 (0.54, 0.61)] before rising slightly at the 2-year mark [0.58 (0.54, 0.62)], and continuing to rise at the 3-year [0.59 (0.55, 0.64)] and 4-year mark [0.62 (0.57, 0.67)], respectively. The AUC starts to climb back up for 3+ events at year 1 [0.60 (0.54, 0.66)], rising steadily up to year 3 [0.67 (0.59, 0.75)] before dipping slightly at year 4 [0.65 (0.55, 0.76)]. The AUC's are the highest overall for 4+ events, beginning at year 1 [0.67 (0.58, 0.76)], with a steady rise at years 2 and 3 [0.68 (0.57, 0.78) and 0.70 (0.57, 0.82), respectively] and leveling off at year 4 [0.70 (0.56, 0.84)].

IHCM 2 examines interactions between treatment groups and the 8 selected risk factors described in the previous section. In Table 6, we report the results of the 3 risk factors that had one or more statistically significant interactions with treatment arms amlodipine and/or lisinopril, compared to chlorthalidone. The interaction of diabetes and amlodipine was positive and statistically significant for HF, which suggests that diabetes conferred a greater risk of developing HF in the amlodipine arm when compared to the risk of HF conferred by diabetes in the chlorthalidone arm. Next, the interaction of black race and lisinopril was positive and statistically significant for stroke. This suggests that blacks were at higher risk of stroke in the lisinopril group, compared to blacks' risk of stroke in the chlorthalidone group. Finally, the interaction of atrial fibrillation and amlodipine, and the interaction of atrial fibrillation and lisinopril, are both negative and statistically significant for death compared to chlorthalidone. This suggests that the risk of death conferred by atrial fibrillation is lower in both amlodipine compared to chlorthalidone and in lisinopril compared to chlorthalidone. The remaining 5 risk

factors, age, sex, kidney disease, hypertension treated at baseline and stage 1/stage 2 hypertension at baseline did not have statistically significant interactions with the treatment arms for MI, stroke, HF or death.

We now turn to the IRHCM. The IRHCM retains the intrinsic hazard covariates of IHCM 1 (Table 4) and the intrinsic hazard parameter values of IRHCM are similar or identical to that of IHCM 1, as expected. The recurrent hazard covariates of IRHCM, having undergone variable selection (modified backward selection as described in the methods section), retained several such covariates in the final IRHCM (Table 7). For β_{MM} , which denotes the risk that MI imparts to its own recurrence, male sex imparts additional risk [0.0218 (0.0079, 0.0357)] to recurrent MI as compared to female sex; similarly, kidney disease imparts risk [0.0246 (0.0061, 0.0431)] to recurrent MI as compared to normal kidney function. For β_{MH} , which denotes the risk that HF imparts to future MI, diabetes imparts additional risk [0.0136 (0.0029, 0.0242)] as compared to nondiabetic. For β_{HM} , which denotes the risk that MI imparts to future HF occurrence, age (both the 65-79 years age group and the over 80+ years age group) imparts risk of [0.0182 (0.0056, 0.0308)] and [0.0627 (0.0232, 0.1022)], respectively. Diabetes [0.0431 (0.0280, 0.0582)], history of OASCVD [0.0183 (0.0023, 0.0342)], and kidney disease [0.0275 (0.0081, 0.0470)] also impart risk to future HF occurrence in those with previous MI. Moreover, the amlodipine treatment arm imparts additional risk [0.0160 (0.0005, 0.0314)] compared to chlorthalidone to future HF in those with previous MI. For β_{HH} , which denotes the risk that HF imparts to its own recurrence, lisinopril lowers risk [-0.0302 (-0.0553, -0.0051)] as compared to chlorthalidone for HF recurrence. For β_{DM} , which denotes the risk that MI imparts to death, age (those 65 years and above) imparts risk [0.0176 (0.0085, 0.0268)]. This holds true for both the remaining two

recurrent hazards for death; for β_{DS} , age (ordinal, with the 55-64 years age group serving as the reference group) for every decade-increase starting at age 65 imparts risk to death from previous stroke [0.0228 (0.0166, 0.0290)]. For β_{DH} , age 65 years and above imparts risk of death from prior HF.

The goodness of fit of IRHCM is detailed in Table 8. The predictive role of the covariates starting at baseline (0 events) is retained and identical to that of IHCM. The AUC drops for 1+ events at 1 year [0.62 (0.60, 0.64)], rising to [0.64 (0.62, 0.66)] at the 2-year mark, and remaining there at 3 years [0.64 (0.62, 0.66)] and rising again at the 4-year point [0.66 (0.64, 0.68)]. The AUC drops further for 2+ events at 1 year [0.59 (0.55, 0.62)] before rising slightly at the 2-year mark [0.60 (0.57, 0.64)], and continuing to rise at the 3-year [0.62 (0.58, 0.66)] and 4-year mark [0.66 (0.61, 0.70)]. The AUC starts remains lower for 3+ events at year 1 [0.59 (0.53, 0.65)], rising steadily up to year 3 [0.65 (0.57, 0.73)] before dipping slightly at year 4 [0.64 (0.53, 0.75)]. The AUC's are highest overall for 4+ events, beginning at year 1 [0.63 (0.54, 0.72)], with a steady rise at years 2 and 3 [0.65 (0.54, 0.76) and 0.73 (0.60, 0.85), respectively] and jumping to [0.80 (0.67, 0.94)] at year 4. Overall, the IRHCM AUC's are improved over that of the IHCM, specifically for the 1+, 2+ and 4+ events.

DISCUSSION

In this paper, we extend our previous work significantly to include important covariates for both the intrinsic hazards for MI, stroke, HF and death [i.e. the so-called major adverse cardiovascular events (MACE)] in IHCM 1, and to include important covariates for both the intrinsic and recurrent hazards in IRHCM. Recently, there has been a great deal of renewed and

significant interest in MACE and our work provides additional, critical insights in this important area.¹²

The majority of survival analysis models, including the Cox proportional hazards model^{13,14} provide hazard ratios/relative risks of risk factors, leaving the baseline hazards, or absolute risks, unspecified. Our model is unique in that it directly provides the absolute risk, in the form of risk in excess to that of a reference group that is easily transformed to the absolute risk for an individual with a certain clinical profile and event history, for each of the MACE outcomes in this model (MI, stroke, HF and death), accounting for the competing nature of these cardiovascular (CV) events. In so doing, our model clearly delineates the risk factors for each particular CV event, allowing that event to have its own set of risk factors, and further delineates the risk factors for CVD recurrence. IHCM 1 showed that age, diabetes, a history of MI or stroke, kidney disease and smoking are common risk factors for all four intrinsic hazards. This is consistent with the vast clinical and epidemiological literature and known pathophysiology of CVD.^{1,3-5,7,12,15,16} It is worth noting that three of these risk factors are included in the original Framingham risk score, the other two being dyslipidemia and hypertension.¹⁷ This allows us to segue into risk factors for specific CV outcomes. ALLHAT's population was comprised of hypertensive individuals aged 55 years or above, with at least one additional CV risk factor. Because each ALLHAT participant was randomized to one three antihypertensive treatment arms, their blood pressure (BP) was managed during the trial. This likely blunted the effect of hypertension in CVD occurrence and recurrence in the course of the trial in comparison to that of a purely observational study, particularly as there were modest differences in mean blood pressure of participants between the three treatment arms at subsequent yearly follow-up visits (given the large sample size of

ALLHAT, even the small mean BP differences between treatment arms were statistically significant). IHCM 1 showed baseline hypertension to be a significant risk factor for stroke and HF, but not MI or death which suggests that stroke and HF are more sensitive to current or past hypertension than are MI and death. Atrial fibrillation was a significant risk factor for stroke, HF and death, but not for MI when adjusted for other risk factors. IHCM 1 also showed that atrial fibrillation conferred its greatest risk to HF and conferred comparatively lower risk to death and stroke. In a similar vein, returning to the risk factors common to all four outcomes, diabetes imparts greater risk to HF than it does to MI or stroke, but imparts its most risk overall to death. There has been a great deal of recent literature and studies focusing on the unique relationship between diabetes and HF, i.e. diabetes increases the risk of HF and worsens HF's disease course and prognosis.^{12,15,16,18,19} Studies have also suggested that diabetes may confer more risk to HF than it does to (nonfatal) MI or stroke, as reflected in our analyses.^{12,18} Kidney disease, in a similar pattern confers more risk to HF than it does to MI or stroke, and its highest risk to death. These patterns of risk factors and their clearly demarcated conferral of risk to specific CVD outcomes – conferring greater risk to some events, less risk to others, and in some cases, no significant risk to an event or events – yields valuable insight into the nature of CVD which in turn guides therapeutic management tailored to an individual's clinical profile. If a patient has certain risk factors, it is imperative to identify which CVD event(s) they are at highest risk for, and to select a treatment regimen that addresses that. For example, in an elderly male (80+ years of age) with diabetes, kidney disease and atrial fibrillation, the most likely nonfatal event would be HF, and they are of course at high risk of death as well; if this individual were to develop HF, their risk of dying at that point or soon thereafter would be high. Since our models showed that amlodipine

conferred risk of HF compared to chlorthalidone, and lisinopril lowered risk of recurrent HF conferred by antecedent HF, this individual would likely benefit from an ACE inhibitor as part of their drug regimen (barring other contraindications) whereas amlodipine should be avoided.

Another important aspect of CVD is CVD-related death. Our model includes all-cause-mortality (death) as one of the four competing events, death being the terminating event that is dependent on, or impacted by, one or more of the other three events (MI, stroke and HF) occurring beforehand. IHCM 1 yields the risk factors for death, which is particularly valuable because it delineates the separate risk that a particular risk factor (e.g. diabetes, kidney disease) confers to death, aside from the risk that that factor poses to CV events which in turn also increase the risk of death. In this manner, we can quantify the additional risk that diabetes, or atrial fibrillation or some other risk factor directly confers to death, and this risk is separate from that already posed by a prior CV event such as MI, stroke or HF. There are individuals who die from long-term complications of a chronic disease like diabetes or kidney disease without ever developing MI, stroke or HF. Our model provides both types of risks – the risk directly posed by a risk factor or disease process, and the risk posed by a prior CV event, which in turn is likely associated with the risk factor(s). This provides valuable risk quantification and stratification in both types of patients – those with risk factors and no prior CV events, and those with risk factors and prior CV events.

We will briefly mention the potential ramifications of the statistically significant interactions between treatment arms and risk factors shown by IHCM 2. First, the positive interaction between black race and lisinopril for stroke risk has been reported previously,^{8,9} and may partially reflect the diminished effectiveness of ACE inhibitors in blacks; their hypertension

is not as well controlled on lisinopril, resulting in increased stroke risk compared to chlorthalidone. The positive interaction of diabetes and amlodipine for HF risk may be partially reflective of the strong association between diabetes and HF; since the amlodipine arm contained a higher incidence of HF, this interaction may be reflective of a synergistic effect of diabetes and amlodipine in HF risk. Finally, the significant interactions between atrial fibrillation and both amlodipine and lisinopril such that both arms show a decreased risk of death compared to chlorthalidone, may suggest a protective role of amlodipine and lisinopril, respectively, compared to chlorthalidone in preventing death in those with atrial fibrillation in the long-term. Amlodipine was shown in a previous ALLHAT paper to lower the risk of death from atrial fibrillation compared to chlorthalidone.²⁰

We now turn to our models' predictive capabilities. IHCM 1 showed the significant role of risk factors in individuals with 0 events (i.e. study baseline), with reasonably good predictive capabilities at the 1, 2, 3 and 4-year time points. The predictive ability of IHCM 1 drops for 1+ events, 2+ events and 3+ events, with the 2+ events faring the worst at the 1-year time point. Prediction improves with by the 3 to 4-year time points, which suggests that the ability of events history to predictive future event occurrence or recurrence improves with increased time elapsed. IHCM 1 performs best in individuals with 4+ events, reaching AUC of 0.70 by the 3-year time point, which is quite good in this context. IRHCM performs better than IHCM for the 1+, 2+ and 4+ events, and comparatively for the 3+ events, which suggests that recurrent hazards covariates play a role in prediction, particularly age (risk of death conferred by prior MI, stroke and HF; risk of HF conferred by prior MI), diabetes (risk of MI conferred by prior HF; risk of HF conferred by prior MI), and kidney disease (risk of MI conferred by prior MI; risk of HF conferred

by prior MI) among others. IRHCM performs particularly well for individuals with 4+ events, reaching AUC of 0.73 at the 3-year mark, and climbing all the way up to 0.80 at the 4-year mark. For 1+ and 2+ events, IRHCM nearly catches up to the baseline/0 events individuals, reaching AUC of 0.66 by the 4-year mark. Both the IHCM 1 and the IRHCM have significant potential for utility as a clinical risk score or decision rule that utilizes both risk factors and event history to assist prediction of future events.

The overall pattern of both IHCM and IRHCM to perform best for individuals at baseline (0 events) and individuals with 4+ events suggest several things. First, the risk factors tailored to each event type play a dominant role in prediction. Second, individuals with 4+ events tend to have 1 or more HF events in their history. Since HF tends to be a late event, in the sense that it tends to have antecedent CV event(s) such as MI, and HF itself is a strong risk factor for future HF, this heightened predictive capability of both IHCM and IRHCM is likely reflective of that.

We now acknowledge a couple of limitations which we view as important future directions and extensions of our work. First, the decrease in AUC's for the 1+, 2+ and 3+ events particularly at the earlier time points can be partially explained by the fact that the increased risk posed by an event may be ameliorated by intervention or management of risk factors at that time, going forward. Such interventions can be addressed by time dependent covariates, whereas we utilized fixed covariates for all of our analyses. Our reasons for doing so are two-fold: first, as in any longitudinal study, there are missing covariates both at baseline and at subsequent follow up time points. We already removed observations with missing baseline covariates for our models, which was fortunately a relatively small proportion (< 10%) and unlikely to be of consequence in our analyses. However, employing time dependent covariates from follow up

time points would ensure removal of additional individuals with missing covariates, which would likely compromise our analyses, particularly given the relatively small total number of recurrent CVD events in the ALLHAT in-trial dataset. The handling of missing covariates, particularly in longitudinal studies, is a very important area of inquiry, and would be an important extension of our work, allowing for and potentially combining with, time-dependent analyses. Second, we wanted our already complex models to handle fixed covariates first in order to determine how well the models performed before attempting to handle time-dependent covariates, which is inherently more complex.

A second limitation was our inability to use biomarkers, in part because ALLHAT was a large, simple trial that did not utilize biomarkers and also because biomarkers are much more ubiquitous today, with many of them having been discovered or repurposed in the last decade, after ALLHAT's in-trial period ended. Biomarkers such as NT-proBNP ²¹⁻²³ which have been extensively validated for HF occurrence and recurrence and more recently linked to stroke occurrence and recurrence ^{22,23} would be a natural covariate to add to our models when the models are applied to longitudinal studies that measure them. Moreover, the addition of biomarkers as covariates would likely improve performance of our models for the individuals with 1+, 2+, 3+ and 4+ events. Finally, we also applied our models to the same dataset for both parameter estimation and to assess predictive capabilities, which did not allow us to validate our model on data it has never seen. This last issue can be addressed by a supervised learning approach, which is the subject of a future work.

In closing, we anticipate that our models will play a significant role in the development of clinical CVD risk scores and related decision rules/algorithms that incorporate both risk factors

and event history, with the exciting addition of biomarkers both old and new, that will aid every physician in the optimal management and treatment of CVD and related disease, including risk factors that are quite often chronic diseases with devastating sequelae of their own. Given the enormous global CVD burden mentioned in the beginning of this paper, such a tool (or tools) cannot arrive soon enough.

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Table 1. Full IHCM 1 covariates

	Variable type	Reference Group	Additional categories or values
Age, years	Categorical	Age 55-64	Age 65-79; Age ≥ 80
Age*	Ordinal	--	0 = Age 55-64 1 = Age 65-74 2 = Age 75-84 3 = Age ≥ 85
Diabetes (at baseline)	Binary	No	Yes
Previous MI or stroke	Binary	No	Yes
Sex	Binary	Female	Male
Black	Binary	Nonblack	Black
Previous CABG	Binary	No	Yes
Hypertension treated at baseline	Binary	No	Yes
Hypertension (at baseline, based on average of two BP readings, mmHg)	Categorical	SBP < 140 and DBP < 90	Stage 1 hypertension (140 ≤ SBP < 160 and 90 < DBP < 100); Stage 2 hypertension (SBP ≥ 160 or DBP ≥ 100)
History of OASCVD	Binary	No	Yes
Atrial fibrillation (baseline or incident, detected by ECG at baseline or follow-up visit)	Binary	No	Yes
Kidney disease (at baseline)	Binary	GFR ≥ 60 mL/min/1.73m ²	GFR < 60 mL/min/1.73m ²
Aspirin use (at baseline)	Binary	No	Yes
Smoking history	Categorical	Nonsmoker	Past smoker; current smoker
LVH by echocardiogram (at baseline)	Binary	No	Yes
Obesity (at baseline)	Binary	BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²
CHD (at baseline)	Binary	No	Yes
Major ST depression or T-wave inversion on ECG (at baseline)	Binary	No	Yes
Treatment arm	Categorical	Chlorthalidone	Amlodipine; Lisinopril

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CHD, coronary heart disease; DBP, diastolic blood pressure; ECG, electrocardiogram; GFR, glomerular filtration rate;

MI, myocardial infarction; OASCVD, other atherosclerotic cardiovascular disease; SBP, systolic blood pressure.

Table 2. Modified backward selection for IHCM 1 covariates

	MI	Stroke	HF	Death
FULL IHCM 1: STATISTICALLY SIGNIFICANT COVARIATES	Age 65-79	Age [†]	Age 65-79	Age 65-79
	Age ≥ 80	Diabetes	Age ≥ 80	Age ≥ 80
	Diabetes	Previous MI or stroke	Diabetes	Diabetes
	Previous MI or stroke	Sex	Previous MI or stroke	Previous MI or stroke
	Sex	Black	Black	Sex
	Black	Stage 1 HTN	Previous CABG	Black
	Previous CABG	Stage 2 HTN	Stage 2 HTN	History of OASCVD
	History of OASCVD	History of OASCVD	History of OASCVD	Atrial fibrillation
	Kidney disease	Atrial fibrillation	Atrial fibrillation	Kidney disease
	Aspirin use	Kidney disease	Kidney disease	Aspirin use
	Past smoker	Current smoker	Past smoker	Past smoker
	Current smoker	CHD	Current smoker	Current smoker
	ST depression*	Amlodipine	LVH Obesity Amlodipine Lisinopril	LVH Obesity
BS 1	REMOVE: Black ST depression	REMOVE: CHD	REMOVE: Obesity [‡]	REMOVE: LVH
BS 2	--	REMOVE: OASCVD [‡]	REMOVE: Past smoker [‡]	REMOVE: Aspirin use [§]
BS 3	--	REMOVE: Stage 1 HTN [‡]	REMOVE: Black [‡]	REMOVE: Obesity [‡]
BS 4	--	REMOVE: Black [‡]	REMOVE: Age 65-79 [‡]	--
FINAL IHCM 1	Age 65-79 Age ≥ 80 Diabetes Previous MI or stroke Sex Previous CABG History of OASCVD	Age [†] Diabetes Previous MI or stroke Sex Stage 2 HTN Atrial fibrillation Kidney disease	Age ≥ 80 Diabetes Previous MI or stroke Previous CABG Stage 2 HTN History of OASCVD Atrial fibrillation	Age 65-79 Age ≥ 80 Diabetes Previous MI or stroke Sex Black History of OASCVD

Kidney disease	Current smoker	Kidney disease	Atrial fibrillation
Aspirin use	Amlodipine	Current smoker	Kidney disease
Past smoker	Lisinopril	LVH	Past smoker
Current smoker		Amlodipine	Current smoker
Amlodipine		Lisinopril	Amlodipine
Lisinopril			Lisinopril

Abbreviations: BS, backward selection; CABG, coronary artery bypass graft; CHD, coronary heart disease; DBP, diastolic blood pressure; HTN, hypertension; LVH, left ventricular hypertrophy; MI, myocardial infarction; OASCVD, other atherosclerotic cardiovascular disease; SBP, systolic blood pressure.

*Refers to major ST depression or T-wave inversion on electrocardiogram (ECG).

[†]For stroke, the age variable is ordinal as detailed in Table 1.

[‡]Removed as a covariate to stabilize the model as the regression covariate vector could not handle all statistically significant covariates.

[§]Aspirin use was found to be statistically not significant for death on the univariate ICHM, so it was removed in the second round of backward selection.

^{||}Treatment arm found to be a statistically significant covariate; treatments arms were retained as covariates for the intrinsic hazards regardless of statistical significance.

Table 3. Modified backward selection for IRHCM recurrent hazards covariates

	MM	MS	MH	SM	SS	SH
STATISTICALLY SIGNIFICANT COVARIATES AT THE START OF BACKWARD SELECTION (BS)	Sex	Atrial fibrillation	Diabetes	Previous MI or stroke Sex Black History of OASCVD Atrial fibrillation Aspirin use Lisinopril	Previous CABG Stage 2 HTN Kidney disease	Amlodipine
BS 1	--	REMOVE: Atrial fibrillation	--	REMOVE: History of OASCVD Atrial fibrillation	REMOVE: Previous CABG	REMOVE: Amlodipine
BS 2	--	--	--	REMOVE: Previous MI or stroke Sex Black Aspirin use Lisinopril	--	--
FINAL STATISTICALLY SIGNIFICANT COVARIATES	Sex Kidney disease*	Intercept	Diabetes	Intercept	Stage 2 HTN Kidney disease	Intercept
	HM	HS	HH	DM	DS	DH
STATISTICALLY SIGNIFICANT COVARIATES AT THE START OF BACKWARD SELECTION (BS)	Age 65-79 Age ≥ 80 Diabetes Previous MI or stroke History of OASCVD Kidney disease	Sex Previous CABG Stage 2 HTN Atrial fibrillation Kidney disease Aspirin use	Black History of OASCVD Lisinopril	Age 65-79	Age ≥ 80 Diabetes Black Previous CABG	Age 65-79 Sex Stage 2 HTN Atrial fibrillation

	Amlodipine	Past smoker Amlodipine				
BS 1	REMOVE: Previous MI or stroke	REMOVE: Kidney disease Past smoker Amlodipine	--	--	REMOVE: Diabetes Black	REMOVE: Sex
BS 2	--	REMOVE: Sex Aspirin use	--	--	REMOVE: Previous CABG	--
BS 3	--	REMOVE: Previous CABG	--	--	--	--
FINAL STATISTICALLY SIGNIFICANT COVARIATES	Age 65-79 Age ≥ 80 Diabetes History of OASCVD Kidney disease Amlodipine	Stage 2 HTN Atrial fibrillation	Black History of OASCVD Lisinopril	Age ≥ 65 [†]	Age [‡]	Age ≥ 65 [†] Stage 2 HTN Atrial fibrillation

Abbreviations: BS, backward selection; CABG, coronary artery bypass graft; HTN, hypertension; LVH, left ventricular hypertrophy; MI, myocardial infarction; OASCVD, other atherosclerotic cardiovascular disease.

*Kidney disease was found to be statistically significant when the full set of **MM** covariates was rerun, after diabetes was retained as a covariate for **MH**; retaining the full set of **MM** covariates improved the model goodness of fit (reflected by higher AUC's) in spite of most of the covariates being statistically not significant, so it was rerun after backward selection was completed for **MM**, **MS** and **MH**.

[†]Age 65-79 covariate was converted to the binary covariate Age ≥ 65 in scenarios in which the Age 65-79 covariate was retained but Age ≥ 80 was dropped during backward selection.

[‡]Age as an ordinal variable (refer to Table 1 for details) was found to yield an improved goodness of fit (reflected by higher AUC's) as compared to Age ≥ 80, so ordinal Age was retained for the final IRHCM.

Table 4. IHCM 1

		Baseline (excess) hazard/absolute risk*
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0011 (0.0001, 0.0022)
	Age	
	65-79	0.0035 (0.0025, 0.0045)
	≥ 80	0.0064 (0.0037, 0.0091)
	Diabetes	0.0030 (0.0019, 0.0040)
	Previous MI or stroke	0.0046 (0.0030, 0.0061)
	Sex	0.0038 (0.0027, 0.0048)
	Previous CABG	0.0089 (0.0066, 0.0112)
	History of OASCVD	0.0019 (0.0007, 0.0032)
	Kidney disease	0.0020 (0.0005, 0.0035)
	Aspirin use	0.0018 (0.0006, 0.0029)
	Smoking	
	Past	0.0013 (0.0002, 0.0023)
	Current	0.0032 (0.0019, 0.0045)
	Amlodipine	-0.0003 (-0.0014, 0.0008)
	Lisinopril	-0.0001 (-0.0012, 0.0009)
	β_{MM}	0.0543 (0.0473, 0.0613)
	β_{MS}	0.0092 (0.0035, 0.0149)
	β_{MH}	0.0123 (0.0070, 0.0175)
Stroke	μ_S	
	Intercept	0.0007 (0.0001, 0.0012)
	Age*	0.0023 (0.0020, 0.0026)
	Diabetes	0.0030 (0.0022, 0.0038)
	Previous MI or stroke	0.0041 (0.0030, 0.0052)
	Sex	0.0013 (0.0007, 0.0019)
	Hypertension (Stage 2)	0.0014 (0.0005, 0.0023)
	Atrial fibrillation	0.0089 (0.0049, 0.0130)
	Kidney disease	0.0013 (0.0002, 0.0024)
	Smoking (Current)	0.0024 (0.0014, 0.0033)
	Amlodipine	-0.0004 (-0.0010, 0.0002)
	Lisinopril	0.0007 (-0.0002, 0.0015)
	β_{SM}	0.0031 (0.0006, 0.0056)
	β_{SS}	0.0226 (0.0160, 0.0291)
	β_{SH}	0.0032 (0.0002, 0.0063)
HF	μ_H	
	Intercept	0.0006 (0.0002, 0.0010)
	Age (≥ 80)	0.0065 (0.0038, 0.0092)
	Diabetes	0.0038 (0.0030, 0.0047)
	Previous MI or stroke	0.0042 (0.0030, 0.0053)

	Previous CABG	0.0039 (0.0023, 0.0054)
	Hypertension (Stage 2)	0.0016 (0.0007, 0.0025)
	History of OASCVD	0.0016 (0.0007, 0.0025)
	Atrial fibrillation	0.0230 (0.0174, 0.0287)
	Kidney disease	0.0037 (0.0024, 0.0050)
	Smoking (Current)	0.0008 (0.0001, 0.0015)
	LVH by echocardiogram	0.0023 (0.0005, 0.0040)
	Amlodipine	0.0020 (0.0011, 0.0029)
	Lisinopril	0.0005 (-0.0002, 0.0011)
	β_{HM}	0.0558 (0.0487, 0.0630)
	β_{HS}	0.0114 (0.0057, 0.0171)
	β_{HH}	0.1230 (0.1110, 0.1350)
Death	μ_D	
	Intercept	0.0008 (-0.0001, 0.0017)
	Age	
	65-79	0.0109 (0.0094, 0.0125)
	≥ 80	0.0564 (0.0503, 0.0625)
	Diabetes	0.0085 (0.0070, 0.0101)
	Previous MI or stroke	0.0088 (0.0067, 0.0109)
	Sex	0.0059 (0.0044, 0.0074)
	Black	0.0029 (0.0016, 0.0043)
	History of OASCVD	0.0027 (0.0011, 0.0043)
	Atrial fibrillation	0.0097 (0.0038, 0.0156)
	Kidney disease	0.0145 (0.0119, 0.0172)
	Smoking	
	Past	0.0032 (0.0018, 0.0046)
	Current	0.0141 (0.0120, 0.0163)
	Amlodipine	0.0003 (-0.0009, 0.0015)
	Lisinopril	-0.0002 (-0.0014, 0.0010)
	β_{DM}	0.0086 (0.0036, 0.0137)
	β_{DS}	0.0419 (0.0315, 0.0523)
	β_{DH}	0.0678 (0.0579, 0.0777)

Abbreviations: CABG, coronary artery bypass graft; LVH, left ventricular hypertrophy; MI, myocardial infarction; OASCVD, other atherosclerotic cardiovascular disease.

*Excess hazard/absolute risk is the additional hazard/risk imparted by a risk factor compared to its reference group.

Table 5. Area under the curve for the IHCM 1.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=30,295	N=3,358	N=940	N=370	N=145
1	0.67 (0.65, 0.68)	0.61 (0.59, 0.63)	0.57 (0.54, 0.61)	0.60 (0.54, 0.66)	0.67 (0.58, 0.76)
2	0.67 (0.66, 0.68)	0.63 (0.61, 0.65)	0.58 (0.54, 0.62)	0.64 (0.58, 0.70)	0.68 (0.57, 0.78)
3	0.68 (0.67, 0.69)	0.63 (0.61, 0.65)	0.59 (0.55, 0.64)	0.67 (0.59, 0.75)	0.70 (0.57, 0.82)
4	0.68 (0.68, 0.69)	0.63 (0.61, 0.65)	0.62 (0.57, 0.67)	0.65 (0.55, 0.76)	0.70 (0.56, 0.84)

Table 6. IHCM 2: Interactions

DIABETES (N=33,357)		Baseline (excess) hazard/absolute risk*
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0102 (0.0093, 0.0111)
	Diabetes	0.0021 (0.0004, 0.0037)
	Amlodipine	0.0002 (-0.0013, 0.0017)
	Lisinopril	-0.0008 (-0.0023, 0.0006)
	Diabetes x Amlodipine	-0.0018 (-0.0044, 0.0008)
	Diabetes x Lisinopril	0.0003 (-0.0024, 0.0029)
	β_{MM}	0.0559 (0.0492, 0.0626)
	β_{MS}	0.0125 (0.0069, 0.0181)
	β_{MH}	0.0152 (0.0100, 0.0203)
Stroke	μ_S	
	Intercept	0.0051 (0.0044, 0.0057)
	Diabetes	0.0031 (0.0019, 0.0044)
	Amlodipine	-0.0001 (-0.0011, 0.0010)
	Lisinopril	0.0011 (<0.0001 [‡] , 0.0023)
	Diabetes x Amlodipine	-0.0011 (-0.0031, 0.0009)
	Diabetes x Lisinopril	-0.0006 (-0.0028, 0.0016)
	β_{SM}	0.0036 (0.0012, 0.0061)
	β_{SS}	0.0246 (0.0184, 0.0309)
	β_{SH}	0.0050 (0.0019, 0.0081)
HF	μ_H	
	Intercept	0.0046 (0.0040, 0.0052)
	Diabetes	0.0027 (0.0015, 0.0040)
	Amlodipine	0.0018 (0.0006, 0.0029)
	Lisinopril	0.0005 (-0.0005, 0.0016)
	Diabetes x Amlodipine	0.0031 (0.0007, 0.0054) [†]
	Diabetes x Lisinopril	0.0009 (-0.0013, 0.0030)
	β_{HM}	0.0578 (0.0508, 0.0648)
	β_{HS}	0.0146 (0.0091, 0.0201)
	β_{HH}	0.1265 (0.1151, 0.1379)
Death	μ_D	
	Intercept	0.0253 (0.0239, 0.0268)
	Diabetes	0.0073 (0.0046, 0.0099)
	Amlodipine	-0.0014 (-0.0037, 0.0010)
	Lisinopril	-0.0006 (-0.0029, 0.0018)
	Diabetes x Amlodipine	-0.0008 (-0.0050, 0.0034)
	Diabetes x Lisinopril	-0.0005 (-0.0048, 0.0038)
	β_{DM}	0.0145 (0.0091, 0.0198)
	β_{DS}	0.0527 (0.0425, 0.0629)

	β_{DH}	0.0725 (0.0629, 0.0821)
	RACE (N=33,357)	
		Baseline (excess) hazard/absolute risk*
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0125 (0.0115, 0.0135)
	Black	-0.0042 (-0.0057, -0.0027)
	Amlodipine	-0.0006 (-0.0022, 0.0011)
	Lisinopril	-0.0014 (-0.0030, 0.0002)
	Black x Amlodipine	0.0005 (-0.0020, 0.0029)
	Black x Lisinopril	0.0019 (-0.0006, 0.0043)
	β_{MM}	0.0555 (0.0488, 0.0622)
	β_{MS}	0.0126 (0.0070, 0.0182)
	β_{MH}	0.0156 (0.0105, 0.0208)
Stroke	μ_S	
	Intercept	0.0059 (0.0052, 0.0066)
	Black	0.0009 (-0.0003, 0.0021)
	Amlodipine	-0.0004 (-0.0015, 0.0008)
	Lisinopril	<0.0001 [‡] (-0.0012, 0.0011)
	Black x Amlodipine	-0.0003 (-0.0023, 0.0016)
	Black x Lisinopril	0.0026 (0.0004, 0.0047) [†]
	β_{SM}	0.0036 (0.0012, 0.0061)
	β_{SS}	0.0249 (0.0186, 0.0312)
	β_{SH}	0.0051 (0.0020, 0.0083)
HF	μ_H	
	Intercept	0.0054 (0.0048, 0.0061)
	Black	0.0003 (-0.0008, 0.0015)
	Amlodipine	0.0033 (0.0020, 0.0046)
	Lisinopril	0.0006 (-0.0005, 0.0018)
	Black x Amlodipine	-0.0010 (-0.0031, 0.0012)
	Black x Lisinopril	0.0005 (-0.0015, 0.0025)
	β_{HM}	0.0583 (0.0513, 0.0653)
	β_{HS}	0.0152 (0.0096, 0.0207)
	β_{HH}	0.1269 (0.1154, 0.1383)
Death	μ_D	
	Intercept	0.0271 (0.0256, 0.0286)
	Black	0.0022 (-0.0003, 0.0048)
	Amlodipine	-0.0020 (-0.0044, 0.0004)
	Lisinopril	-0.0017 (-0.0041, 0.0007)
	Black x Amlodipine	0.0010 (-0.0031, 0.0051)
	Black x Lisinopril	0.0025 (-0.0017, 0.0067)
	β_{DM}	0.0146 (0.0092, 0.0199)
	β_{DS}	0.0531 (0.0428, 0.0633)

	β_{DH}	0.0730 (0.0634, 0.0826)
ATRIAL FIBRILLATION (N=32,026)		
	Baseline (excess) hazard/absolute risk*	
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0111 (0.0103, 0.0119)
	Atrial fibrillation	0.0011 (-0.0041, 0.0063)
	Amlodipine	-0.0005 (-0.0017, 0.0008)
	Lisinopril	-0.0009 (-0.0022, 0.0004)
	Atrial fibrillation x Amlodipine	0.0044 (-0.0046, 0.0134)
	Atrial fibrillation x Lisinopril	0.0059 (-0.0034, 0.0153)
	β_{MM}	0.0560 (0.0492, 0.0628)
	β_{MS}	0.0121 (0.0064, 0.0177)
	β_{MH}	0.0156 (0.0103, 0.0208)
Stroke	μ_S	
	Intercept	0.0060 (0.0054, 0.0066)
	Atrial fibrillation	0.0097 (0.0038, 0.0155)
	Amlodipine	-0.0005 (-0.0014, 0.0004)
	Lisinopril	0.0009 (-0.0001, 0.0019)
	Atrial fibrillation x Amlodipine	0.0014 (-0.0080, 0.0108)
	Atrial fibrillation x Lisinopril	0.0008 (-0.0089, 0.0105)
	β_{SM}	0.0039 (0.0014, 0.0065)
	β_{SS}	0.0241 (0.0178, 0.0304)
	β_{SH}	0.0040 (0.0010, 0.0071)
HF	μ_H	
	Intercept	0.0051 (0.0046, 0.0056)
	Atrial fibrillation	0.0265 (0.0179, 0.0350)
	Amlodipine	0.0027 (0.0017, 0.0037)
	Lisinopril	0.0009 (<0.0001 [‡] , 0.0018)
	Atrial fibrillation x Amlodipine	0.0021 (-0.0117, 0.0160)
	Atrial fibrillation x Lisinopril	-0.0105 (-0.0231, 0.0020)
	β_{HM}	0.0580 (0.0510, 0.0650)
	β_{HS}	0.0132 (0.0077, 0.0187)
	β_{HH}	0.1251 (0.1135, 0.1366)
Death	μ_D	
	Intercept	0.0263 (0.0251, 0.0275)
	Atrial fibrillation	0.0260 (0.0153, 0.0366)
	Amlodipine	-0.0008 (-0.0028, 0.0011)
	Lisinopril	-0.0003 (-0.0023, 0.0017)
	Atrial fibrillation x Amlodipine	-0.0189 (-0.0337, -0.0040) [†]
	Atrial fibrillation x Lisinopril	-0.0186 (-0.0341, -0.0031) [†]
	β_{DM}	0.0145 (0.0091, 0.0198)
	β_{DS}	0.0524 (0.0421, 0.0627)

β_{DH}

0.0720 (0.0624, 0.0816)

Abbreviations: HF, heart failure; MI, myocardial infarction.

*Excess hazard/absolute risk is the additional hazard/risk imparted by a risk factor compared to its reference group.

[†]Statistically significant interaction

[‡]Due to rounding; absolute value is between 0 and 0.0001

Table 7. Final IRHCM

		Baseline (excess) hazard/absolute risk*
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0012 (0.0001, 0.0022)
	Age	
	65-79	0.0036 (0.0026, 0.0045)
	≥ 80	0.0066 (0.0039, 0.0093)
	Diabetes	0.0029 (0.0018, 0.0039)
	Previous MI or stroke	0.0046 (0.0030, 0.0061)
	Sex	0.0037 (0.0026, 0.0047)
	Previous CABG	0.0089 (0.0066, 0.0112)
	History of OASCVD	0.0019 (0.0007, 0.0032)
	Kidney disease	0.0019 (0.0004, 0.0034)
	Aspirin use	0.0018 (0.0007, 0.0030)
	Smoking	
	Past	0.0012 (0.0002, 0.0023)
	Current	0.0032 (0.0019, 0.0045)
	Amlodipine	-0.0003 (-0.0014, 0.0008)
	Lisinopril	-0.0002 (-0.0012, 0.0009)
	β_{MM}	
	Intercept	0.0342 (0.0228, 0.0456)
	Sex	0.0218 (0.0079, 0.0357)
	Kidney disease	0.0246 (0.0061, 0.0431)
	β_{MS}	0.0090 (0.0034, 0.0147)
	β_{MH}	
	Intercept	0.0060 (<0.0001 [‡] , 0.0120)
	Diabetes	0.0136 (0.0029, 0.0242)
Stroke	μ_S	
	Intercept	0.0007 (0.0001, 0.0012)
	Age ¹	0.0023 (0.0020, 0.0026)
	Diabetes	0.0030 (0.0022, 0.0038)
	Previous MI or stroke	0.0041 (0.0030, 0.0052)
	Sex	0.0013 (0.0007, 0.0019)
	Hypertension (Stage 2)	0.0014 (0.0005, 0.0023)
	Atrial fibrillation	0.0089 (0.0049, 0.0130)
	Kidney disease	0.0013 (0.0002, 0.0024)
	Smoking (Current)	0.0024 (0.0014, 0.0033)
	Amlodipine	-0.0004 (-0.0010, 0.0002)
	Lisinopril	0.0007 (-0.0002, 0.0015)
	β_{SM}	0.0031 (0.0006, 0.0056)
	β_{SS}	0.0226 (0.0160, 0.0291)
	β_{SH}	0.0032 (0.0002, 0.0063)

HF	μ_H	
	Intercept	0.0007 (0.0002, 0.0011)
	Age (≥ 80)	0.0062 (0.0036, 0.0088)
	Diabetes	0.0037 (0.0029, 0.0046)
	Previous MI or stroke	0.0043 (0.0031, 0.0054)
	Previous CABG	0.0039 (0.0023, 0.0055)
	Hypertension (Stage 2)	0.0016 (0.0008, 0.0025)
	History of OASCVD	0.0015 (0.0006, 0.0024)
	Atrial fibrillation	0.0228 (0.0172, 0.0284)
	Kidney disease	0.0036 (0.0023, 0.0049)
	Smoking (Current)	0.0008 (0.0001, 0.0016)
	LVH by echocardiogram	0.0023 (0.0005, 0.0040)
	Amlodipine	0.0020 (0.0011, 0.0028)
	Lisinopril	0.0005 (-0.0002, 0.0012)
	β_{HM}	
	Intercept	0.0124 (0.0033, 0.0216)
	Age	
	65-79	0.0182 (0.0056, 0.0308)
	≥ 80	0.0627 (0.0232, 0.1022)
	Diabetes	0.0431 (0.0280, 0.0582)
	History of OASCVD	0.0183 (0.0023, 0.0342)
	Kidney disease	0.0275 (0.0081, 0.0470)
	Amlodipine	0.0160 (0.0005, 0.0314)
	β_{HS}	0.0114 (0.0058, 0.0171)
	β_{HH}	
	Intercept	0.1278 (0.1135, 0.1422)
	Lisinopril	-0.0302 (-0.0553, -0.0051)
Death	μ_D	
	Intercept	0.0009 (-0.0001, 0.0018)
	Age	
	65-79	0.0104 (0.0089, 0.0120)
	≥ 80	0.0551 (0.0491, 0.0612)
	Diabetes	0.0088 (0.0072, 0.0104)
	Previous MI or stroke	0.0089 (0.0068, 0.0110)
	Sex	0.0061 (0.0046, 0.0076)
	Black	0.0029 (0.0015, 0.0043)
	History of OASCVD	0.0027 (0.0011, 0.0043)
	Atrial fibrillation	0.0093 (0.0034, 0.0151)
	Kidney disease	0.0146 (0.0119, 0.0172)
	Smoking	
	Past	0.0033 (0.0019, 0.0047)
	Current	0.0143 (0.0122, 0.0164)

Amlodipine	0.0003 (-0.0009, 0.0015)
Lisinopril	-0.0002 (-0.0014, 0.0010)
<hr/>	
β_{DM}	
Intercept	-0.0013 (-0.0069, 0.0042)
Age ≥ 65	0.0176 (0.0085, 0.0268)
<hr/>	
β_{DS}	
Intercept	0.0228 (0.0114, 0.0342)
Age [†]	0.0228 (0.0166, 0.0290)
<hr/>	
β_{DH}	
Intercept	0.0524 (0.0365, 0.0684)
Age ≥ 65	0.0203 (0.0002, 0.0403)

*Excess hazard/absolute risk is the additional hazard/risk imparted by a risk factor compared to its reference group.

[†]Age as an ordinal variable (see Table 1 for details) was found to yield an improved goodness of fit (reflected by higher AUC's) as compared to Age ≥ 80 , so ordinal Age was retained for the final IRHCM.

[‡]Due to rounding; absolute value is between 0 and 0.0001

Table 8. Area under the curve for the IRHCM.

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=30,295	N=3,358	N=940	N=370	N=145
1	0.67 (0.65, 0.68)	0.62 (0.60, 0.64)	0.59 (0.55, 0.62)	0.59 (0.53, 0.65)	0.63 (0.54, 0.72)
2	0.67 (0.66, 0.68)	0.64 (0.62, 0.66)	0.60 (0.57, 0.64)	0.64 (0.57, 0.70)	0.65 (0.54, 0.76)
3	0.68 (0.67, 0.69)	0.64 (0.62, 0.66)	0.62 (0.58, 0.66)	0.65 (0.57, 0.73)	0.73 (0.60, 0.85)
4	0.68 (0.68, 0.69)	0.66 (0.64, 0.68)	0.66 (0.61, 0.70)	0.64 (0.53, 0.75)	0.80 (0.67, 0.94)

CHAPTER 4: JOURNAL ARTICLE 3

A Supervised Learning Approach to a Competing Risk Model for Multi-type Recurrent Events

ABSTRACT

We adopt a supervised learning approach, utilizing bagged training sets and test sets to stabilize and validate our models described previously (IHCM 1 and IRHCM) to quantify multi-type recurrent events hazards in a competing risk framework, with death as the dependent terminating event. A total of 250 bagged training sets at 70% and 60% yielded similar tuned parameter estimates for IHCM 1, with smaller standard errors for 70% bagging, which showed lisinopril to impart a statistically significant intrinsic hazard of stroke and HF compared to chlorthalidone. Bagging at 70% and 60% showed similar performance in predictive capabilities on the full ALLHAT dataset and on corresponding test sets (30% and 40%, respectively). IRHCM bagged training sets at 70% yielded tuned parameter estimates with smaller standard errors compared to previous IRHCM results and similar results for lisinopril as bagged IHCM 1 (70%). IRHCM also performed similarly on the full dataset and relatively well on its corresponding test sets (30%). Bagging in a supervised learning framework accomplished our aims of stabilizing and validating our models in conjunction with variable selection.

INTRODUCTION

In our previous work, we first proposed a dynamic competing risk model for multi-type recurrent events and applied the model in the important setting of cardiovascular disease (CVD) to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study.¹ We subsequently extended the model to incorporate CVD risk factors as covariates for multiple cardiovascular (CV) outcomes in a competing risk framework for both incident and

recurrent CVD events [myocardial infarction (MI), stroke, heart failure (HF) and death from any cause (death)] with significant potential to develop a CV risk assessment/risk score tailored to the individual's clinical profile, that would be widely utilized by physicians for therapeutic management.² In this paper, we will implement a supervised learning approach to further develop our model in the following ways: 1) tune the estimated parameters for the models described in our second paper, IHCM 1 and IRHCM ²; 2) utilize the tuned parameters and their newly constructed 95% confidence intervals (CI) for potential variable selection; and 3) validate the model with the use of training sets and test sets.

METHODS

Parameter tuning and construction of confidence interval

All of our statistical analyses were carried out in R 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). For IHCM 1, we first split the full ALLHAT dataset ($n = 30,295$) described in detail in our second paper ² into 4 subsets: individuals that had 0 events throughout the in-trial portion of ALLHAT ($n = 26,937$); individuals who had 1 event ($n = 2,418$); individuals who had 2 events ($n = 570$); and individuals who had 3 or more events ($n = 370$). We then created 250 bagged training sets by randomly selecting 70% of observations from each of the 4 subsets, i.e. we randomly selected 70% of observations ($n = 18,856$) from individuals who had 0 events, 70% of observations ($n = 1,693$) from individuals who had 1 event, 70% of observations ($n = 399$) from individuals who had 2 events, and 70% of observations ($n = 259$) from individuals who had 3+ events, and combining all of these observations into a single bagged training set ($n = 21,207$). This was done to ensure that each bagged training set was balanced

with respect to preserving the relative proportions of CVD events of the original ALLHAT dataset. This procedure was repeated for a total of 250 bagged training sets.

We fitted IHCM 1 for each bagged training set to obtain the parameter estimates via the modified Newton Raphson optimization algorithm described in our first paper.¹ We obtained the final parameter estimates for IHCM 1 by taking the mean of the 250 bagged parameter estimates, and the standard error of each final parameter estimate by taking the standard deviation of the 250 bagged parameter estimates for each parameter. We then constructed the 95% Wald CI for each parameter using the final parameter estimate and its standard error.

We then applied the IHCM 1 parameter estimates, tuned by the 250 bagged training sets, to the original ALLHAT dataset ($n = 30,295$) to assess the goodness of fit for IHCM 1 using the approach that we described in our previous papers.^{1,2} Very briefly, we predicted event-free survival at 1-year, 2-year, 3-year and 4-year increments for all individuals at baseline, individuals that had 1 or more events, individuals that had 2 or more events, individuals that had 3 or more events and individuals that had 4 or more events. The ALLHAT dataset contained the binary result of whether or not that individual had any event, nonfatal or fatal, within that time frame; censored observations were handled in a manner identical to that detailed in our previous work.^{1,2} The estimated area under the curve (AUC) and its standard error of the resulting receiver operating characteristic (ROC) curve for each time frame and number of events were obtained and this AUC was a measure of goodness of fit for the model.

We repeated the above procedures for IHCM 1 with 250 bagged training sets of 60%, i.e. each training set contained randomly selected 60% of observations from each of the 4 subsets [60% of observations ($n = 16,162$) from individuals who had 0 events, 60% of observations ($n =$

1,451) from individuals who had 1 event, 60% of observations ($n = 342$) from individuals who had 2 events, and 60% of observations ($n = 222$) from individuals who had 3+ events, and combining all of these observations into a single bagged training set ($n = 18,177$)]. The final parameter estimates and their 95% CI's were constructed in the same manner and the goodness of fit assessed.

We repeated the entire procedure for the IRHCM described in our second paper ² to obtain 200 bagged training sets, the final IRHCM parameter estimates and their 95% CI's and goodness of fit. IRHCM has more parameters (77) than IHCM 1 (64) and takes longer to converge; due to constraints of computing speed and resources, we opted for 200 bagged training sets for IRHCM.

Supervised learning and model validation

For IHCM 1, each bagged training set (70% and 60%, respectively) had a corresponding test set (30% and 40%, respectively). The IHCM 1 parameters estimated from each bagged training set were applied to its corresponding test set (which was data that the model had never seen before, having been trained on the training set only). The resulting goodness of fit for the test set was obtained in the same manner described in the preceding section, with a slight adjustment: due to the small size of the test set (30%, $n = 9,088$; and 40%, $n = 12,118$), we predicted event-free survival at 1-year, 2-year and 3-year increments for all individuals at baseline (30%, $n = 9,088$; and 40%, $n = 12,118$), individuals that had 1 or more events (30%, $n = 1,007$; and 40%, $n = 1,343$), individuals that had 2 or more events (30%, $n = 282$; and 40%, $n = 376$) and individuals that had 3 or more events (30%, $n = 111$; and 40%, $n = 148$). The resulting goodness of fit AUC's for the 250 bagged test sets (30% and 40%, respectively) were

averaged, and the resulting mean goodness of fit AUC was the final estimate. The standard errors of each AUC final estimate were obtained by taking the standard deviation of the corresponding 250 bagged goodness of fit AUC's, and subsequently used to construct the 95% Wald CI for each AUC estimate.

The above procedure was repeated for the IRHCM for the 200 bagged training sets (70%) and their corresponding test sets (30%) and the final goodness of fit AUC's and their standard errors calculated, with resulting 95% Wald CI for each AUC.

RESULTS

The tuned parameters and their 95% CI's of IHCM 1 for both the 70% and 60% bagged training sets are reported in Table 1. The tuned parameter estimates for the 70% and 60% bagged training sets are very close or identical to one another. The corresponding standard errors for the 60% bagged sets are larger for every parameter estimate than that of the 70% bagged sets; as a result, the corresponding 95% CI for each parameter is wider for the 60% bagged sets than the 70% bagged sets. The lisinopril treatment arm compared to chlorthalidone imparts a statistically significant intrinsic hazard for stroke [0.0007 (<0.0001¹, 0.0013)] and HF [0.0005 (<0.0001¹, 0.0009)], respectively for the 70% bagged sets; in contrast, lisinopril does not impart a statistically significant hazard compared to chlorthalidone for stroke and HF in the 60% bagged sets. Both the tuned parameters of the 70% (Table 2a) and the 60% bagged sets (Table 2b) yield essentially identical AUC's as goodness of fit measures when applied to the original ALLHAT dataset ($n = 30,295$). The 70% bagged training set parameters' performance on their corresponding

¹Due to rounding; lower 95% CI limit is between 0 and 0.0001

30% test sets (Table 3a) is nearly identical to that of the 60% bagged training set parameters' performance on their 40% test sets (Table 3b), with the 70% performing slightly better for individuals with 2+ events at the 1-year mark, and for individuals with 3+ events at the 3-year mark. Both the 70% and the 60% bagged training set parameters essentially retain their predictive abilities for individuals at baseline (0 events), with a decrease in prediction for individuals with 1+ events, further decrease in prediction for individuals with 2+ events, and then increase in prediction for individuals with 3+ events, which continues to improve from the 1-year mark to the 3-year mark, at which point it essentially catches up to the 3-year mark for all individuals (0 events).

The tuned parameters and their 95% CI's of IRHCM for the 200 bagged training sets (70%) are reported in Table 4. Similar to the bagged IHCM 1, the lisinopril treatment arm compared to chlorthalidone imparts a statistically significant intrinsic hazard for stroke [0.0007 ($<0.0001^1$, 0.0013)] and HF [0.0005 (0.0001, 0.0010)], respectively. In contrast, the IRHCM from our previous paper ² did not show lisinopril (compared to chlorthalidone) as a statistically significant covariate for intrinsic hazard of stroke, nor HF. The tuned parameters of IRHCM yielded by the bagged training sets is overall very similar or identical to IRHCM of our previous paper, ² with smaller standard errors reflected in narrower 95% CI's for the bagged IRHCM parameters. Moreover, the tuned IRHCM parameters of the 70% bagged sets (Table 5) yield identical AUC's as goodness of fit measures when applied to the original ALLHAT dataset ($n = 30,295$), as the original IRHCM parameters reported previously.² The IRHCM 70% bagged training set parameters' performance on their corresponding 30% test sets is reported in Table 6. IRHCM performs comparatively to IHCM 1's 70% bagged training set parameters for individuals at baseline (0 events); IRHCM

slightly outperforms IHCM 1 for individuals with 1+ and 2+ events, and slightly decreases in predictive performance for individuals with 3+ events compared to IHCM 1.

DISCUSSION

In this paper, we wished to further develop our model in several important ways: first, we wanted to improve our parameter estimates for our previously described models (IHCM 1 and IRHCM) with the potential for variable selection. We also wanted to stabilize the models by reducing the standard errors of the parameter estimates and finally, we wished to validate our models by assessing its predictive capabilities on data it has never seen.

To accomplish all of these aims, we elected a supervised learning approach by training our models on a subset of the full ALLHAT dataset ($n = 30,295$) utilized in our second paper ² and then running the trained models on the remaining subset. Supervised learning is a well-established type of machine learning algorithm that can address and improve common problems of statistical models including overfitting.³ Specifically, bagging (also known as bootstrap aggregating) is a machine learning algorithm designed to improve the stability and accuracy of models and reduces variance and overfitting.⁴ It is easily incorporated into a supervised learning approach in the manner described here.

Our bagged training sets (70%) yielded stable parameter estimates for IHCM and IRHCM with reduced standard errors which resulted in tighter 95% CI's for each parameter estimate. This directly resulted in a type of variable selection, in that the lisinopril treatment arm (in comparison to chlorthalidone) was found to impart a statistically significant intrinsic hazard for stroke and HF. A statistically significant higher risk of stroke in the lisinopril arm compared to chlorthalidone, and a statistically significant higher risk of HF in the lisinopril arm compared to

chlorthalidone have been reported previously.^{5,6} Our updated IHCM 1 and IRHCM results are thus consistent with previous ALLHAT results. Due to the tuned parameter estimates for IHCM 1 and IRHCM in this paper being very close or identical to our previously reported IHCM 1 and IRHCM results, they performed comparatively with respect to goodness of fit measures on the full ALLHAT dataset.

We also validated our model by running each model trained on the bagged training set, on its corresponding test set. Both the 70% and the 60% training set models for both IHCM 1 and IRHCM performed comparatively with respect to their predictive capabilities on their 30% and 40% test sets, respectively. IHCM 1 and IRHCM retained their predictive abilities on the test set, i.e. data it has never seen before, for all individuals at baseline (0 events), with similar decreases for individuals with 1+ and 2+ events, and again increasing for individuals with 3+ events, and improvement with later time points (3-year mark vs 1-year mark). These results suggest that our model is robust and performs relatively well on data it has never seen, and does not suffer from the common problem of overfitting.

We acknowledge one or two limitations that should be considered as future directions and further extensions of our work. Due to the computing resources and length of time required for our models to converge, particularly the IRHCM, we limited our number of bagged training sets to 250 and 200, respectively for IHCM 1 and IRHCM. It is likely and in fact probable, that our models would have been improved if we had performed 1,000 bagged training sets which would have resulted in more stable estimates with smaller standard errors and tighter 95 CI's. This may have yielded improved goodness of fit measures on the original ALLHAT dataset, whereas our current models performed about the same. Furthermore, the IRHCM dropped slightly in its

predictive capabilities for individuals with 3+ events compared to IHCM 1, and this was likely driven by IRHCM performing slightly worse in individuals with 3 events; since individuals who had 4+ events were combined with this group, IRHCM's likely better performance in that group was not captured. In any case, the lowered performance for both IHCM 1 and IRHCM for individuals with 1+, 2+ and 3+ events compared to all individuals at baseline (0 events) and individuals with 4+ events has been discussed at length in our previous paper, with ways to address it in future work.²

Overall, we accomplished our aims of stabilizing our model, with reduced standard errors and tighter confidence intervals that resulted in a type of variable selection with important ramifications (i.e. lisinopril imparts a statistically significant intrinsic hazard for stroke and HF, relative to chlorthalidone). Furthermore, we validated our model by showing its ability to perform relatively well and retain its predictive capabilities in data it has never seen, and in so doing, we directly addressed a limitation in our previous work in which we trained the models on the full dataset and assessed prediction on the same dataset. Bagging in a supervised learning framework is a valuable and powerful tool to improve and stabilize existing models, as well as validating them.

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Table 1. IHCM, tuned parameters from 250 bagged datasets

		Baseline (excess) hazard/absolute risk*	
		70/30	60/40
	Parameter	Estimate (95% CI)	Estimate (95% CI)
MI	μ_M		
	Intercept	0.0011 (0.0003, 0.0018)	0.0010 (0.0001, 0.0020)
	Age		
	65-79	0.0035 (0.0028, 0.0042)	0.0035 (0.0026, 0.0044)
	≥ 80	0.0064 (0.0047, 0.0080)	0.0064 (0.0042, 0.0085)
	Diabetes	0.0030 (0.0023, 0.0037)	0.0031 (0.0022, 0.0039)
	Previous MI or stroke	0.0046 (0.0036, 0.0056)	0.0046 (0.0034, 0.0058)
	Sex	0.0038 (0.0031, 0.0044)	0.0038 (0.0030, 0.0046)
	Previous CABG	0.0089 (0.0074, 0.0103)	0.0089 (0.0072, 0.0106)
	History of OASCVD	0.0020 (0.0011, 0.0028)	0.0020 (0.0009, 0.0031)
	Kidney disease	0.0019 (0.0009, 0.0029)	0.0019 (0.0007, 0.0032)
	Aspirin use	0.0018 (0.0010, 0.0026)	0.0018 (0.0008, 0.0028)
	Smoking		
	Past	0.0013 (0.0005, 0.0020)	0.0013 (0.0004, 0.0022)
	Current	0.0033 (0.0024, 0.0042)	0.0033 (0.0022, 0.0044)
	Amlodipine	-0.0003 (-0.0011, 0.0004)	-0.0003 (-0.0013, 0.0006)
	Lisinopril	-0.0001 (-0.0009, 0.0006)	-0.0001 (-0.0011, 0.0008)
	β_{MM}	0.0541 (0.0499, 0.0582)	0.0540 (0.0492, 0.0589)
	β_{MS}	0.0091 (0.0053, 0.0129)	0.0092 (0.0043, 0.0141)
	β_{MH}	0.0123 (0.0090, 0.0155)	0.0122 (0.0081, 0.0163)
Stroke	μ_S		
	Intercept	0.0006 (0.0002, 0.0011)	0.0006 (<0.0001, 0.0013)
	Age*	0.0023 (0.0019, 0.0027)	0.0023 (0.0018, 0.0028)
	Diabetes	0.0030 (0.0025, 0.0036)	0.0031 (0.0023, 0.0038)
	Previous MI or stroke	0.0041 (0.0033, 0.0049)	0.0041 (0.0032, 0.0050)
	Sex	0.0013 (0.0008, 0.0019)	0.0014 (0.0007, 0.0021)
	Hypertension (Stage 2)	0.0014 (0.0008, 0.0020)	0.0014 (0.0006, 0.0022)
	Atrial fibrillation	0.0090 (0.0061, 0.0118)	0.0090 (0.0056, 0.0125)
	Kidney disease	0.0013 (0.0005, 0.0021)	0.0013 (0.0004, 0.0023)
	Smoking (Current)	0.0024 (0.0018, 0.0030)	0.0024 (0.0016, 0.0032)
	Amlodipine	-0.0005 (-0.0012, 0.0002)	-0.0005 (-0.0014, 0.0003)
	Lisinopril	0.0007 (<0.0001 [‡] , 0.0013) [†]	0.0007 (-0.0001, 0.0014)
	β_{SM}	0.0032 (0.0014, 0.0049)	0.0032 (0.0008, 0.0055)
	β_{SS}	0.0227 (0.0186, 0.0267)	0.0227 (0.0177, 0.0277)
	β_{SH}	0.0032 (0.0012, 0.0052)	0.0033 (0.0007, 0.0059)
HF	μ_H		
	Intercept	0.0006 (0.0004, 0.0009)	0.0006 (0.0003, 0.0010)
	Age (≥ 80)	0.0065 (0.0046, 0.0084)	0.0065 (0.0041, 0.0088)

	Diabetes	0.0038 (0.0033, 0.0044)	0.0039 (0.0032, 0.0045)
	Previous MI or stroke	0.0042 (0.0033, 0.0050)	0.0041 (0.0032, 0.0051)
	Previous CABG	0.0039 (0.0028, 0.0050)	0.0039 (0.0025, 0.0053)
	Hypertension (Stage 2)	0.0016 (0.0010, 0.0022)	0.0016 (0.0009, 0.0024)
	History of OASCVD	0.0016 (0.0010, 0.0022)	0.0016 (0.0008, 0.0023)
	Atrial fibrillation	0.0229 (0.0194, 0.0264)	0.0229 (0.0187, 0.0271)
	Kidney disease	0.0037 (0.0028, 0.0046)	0.0037 (0.0025, 0.0048)
	Smoking (Current)	0.0008 (0.0003, 0.0013)	0.0008 (0.0002, 0.0015)
	LVH by echocardiogram	0.0023 (0.0011, 0.0035)	0.0023 (0.0009, 0.0038)
	Amlodipine	0.0019 (0.0014, 0.0025)	0.0019 (0.0012, 0.0027)
	Lisinopril	0.0005 (<0.0001 [‡] , 0.0009) [†]	0.0005 (-0.0001, 0.0011)
	β_{HM}	0.0556 (0.0507, 0.0606)	0.0557 (0.0496, 0.0618)
	β_{HS}	0.0115 (0.0077, 0.0153)	0.0115 (0.0071, 0.0159)
	β_{HH}	0.1227 (0.1143, 0.1312)	0.1226 (0.1115, 0.1337)
Death	μ_D		
	Intercept	0.0008 (-0.0002, 0.0017)	0.0007 (-0.0005, 0.0020)
	Age		
	65-79	0.0109 (0.0099, 0.0120)	0.0109 (0.0097, 0.0122)
	≥ 80	0.0563 (0.0525, 0.0601)	0.0563 (0.0515, 0.0611)
	Diabetes	0.0085 (0.0074, 0.0095)	0.0085 (0.0071, 0.0098)
	Previous MI or stroke	0.0088 (0.0076, 0.0101)	0.0088 (0.0071, 0.0105)
	Sex	0.0060 (0.0049, 0.0070)	0.0060 (0.0046, 0.0073)
	Black	0.0030 (0.0021, 0.0039)	0.0030 (0.0019, 0.0042)
	History of OASCVD	0.0028 (0.0017, 0.0038)	0.0028 (0.0014, 0.0042)
	Atrial fibrillation	0.0097 (0.0061, 0.0133)	0.0097 (0.0051, 0.0144)
	Kidney disease	0.0146 (0.0129, 0.0163)	0.0146 (0.0123, 0.0169)
	Smoking		
	Past	0.0033 (0.0023, 0.0044)	0.0034 (0.0021, 0.0047)
	Current	0.0142 (0.0128, 0.0156)	0.0143 (0.0125, 0.0160)
	Amlodipine	0.0003 (-0.0008, 0.0014)	0.0003 (-0.0011, 0.0017)
	Lisinopril	-0.0004 (-0.0016, 0.0009)	-0.0004 (-0.0020, 0.0011)
	β_{DM}	0.0086 (0.0053, 0.0120)	0.0085 (0.0043, 0.0127)
	β_{DS}	0.0418 (0.0347, 0.0488)	0.0419 (0.0336, 0.0502)
	β_{DH}	0.0679 (0.0613, 0.0745)	0.0679 (0.0599, 0.0759)

*Excess hazard/absolute risk is the additional hazard/risk imparted by a risk factor compared to its reference group.

[†]Statistically significant covariate from bagging

[‡]Due to rounding; absolute value is between 0 and 0.0001

Table 2a. Area under the curve for the tuned IHCM (70/30)

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=30,295	N=3,358	N=940	N=370	N=145
1	0.67 (0.65, 0.68)	0.61 (0.59, 0.63)	0.57 (0.54, 0.61)	0.60 (0.54, 0.66)	0.67 (0.58, 0.76)
2	0.67 (0.66, 0.68)	0.63 (0.61, 0.65)	0.58 (0.54, 0.62)	0.64 (0.58, 0.70)	0.68 (0.57, 0.78)
3	0.68 (0.67, 0.69)	0.63 (0.61, 0.65)	0.59 (0.55, 0.64)	0.67 (0.59, 0.75)	0.70 (0.57, 0.82)
4	0.68 (0.68, 0.69)	0.63 (0.61, 0.65)	0.62 (0.57, 0.67)	0.65 (0.55, 0.76)	0.70 (0.56, 0.84)

Table 2b. Area under the curve for the tuned IHCM (60/40)

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=30,295	N=3,358	N=940	N=370	N=145
1	0.67 (0.65, 0.68)	0.61 (0.59, 0.63)	0.57 (0.54, 0.61)	0.60 (0.54, 0.66)	0.67 (0.58, 0.76)
2	0.67 (0.66, 0.68)	0.63 (0.61, 0.65)	0.58 (0.54, 0.62)	0.64 (0.58, 0.70)	0.68 (0.57, 0.78)
3	0.68 (0.67, 0.69)	0.63 (0.61, 0.65)	0.59 (0.55, 0.64)	0.67 (0.59, 0.75)	0.70 (0.57, 0.82)
4	0.68 (0.68, 0.69)	0.63 (0.61, 0.65)	0.62 (0.57, 0.67)	0.65 (0.55, 0.76)	0.70 (0.56, 0.84)

Table 3a. Area under the curve for IHCM test set (70/30)

Year	0 events	1+ events	2+ events	3+ events
	N=9,088	N=1,007	N=282	N=111
1	0.67	0.61	0.58	0.60
	(0.65, 0.69)	(0.58, 0.64)	(0.53, 0.63)	(0.50, 0.70)
2	0.67	0.63	0.58	0.64
	(0.66, 0.69)	(0.60, 0.65)	(0.54, 0.63)	(0.56, 0.72)
3	0.68	0.63	0.60	0.68
	(0.66, 0.69)	(0.60, 0.65)	(0.55, 0.65)	(0.58, 0.77)

Table 3b. Area under the curve for IHCM test set (60/40)

Year	0 events	1+ events	2+ events	3+ events
	N=12,118	N=1,343	N=376	N=148
1	0.67	0.61	0.57	0.60
	(0.65, 0.69)	(0.59, 0.64)	(0.54, 0.61)	(0.53, 0.68)
2	0.67	0.63	0.58	0.64
	(0.66, 0.69)	(0.61, 0.65)	(0.55, 0.62)	(0.57, 0.71)
3	0.68	0.63	0.60	0.67
	(0.67, 0.69)	(0.61, 0.64)	(0.56, 0.64)	(0.60, 0.75)

Table 4. IRHCM, tuned parameters from 200 bagged datasets (70/30)

		Baseline (excess) hazard/absolute risk*
	Parameter	Estimate (95% CI)
MI	μ_M	
	Intercept	0.0011 (0.0004, 0.0018)
	Age	
	65-79	0.0035 (0.0029, 0.0042)
	≥ 80	0.0066 (0.0048, 0.0083)
	Diabetes	0.0029 (0.0022, 0.0036)
	Previous MI or stroke	0.0046 (0.0036, 0.0056)
	Sex	0.0037 (0.0030, 0.0044)
	Previous CABG	0.0089 (0.0074, 0.0103)
	History of OASCVD	0.0019 (0.0011, 0.0028)
	Kidney disease	0.0018 (0.0008, 0.0028)
	Aspirin use	0.0018 (0.0010, 0.0027)
	Smoking	
	Past	0.0013 (0.0005, 0.0020)
	Current	0.0033 (0.0024, 0.0042)
	Amlodipine	-0.0003 (-0.0011, 0.0004)
	Lisinopril	-0.0002 (-0.0009, 0.0006)
	β_{MM}	
	Intercept	0.0340 (0.0256, 0.0424)
	Sex	0.0217 (0.0124, 0.0310)
	Kidney disease	0.0242 (0.0102, 0.0382)
	β_{MS}	0.0089 (0.0050, 0.0129)
	β_{MH}	
	Intercept	0.0060 (0.0020, 0.0099)
	Diabetes	0.0138 (0.0066, 0.0210)
Stroke	μ_S	
	Intercept	0.0006 (0.0002, 0.0011)
	Age*	0.0023 (0.0019, 0.0027)
	Diabetes	0.0031 (0.0025, 0.0036)
	Previous MI or stroke	0.0041 (0.0033, 0.0049)
	Sex	0.0013 (0.0008, 0.0018)
	Hypertension (Stage 2)	0.0014 (0.0007, 0.0020)
	Atrial fibrillation	0.0089 (0.0060, 0.0117)
	Kidney disease	0.0013 (0.0006, 0.0021)
	Smoking (Current)	0.0024 (0.0018, 0.0030)
	Amlodipine	-0.0005 (-0.0012, 0.0002)
	Lisinopril	0.0007 (<0.0001 [‡] , 0.0013) [†]
	β_{SM}	0.0032 (0.0014, 0.0050)
	β_{SS}	0.0227 (0.0186, 0.0267)
	β_{SH}	0.0032 (0.0012, 0.0052)

HF	μ_H	
	Intercept	0.0007 (0.0004, 0.0009)
	Age (≥ 80)	0.0062 (0.0044, 0.0079)
	Diabetes	0.0037 (0.0032, 0.0043)
	Previous MI or stroke	0.0042 (0.0034, 0.0050)
	Previous CABG	0.0040 (0.0029, 0.0050)
	Hypertension (Stage 2)	0.0017 (0.0011, 0.0023)
	History of OASCVD	0.0015 (0.0009, 0.0022)
	Atrial fibrillation	0.0227 (0.0192, 0.0261)
	Kidney disease	0.0036 (0.0027, 0.0045)
	Smoking (Current)	0.0009 (0.0003, 0.0014)
	LVH by echocardiogram	0.0023 (0.0011, 0.0035)
	Amlodipine	0.0019 (0.0013, 0.0025)
	Lisinopril	0.0005 (0.0001, 0.0010) [†]
	β_{HM}	
	Intercept	0.0126 (0.0063, 0.0189)
	Age	
	65-79	0.0178 (0.0093, 0.0262)
	≥ 80	0.0628 (0.0319, 0.0937)
	Diabetes	0.0430 (0.0322, 0.0538)
	History of OASCVD	0.0189 (0.0070, 0.0308)
	Kidney disease	0.0273 (0.0128, 0.0417)
	Amlodipine	0.0160 (0.0052, 0.0268)
	β_{HS}	0.0116 (0.0077, 0.0154)
	β_{HH}	
	Intercept	0.1274 (0.1170, 0.1377)
	Lisinopril	-0.0300 (-0.0509, -0.0091)
Death	μ_D	
	Intercept	0.0008 (-0.0001, 0.0017)
	Age	
	65-79	0.0105 (0.0094, 0.0116)
	≥ 80	0.0551 (0.0515, 0.0586)
	Diabetes	0.0088 (0.0077, 0.0098)
	Previous MI or stroke	0.0089 (0.0076, 0.0102)
	Sex	0.0061 (0.0050, 0.0072)
	Black	0.0030 (0.0021, 0.0039)
	History of OASCVD	0.0027 (0.0017, 0.0038)
	Atrial fibrillation	0.0093 (0.0056, 0.0129)
	Kidney disease	0.0146 (0.0128, 0.0164)
	Smoking	
	Past	0.0034 (0.0023, 0.0044)
	Current	0.0144 (0.0130, 0.0158)

Amlodipine	0.0003 (-0.0007, 0.0014)
Lisinopril	-0.0004 (-0.0017, 0.0009)
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β_{DM}	
Intercept	-0.0013 (-0.0049, 0.0023)
Age \geq 65	0.0176 (0.0121, 0.0231)
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β_{DS}	
Intercept	0.0227 (0.0137, 0.0317)
Age [*]	0.0227 (0.0139, 0.0315)
<hr/>	
β_{DH}	
Intercept	0.0524 (0.0413, 0.0636)
Age \geq 65	0.0206 (0.0071, 0.0341)

*Excess hazard/absolute risk is the additional hazard/risk imparted by a risk factor compared to its reference group.

[†]Statistically significant covariate from bagging

[‡]Due to rounding; absolute value is between 0 and 0.0001

Table 5. Area under the curve for the tuned IRHCM (70/30)

Year	0 events	1+ events	2+ events	3+ events	4+ events
	N=30,295	N=3,358	N=940	N=370	N=145
1	0.67 (0.65, 0.68)	0.62 (0.60, 0.64)	0.59 (0.55, 0.62)	0.59 (0.53, 0.65)	0.63 (0.54, 0.72)
2	0.67 (0.66, 0.68)	0.64 (0.62, 0.66)	0.60 (0.57, 0.64)	0.64 (0.57, 0.70)	0.65 (0.54, 0.76)
3	0.68 (0.67, 0.69)	0.64 (0.62, 0.66)	0.62 (0.58, 0.66)	0.65 (0.57, 0.73)	0.73 (0.60, 0.85)
4	0.68 (0.68, 0.69)	0.66 (0.64, 0.68)	0.66 (0.61, 0.70)	0.64 (0.53, 0.75)	0.80 (0.67, 0.94)

Table 6. Area under the curve for IRHCM test set (70/30)

Year	0 events	1+ events	2+ events	3+ events
	N=9,088	N=1,007	N=282	N=111
1	0.67 (0.65, 0.69)	0.62 (0.58, 0.65)	0.58 (0.54, 0.63)	0.59 (0.50, 0.68)
2	0.67 (0.66, 0.69)	0.64 (0.61, 0.66)	0.60 (0.55, 0.65)	0.63 (0.55, 0.71)
3	0.68 (0.66, 0.69)	0.64 (0.62, 0.66)	0.62 (0.57, 0.67)	0.65 (0.54, 0.76)

CHAPTER 5: CONCLUSIONS

This dissertation proposed a dynamic risk model that handles multi-type recurrent events with a dependent terminating event in a competing risk framework. A unique feature of the model is that it directly provides the baseline hazard for each type of recurrent event and the terminating event, and the additional hazard that each recurrent event confers to all other events. This quantifies positive and negative associations and relationships between all event types, recurrent and terminating. The baseline hazard is dynamically updated with each event occurrence, and is affected by event history (the number and types of past events) and covariates. In the first paper, we derived and formulated the model and then validated the model with a simulation study. The model was applied to the model to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study and a procedure developed to assess goodness of fit of the model, therefore accomplishing aims 1 and 2 in the important arena of CVD.

We extended the model to incorporate risk factors for intrinsic hazards of the nonfatal CVD events MI, stroke and HF, and all-cause mortality (death) (IHCM 1) and further extended the model to incorporate risk factors for recurrent hazards, or for hazards imparted by antecedent nonfatal MI, stroke and/or HF (IRHCM). Heterogeneity of treatment effects on subgroups of patients was examined (IHCM 2). Goodness of fit for IHCM 1 and IRHCM was markedly improved for all individuals at baseline (0 events) and with 4+ events, and modestly improved for IRHCM for individuals with 1+ and 2+ events. Therefore, we conclude that CVD risk factors and antecedent CVD events are predictive of future CVD events and mortality, satisfying aim 3. Incorporation of biomarkers and time-dependent covariates in conjunction with methods to

handle missing covariates in longitudinal data would further augment the models and should be considered as an important future direction of this research.

Finally, IHCM 1 and IRHCM were stabilized and validated with a supervised learning approach. Bootstrap aggregated (bagged) training sets were utilized to stabilize the parameter estimates and construct 95% confidence intervals for every parameter using the standard deviations of the parameter's bagged estimates. This in turn led to potential variable selection from stabilized parameter estimates with shrinkage of standard errors resulting in tighter 95% CI's. Each training set's estimated parameters was assessed for goodness of fit on its corresponding test set. IHCM 1 and IRHCM performed comparably on test sets, which suggests that both models are stable and do not have the problem of overfitting, satisfying our 4th and final aim.

Our proposed multi-type recurrent events model has great potential to develop into a clinical risk assessment tool or risk score for CVD that incorporates both risk factors and event history and is tailored to the individual's clinical profile, and provide head-to-head comparisons between treatment and therapeutic approaches for CVD. This would be of significant import in reducing the enormous public health and clinical burden of CVD, in the United States and worldwide.

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